THE ACID-CATALYSED HYDRATION OF SYM-DICHLOROACETONE

A thesis submitted for the
degree of Doctor of Philosophy
in the University of Stirling

J. E. Critchlow.

August 1969

Department of Chemistry

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Part of a continuing study on the kinetics and mechanism of the hydration of carbonyl compounds is reported. The kinetic effect of varying the composition of the aqueous dioxan solvent mixture was investigated for catalysis by water and seven acids, in order to provide a further test of the suggestion of Bell, Millington, and Pink (Proc.Roy.Soc. A 1968, 303, 1) that the water-catalysed reaction passes through a cyclic transition-state made up of the substrate and three water molecules, of which either one or two can be replaced by a molecule of catalyst according to its structure. Solvent deuterium isotope effects were also measured with a view to investigating the configuration of the transition-state.

The kinetics and equilibria of the hydration of sym-dichloroacetone were measured spectrophotometrically at 25°C in solutions of water mole fraction 0.086–0.320. The isotope effect on the dissociation constant, K, of the ketone hydrate was found to be

$$K_D/K_H = 0.91_5$$

Appreciable concentrations of catalyst led to increased values of K, which were analysed in terms of ground-state hydration of the catalysts.

The following kinetic orders with respect to water mole fraction were found for the hydration reaction:

CCl_3COOH 0.91, $CH_2ClCOOH$ 0.98, C_6H_5COOH 0.92, CH_3COOH 0.98, o-$C_6H_3Cl_2COOH$ 2.5, H_2O 3.65.

From the linear kinetic order plots it is argued that the slopes provide an approximate measure of the number of water molecules taken up in an intimate fashion in the activation equilibrium. Combination of these results with estimates of the degree of hydration of the catalyst suggests on balance, and in company with other evidence, that all the transition-states have similar structures.

Solvent isotope effect studies indicated that at least three water molecules are taken up in the water catalysed reaction, that the fractionation factor products for the different transition-states are very similar, and that there is a primary contribution. For the hydration reaction k_H/k_D was found to be

HCl 1.23, $HClO_4$ 1.29, CCl_3COOH 2.46, $CH_2ClCOOH$ 2.92,
C_6H_5COOH 2.76, CH_3COOH 2.94, H_2O 3.97.

A simple model is proposed for the prediction of transition-state configurations and energies, and gives a reasonable account of the observed catalytic behaviour, isotope effects, and structure-reactivity relations. Carbon-oxygen bond formation occurs synchronously with proton transfer from the acid in the transition-state, but the other proton transfers have been already carried to completion or have not yet started.

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INTRODUCTION

CHAPTER I

The Hydration of Aldehydes and Ketones

The addition of water to aldehydes and ketones

$$R_1R_2CO + H_2O \rightleftharpoons R_1R_2C(OH)_2$$

is the simplest example of the important class of reversible additions to the carbonyl group. The subject has been thoroughly reviewed by Bell (1), and is summarised in the present chapter with special reference both to more recent work and to theories relating to the mechanism of the reaction.

1. Experimental determination of the equilibrium constant

The most frequently applied method of investigating the fraction of the carbonyl compound which is hydrated in aqueous solution makes use of the decrease in the intensity of the characteristic ultra-violet absorption of such compounds when dissolved in water. This rather broad band, attributable to an $n \longrightarrow \pi^*$ transition of the carbonyl group, occurs at about 280 mμ and is assumed to be absent in the spectrum of the hydrate. The chief problem attaching to the method lies in the determination of the maximum molar extinction coefficient ϵ_o of the unhydrated species in water, which the earlier workers took as equal to the value in some non-aqueous solvent such as cyclohexane, as in the work of Bell and McDougall (2). Recent studies by Greenzaid, Rappoport, and Samuel (3) on the absorption spectra of a number of aldehydes and ketones in solvents of different polarity have demonstrated that this procedure can lead to large errors in the equilibrium constants and that reliable application of the spectrophotometric method therefore requires a different strategy.

Greenzaid and co-workers found that although ϵ_o changed monotonically with increase in solvent polarity, increasing for aliphatic aldehydes but decreasing in the case of the chloroketones, no quantitative correlation could be found with any established solvent polarity parameter. On the other hand a linear correlation could be found with the values of ϵ_o for a carbonyl compound of similar type but which shows practically no tendency to hydration, e.g. pivaldehyde with acetone, monochloroacetone with α-chlorocyclohexanone, and this allowed estimation of the required value of ϵ_o in water.

The earliest reliable spectrophotometric method was devised for acetaldehyde by Bell and Clunie (4), who chose the value of ϵ_o which corresponded to a set of equilibrium constants whose variation with temperature agreed with the independently measured enthalpy of hydration. Gruen and McTigue (5) merely required that the plot of log K against 1/T should be linear, without the discipline imposed by the value of its slope, a method which as Bell has pointed out is subject to large errors.

The third and most direct way of obtaining ϵ_o is by back extrapolating to zero time the kinetic measurements obtained on adding the unhydrated carbonyl compound to water. This has been applied by Bell, Millington, and Pink (6) to the hydration of sym-dichloroacetone in dioxan-water and acetonitrile-water solutions at 25°C., by Kurtz (7) to the hydration of acetaldehyde in deuterium oxide at 15°C., and by Pocker, Meany, and Nist (8) to the study of 2- and 4-pyridine aldehydes at 0°C. The sensitivity of the method depends on the fraction of the half-life elapsing before the first reading can be taken, and in most cases the reaction is too fast for this to be undertaken in pure water.

The other widely applicable method for the measurement of hydration equilibria is proton magnetic resonance (p.m.r.), which makes use of upfield shifts on hydration of about 0.8 p.p.m. for hydrogens attached to an α-carbon atom and about 5.0 p.p.m. for an aldehydic proton. This has the great advantage of not requiring any calibration, since under suitable conditions the relative concentrations of hydrated and unhydrated compound are given by the areas under their peaks, but has the disadvantage of making necessary the use of fairly high concentrations with the accompanying danger of activity coefficient changes or, as observed by Ahrens and Strehlow (9), the formation of a hemihydrate between the carbonyl compound and a molecule of the hydrate. Integration of p.m.r. spectra is also prone to a number of sources of error, especially in the presence of an intense solvent peak, and is generally less accurate than spectrophotometry. The method has been used by Greenzaid and co-workers (3,10), who have been able to confirm the revised values of equilibrium constants obtained by their spectrophotometric technique. P.m.r. is to be much preferred over spectrophotometry when the degree of hydration is high or low, as for example in the estimation by Hine and Redding (reported in reference 1) that acetone is 0.2 ± 0.1% hydrated in aqueous solution.

The only other accurate method employed to date is the use of oscillographic polarography by Valenta (reported in reference 1) to determine the fraction of formaldehyde remaining unhydrated. A rather less accurate technique based on a similar principle consists in determining the amount of a carbonyl reagent such as semicarbazide which reacts instantaneously on addition to an aqueous solution of the carbonyl compound, under conditions in which this reaction is considerably faster than the rate of dehydration of the carbonyl hydrate. This chemical method has been applied by Bell and Evans (11) to the study of acetaldehyde, and by Le Hénaff (12) to a number of aliphatic aldehydes.

Greenzaid, Luz, and Samuel (10) have recently employed ^{17}O nuclear magnetic resonance in the study of a number of aldehydes and ketones whose degrees of hydration are fairly well established. After equilibration of the substrate in water enriched with 4-8 atom % of $H_2{}^{17}O$, two peaks were observed, one about 60 p.p.m. downfield from the solvent peak in the region occupied by alcohols and the other about 530 p.p.m. downfield and attributable to the carbonyl oxygen. Integrations were of low accuracy on account of the low signal/noise ratio and the fact that the first derivative of the absorption mode is the quantity recorded, but semi-quantitative agreement was obtained with established values. Bell (1) mentions the use of Raman spectroscopy and measurement of the partial vapour pressure of the carbonyl compound over its aqueous solution as other semi-quantitative techniques.

2. Magnitudes of equilibrium constants and their interpretation

A non-dimensional equilibrium constant can be defined for aqueous solution by the relation,

$$K_d = \frac{[R_1R_2CO]}{[R_1R_2C(OH)_2]}$$

and a selection of the more reliable values is presented in Table (1). A much more comprehensive table is provided in Bell's review, but a number of these values are unreliable as they depend on an uncertain value of ϵ_o and are therefore omitted. The same applies to the recent values obtained by Ahrens (13) for a number of α-keto acids and their derivatives, since these depend on ϵ_o values measured in sulphuric acid or tetrahydrofuran.

High accuracy is not claimed for the first two and last two values in the table, these being included to show the range of compounds studied, although for formaldehyde and monochloroacetone these approximate values are supported by more than one method (1,3). The remaining three compounds are the only ones in the literature for which two methods give concordant and reasonably precise results. Acetaldehyde has been by far the most studied,

TABLE (1)

Compound	K_d (25°C.)	Method	Reference
CCl_3CHO	$\sim 3.6 \times 10^{-5}$	U.V.	5
HCHO	$\sim 5.0 \times 10^{-4}$	Polarography	1
$(CH_2Cl)_2CO$	0.17	p.m.r., U.V.	3
CH_3CHO	0.82	U.V., p.m.r.	4,9
$(CH_3)_3CCHO$	4.3	p.m.r., U.V.	10,3
$CH_2ClCOCH_3$	~ 13	p.m.r.	3
$(CH_3)_2CO$	~ 500	p.m.r.	1

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and the value quoted above is that recalculated by Kurtz (7) from the results of Bell and Clunie. Kurtz himself has obtained the higher value of 0.94 both by Bell and Clunie's method, where the difference is due to a different enthalpy of reaction, and by the back extrapolation spectrophotometric technique, but the value of 0.82 is identical with the p.m.r. result obtained by Ahrens and Strehlow. Of the three values which are less than 0.7 quoted by Bell for acetaldehyde, that obtained by the chemical method of Bell and Evans (11) does not agree with a similarly obtained result of Le Hénaff (12), another is from the p.m.r. work of Lombardi and Sogo (14) who appear to have averaged results obtained in light and heavy water, and the third is a spectrophotometric result obtained by Rumpf and Bloch (15) with an untested assumption as to the value of ϵ_o.

It is apparent even from the small number of values in the above table that the degree of hydration decreases from formaldehyde to the other aldehydes and from these to the ketones, and that within one class of compounds it increases with the electron-withdrawing power of the substituent. This can be seen more clearly from the more comprehensive compilations of data for saturated aliphatic aldehydes and ketones given by Bell (1) and by Greenzaid, Luz, and Samuel (10). The latter workers show that if $-\log K_d$ is plotted against Taft's polar substituent constants σ^* two very good straight lines are obtained, a lower one for the ketones, a higher one for the aldehydes, and a point for formaldehyde at about an equal separation above this. This is an example of an α-hydrogen effect on a linear free energy relation, of which Leffler and Grunwald (16) cite as further examples the acid-catalysed hydrolysis of diethyl acetals and ketals in a 50% dioxan-water mixture at 25°C. and the equilibrium constants for the hydrogenation of aldehydes and ketones in toluene at 60°C.

In order to bring all the values onto a common straight line it is obviously necessary to introduce another parameter. Bell (1) achieves this by the use of Taft's steric substituent constants,

$$\log K_d = 2.7 - 2.6\sum\sigma^* - 1.3\,E_s\,,$$

although he points out that the summation of these steric parameters over two groups bonded to the same carbon atom is an operation not normally carried out and difficult to justify physically. This procedure also causes some dispersion of the points for each class of compound, especially for a compound like pivaldehyde, in view of which Greenzaid, Luz, and Samuel (10) propose the alternative equation:

$$\log K_d = 2.8 - 1.7\sum\sigma^* - 2.0\Delta,$$

in which the parameter Δ is equal to the number of aldehydic protons in the molecule. From a consideration of the calculation of the energy of a non-conjugated system by the molecular-orbital perturbation method Dewar and Pettit (107) concluded that the total energy should be an additive function of a universal set of individual bond energies plus the sum of interaction terms representing all pairs of adjacent bonds, and showed that such a system can account well for the variations in experimentally determined thermochemical data. Greenzaid and co-workers suggest that this theory of adjacent bond interaction can provide a physical interpretation of the Δ parameter, although they fail to explain why it does not appear in the ester hydrolysis reactions on which the σ^* constants are based.

The sparse data available for conjugated carbonyl compounds indicates that they are little hydrated, as is found for the carbonyl moiety of the ester group. Le Hénaff (12) has reported that both acrolein and crotonaldehyde are less than 2% hydrated at 25°C., while the values of around 50% found by Pocker and co-workers (8) for the degree of hydration of 2- and 4-pyridine aldehydes can be explained by the small opportunity for conjugation in these compounds.

3. Experimental determination of kinetic data

The first quantitative investigations of reaction rates in this system were carried out by Bell's school with the use of a dilatometric method (17,18). Their subsequent development of the thermal maximum method for reactions with half-lives of the order of a few seconds allowed the first systematic study of the hydration of acetaldehyde in aqueous solution at 25°C. (19) to be undertaken; this technique depended on measurement of the maximum temperature reached when the reaction was conducted in a calorimeter under conditions of controlled heat loss. Kurtz and Coburn (20) have recently studied the kinetics of acetaldehyde hydration by measuring the rate of evolution of heat under adiabatic conditions.

A conventional spectrophotometric method has been used by Bell and Jensen (21) to measure the rate of hydration of sym-dichloroacetone, made suitably slow by the use of a 5% water + dioxan mixture as solvent. Pocker and co-workers (22-26) achieved rates slow enough for the use of this technique in their extensive study of the catalytic effects of general acids and bases, metal ions, and an enzyme on the hydrations of acetaldehyde and of 2- and 4-pyridine aldehydes by conducting experiments at 0°C. The considerable volume and heat changes accompanying the hydration reaction and made use of in the earlier investigations have been applied more recently by Eigen and his collaborators in kinetic studies on some α-keto acids by the pressure- and temperature-jump relaxation methods (27,13); the equilibrium conditions are perturbed by a rapid change in pressure or temperature, after which the rate of re-establishment of chemical equilibrium is followed by fast recording spectrophotometry.

Proton magnetic resonance has been used by Ahrens and Strehlow (9), who observed the line-broadening caused by the addition of various concentrations of hydrochloric acid to aqueous solutions of acetaldehyde; at high acetaldehyde concentrations a term second order with respect to substrate was attributed to a dynamic equilibrium between aldehyde, hydrate, and hemihydrate. A similar ^{17}O line-broadening technique has recently been applied by Greenzaid, Luz, and Samuel (28) to the carbonyl oxygen of acetaldehyde, and the results, although of a low order of accuracy, are in agreement with determinations by other methods.

The isotope exchange method was pioneered in 1938 by Cohn and Urey (106) in their studies of the rate of hydration of acetone by mass spectrometric analysis for ^{18}O, and in the last few years a number of semi-quantitative studies by this and similar methods have been made on the slow rates of the carbonyl oxygen exchange in aqueous solution of compounds whose degrees of hydration are negligibly small. Greenzaid and co-workers have investigated acetone (29), which in neutral solution has a half-life of exchange of about 10 hours, and the alicyclic ketones from cyclobutanone to cycloheptanone (30) by following the rate of diminution of the carbonyl ^{17}O peak by nuclear magnetic resonance when enriched substrate was dissolved in water. Byrn and Calvin (31) obtained a qualitative order of reactivity by using infra-red absorption intensity measurements to follow the incorporation of ^{18}O from enriched water in organic media into a series of ketones and aromatic aldehydes, and Dahn and Aubort (32) employed mass spectrometric measurements to obtain quantitative kinetic data for a number of p-benzoquinones under similar conditions.

While the above methods all measure the approach to equilibrium, the techniques chiefly employed for formaldehyde depend on rapid removal of the aldehyde as a means of measuring the rate of dehydration. Bell and Evans (11) carried out a thorough study of acid and base catalysis of this reaction by chemical scavenging, and Bell's review mentions the analogous application of polarography.

4. Kinetic results and relations between them

Bell and co-workers have obtained extensive catalytic data for the hydration reactions of acetaldehyde (19) and formaldehyde (11) in water, of acetaldehyde in 10% aqueous acetone (17), and of sym-dichloroacetone (21) in a 5% v/v solution of water in dioxan, all at 25°C. The results follow the Brönsted relation, which can be written for general acid and base catalysis respectively as:

$$\frac{k_a}{p} = G_a\left(\frac{qK}{p}\right)^{\alpha} \quad , \quad \frac{k_b}{q} = G_b\left(\frac{p}{qK}\right)^{\beta}$$

where k_a and k_b are the second order catalytic rate constants, K the acid dissociation constant of the catalyst, and p and q are statistical corrections equal respectively to the number of equivalent ionizable protons in the acid and the number of equivalent basic sites in the conjugate base. The G's, α, and β, are constants for a particular substrate. In the present case these relations correlate a large amount of data covering a wide variation in acidic and basic strength, and show dispersion due to differences in charge-type only when the solvent has a low dielectric constant. Bell (1) has suggested that the low incidence of deviations is attributable to the fact that the transfers occur between the acid or base and an oxygen atom, just as in the acid dissociation reaction to which K refers. Positive deviations have been observed by Bell and co-workers for catalysis by oximes in the reactions of acetaldehyde and sym-dichloroacetone and for the ions $H_2PO_4^-$, $H_2PO_3^-$, and $H_2AsO_4^-$ in the dehydration of formaldehyde, and also by Pocker and Meany (22) for $H_2PO_4^-$ and HPO_4^{2-} in the reaction of acetaldehyde, and by Greenzaid et al. (29) for $H_2PO_4^-$ in the oxygen exchange of acetone. Negative deviations have been found by Bell's group for 2,6-substituted pyridines and their conjugate acids.

Pocker and Meany (22,23) found that metal ions have a generally weak catalytic effect, except in the case of 2-pyridine aldehyde where Cu^{2+}, Co^{2+}, Ni^{2+}, and Zn^{2+} are more effective than the hydronium ion, and for which co-ordination with the substrate provides a ready explanation. These workers have also demonstrated (24-26) that the enzyme erythrocyte carbonic anhydrase, which catalyses the reversible hydration of carbon dioxide, is a very efficient catalyst in aldehyde hydrations, and have studied solvent deuterium isotope effects and inhibition by the substrate and by acetazolamide in an attempt to understand the mechanism of its action. Since both zinc ion and imidazole occur near the active site of the enzyme, it is of interest that they have demonstrated a considerable synergistic effect between the two substances in the catalysis of the hydration of acetaldehyde (22).

Turning to a comparison of different aldehydes and ketones, a general correlation is apparent between the rate of water-catalysed hydration and the fraction of the compound hydrated at equilibrium. Examination of the values at 25°C. for the first-order hydration and dehydration rate constants k_h and k_d in Table (2) shows that k_h

accounts for practically all the variation in K_d.

TABLE (2)

Compound	K_d	k_h (sec^{-1})	k_d (sec^{-1})	Reference
HCHO	$\sim 5.0 \times 10^{-4}$	~ 10	5.1×10^{-3}	11
CH_3CHO	0.82	4.3×10^{-3}	3.6×10^{-3}	19
$(CH_3)_2CO$	~ 500	$\sim 10^{-5}$	$\sim 5.0 \times 10^{-3}$	29

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A similar correlation is observable qualitatively in the hydroxide-catalysed hydration of alicyclic ketones (30), in the results of Byrn and Calvin for water-catalysis (31), and in the observation by Le Hénaff (12) that the hydrates formed from a number of aliphatic aldehydes are dehydrated at approximately equal rates at a pH of 5.0. A number of the results for catalysis by mineral acids indicate that the above order of reactivity in hydration can sometimes be reversed, and Greenzaid and co-workers have suggested (29,30) that this represents a basicity effect. For example the orders cyclobutanone < cyclohexanone (30), mono- and sym-dichloroacetone < acetone (29), and pyruvic acid < ethyl pyruvate < pyruvate anion (13) all indicate a dependence of rate on basicity in preference to dependence on the observed or expected order of hydration equilibria. The same workers have pointed out that the Brönsted coefficient α for acid catalysis increases in the series $HCHO < CH_3CHO < (CH_3)_2CO$. No attempt appears to have been made so far to present a general correlation of kinetic with thermodynamic data or to relate any of the above observations to the configuration of the transition-state for the hydration reaction, and this subject will be returned to in the Discussion.

5. Mechanism of the reaction and the purpose of the present work

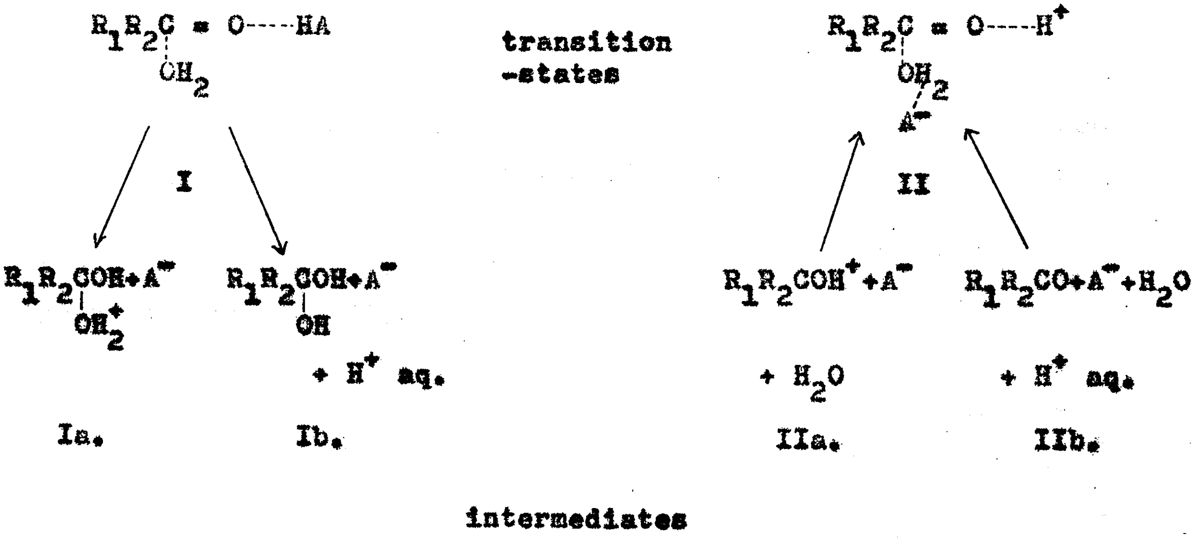
Arguments relating to the logical first step in the establishment of a reaction mechanism, the composition of the transition-state, were presented by Bell and Higginson (17) in their early paper reporting the first systematic kinetic data. The observation that the reaction is kinetically of the first order with respect to both the substrate and the acid or base catalyst is concordant with a transition-state containing one molecule of each of these species; general acid catalysis, for example, argues against the representation of the acid in the transition-state solely by the presence of a proton. The drawing of further conclusions requires consideration of the stable intermediates through which the reaction is likely to pass in approaching the transition-state from either direction. Such considerations have been criticised by Swain as anthropomorphic (33) on the grounds that they lie outside the sphere of transition-state theory, but in accepting the statistical thermodynamic methods of the latter there is no reason to reject the dynamic view of the approach of the system to the activated complex by a series of collisions with the molecules of the solvent, and under such circumstances there is good reason to believe that the activated state will be preceded and followed by the stable systems it most closely resembles.

The most likely intermediates surrounding a transition-state of the above composition are the reactants and products of the reaction step:

$$R_1R_2CO + HA \rightleftharpoons R_1R_2COH^+ + A^-$$

According to Table 2, the pK_a of protonated formaldehyde would then have to be no less than 4.0 in order to avoid a deprotonation rate greater than that of diffusion control when HA is a water molecule. In addition Eigen has shown (34) that for transfer of a proton between an oxygen atom and another atom of oxygen or of nitrogen in a reaction in which the pK_a's of the reactant and product acids differ by more than two or three units, the Brönsted coefficient is very close to unity for the "uphill" reaction and to zero for the "downhill", which in the present case is contrary to the intermediate values of α and β observed over a wide range of catalyst strength. Both these considerations require that the transition-state should contain an active molecule of water, presumably undergoing nucleophilic attack on the carbonyl group, i.e. the reaction must be termolecular and concerted.

Two basically different types of structure are now possible, as depicted below; the following discussion applies directly to the case of acid catalysis, but can readily be adapted for catalysis by bases.



Below each of the possible transition-state structures depicted above are the intermediates concerned in the only physically reasonable paths for the reaction. In case I the intermediates follow the transition-state in going from the aldehyde or ketone to the hydrate, while in case II the sequence is reversed; the dotted lines are not meant to imply any particular degree of bond formation. The four possible mechanisms are given below with the respective calculations for acetaldehyde in the absence of catalysts other than water. Structure I corresponds to the mechanism proposed by Bell and Higginson on the basis of evidence of the above type, while structure II is an alternative one put forward by Gruen and McTigue (35), in which general acid catalysis results from a combination of specific acid and general base catalysis.

It appears that the above scheme can also be criticised, as shown by Eigen (36) for the particular case Ia., and demonstrated in general below. The argument consists in calculating in each case the equilibrium constant for the prototropic reaction between the above intermediates and the reactants for catalysis by a weak acid, and combining this with the observed rate constant to obtain the rate at which the intermediates must react to give the products; if this is unreasonably fast the mechanism fails. The weakest acid catalyst studied in aqueous solution is water, which for acetaldehyde gives the first-order rate constants listed in Table (2). The pK_a of the conjugate acid of acetaldehyde hydrate is taken as -2 following Eigen, and the corresponding value for that of the aldehyde as -8 after Ahrens and Strehlow (9).

The second-order rate constant k_2 calculated for the passage of the reaction from the intermediates Ia. through the transition-state I is about two orders of magnitude larger than either the experimental recombination rate of H_3O^+ and OH^- or the rate of diffusion-controlled encounter as calculated from the Debye theory (37), while in the case IIa. the corresponding second-order rate constant is even larger. Although the theoretical magnitude of the diffusion-controlled rate for a termolecular encounter is less clear, similar remarks almost certainly apply to Ib. and IIb. Calculation of the appropriate quantities for stronger catalysts would give rise to lower values, but as pointed out by Eigen a

Ia. $\mathrm{MeCH(OH)_2 + H_2O \overset{K}{\rightleftharpoons} MeCH(OH)_2H^+ + OH^-}$

$$\mathrm{MeCH(OH)_2H^+ + OH^- \xrightarrow{k_2} MeCHO + 2H_2O}$$

$$\text{rate} = k_d[\mathrm{MeCH(OH)_2}] = k[\mathrm{MeCH(OH)_2}][\mathrm{H_2O}]$$

$$= k_2[\mathrm{MeCH(OH)_2H^+}][\mathrm{OH^-}] = k_2K[\mathrm{MeCH(OH)_2}][\mathrm{H_2O}]$$

$K = 2\mathrm{x}10^{-18}$, $k = 7\mathrm{x}10^{-5}M^{-1}\mathrm{sec.}^{-1}$, therefore $k_2 = 3.5\mathrm{x}10^{13}M^{-1}\mathrm{sec.}^{-1}$

Ib. $\mathrm{H_2O + H_2O \overset{K}{\rightleftharpoons} H_3O^+ + OH^-}$

$$\mathrm{MeCH(OH)_2 + H_3O^+ + OH^- \xrightarrow{k_3} MeCHO + 3H_2O}$$

$$\text{rate} = k_d[\mathrm{MeCH(OH)_2}] = k[\mathrm{MeCH(OH)_2}][\mathrm{H_2O}]^2$$

$$= k_3[\mathrm{MeCH(OH)_2}][\mathrm{H_3O^+}][\mathrm{OH^-}] = k_3[\mathrm{MeCH(OH)_2}]K[\mathrm{H_2O}]^2$$

$K = 4\mathrm{x}10^{-18}$, $k = 1.4\mathrm{x}10^{-6}M^{-2}\mathrm{sec.}^{-1}$, therefore $k_3 = 3.5\mathrm{x}10^{11}M^{-2}\mathrm{sec.}^{-1}$

IIa. $\mathrm{MeCHO + H_2O \overset{K}{\rightleftharpoons} MeCHOH^+ + OH^-}$

$$\mathrm{MeCHOH^+ + OH^- + H_2O \xrightarrow{k_3} MeCH(OH)_2 + H_2O}$$

$$\text{rate} = k_h[\mathrm{MeCHO}] = k[\mathrm{MeCHO}][\mathrm{H_2O}]^2$$

$$= k_3[\mathrm{MeCHOH^+}][\mathrm{OH^-}][\mathrm{H_2O}] = k_3K[\mathrm{MeCHO}][\mathrm{H_2O}]^2$$

$K = 2 \times 10^{-24}$, $k = 1.7 \times 10^{-6}M^{-2}\mathrm{sec}^{-1}$,

therefore $k_3 = 8.5 \times 10^{17}M^{-2}\mathrm{sec.}^{-1}$ and $k_2 = 4.2 \times 10^{19}M^{-1}\mathrm{sec.}^{-1}$

IIb. $\mathrm{H_2O + H_2O \overset{K}{\rightleftharpoons} H_3O^+ + OH^-}$

$$\mathrm{MeCHO + H_3O^+ + OH^- + H_2O \xrightarrow{k_4} MeCH(OH)_2 + 2H_2O}$$

$$\text{rate} = k_h[\mathrm{MeCHO}] = k[\mathrm{MeCHO}][\mathrm{H_2O}]^3$$

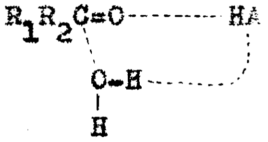
$$= k_4[\mathrm{MeCHO}][\mathrm{H_3O^+}][\mathrm{OH^-}][\mathrm{H_2O}] = k_4[\mathrm{MeCHO}]K[\mathrm{H_2O}]^3$$

$K = 4 \times 10^{-18}$, $k = 3.4 \times 10^{-8}$

therefore $k_4 = 8.5 \times 10^{9}M^{-3}\mathrm{sec.}^{-1}$ and $k_3 = 4.2 \times 10^{11}M^{-2}\mathrm{sec.}^{-1}$

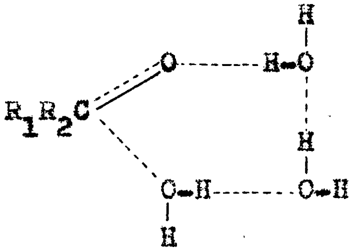
curvature of the Brönsted plot would then be expected, corresponding to passage from a constant limiting rate to one depending on the activation energy for each catalyst. It is also tempting to argue that high rates would not be expected for a reaction step in which a carbon-oxygen bond is broken or formed, but the very high rates recently reported by Barnett and Jencks (38) for the hydroxide-catalysed decomposition of hemithioacetals throws doubt on such considerations.

In view of the above objections Eigen (36) has postulated that the reaction occurs through a cyclic transition-state which avoids the need to pass through separate ionized intermediates. Such a structure had already been put forward by Bunton and Shiner (39) without any reasons for preferring it, and can be written for acid catalysis as:



with the inclusion of as many other water molecules as required. Bell has pointed out (6) that such a system allows an acid to donate a proton at one position and abstract one from another without requiring time as in the previous mechanism for the conjugate base to diffuse away and another to re-enter the reaction complex, and also that it allows the transition-states I and II to be replaced by a series of possible structures differing in the number and position of extra water molecules.

A certain amount of experimental data has recently been obtained in support of a transition-state containing several water molecules, as would be required by any reasonable model of the cyclic structure. Bell, Millington, and Pink (6) found that the kinetic dependence of the water-catalysed hydration of sym-dichloroacetone on the concentration of water in either dioxan or acetonitrile lay close to the third order over a considerable range of concentrations, and the constancy of this result led them to the conclusion that the appropriate ratio of the activity coefficients of water and the transition-state was constant and that the transition-state contained three water molecules, i.e.

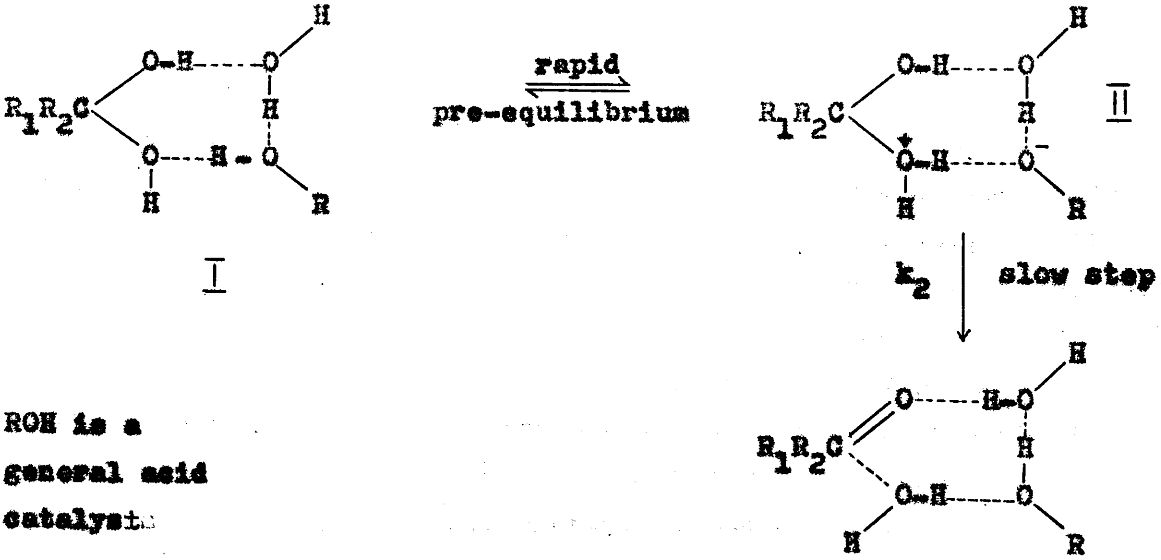


From the observed orders with respect to water of 0.7 for benzoic acid and 2.0 for triethylamine, they concluded that these catalysts could replace two and one water molecule, respectively, but for benzoate anion and hydrochloric acid negative orders were obtained and were attributed to hydration of the catalyst in the ground state. Dahn and Aubort (32) found similar results for the water-catalysed hydration of halo-p-benzoquinones in aqueous tetrahydrofuran, but did not study any other catalysts. Haldna and co-workers (40) investigated the variation of the rate of hydration of monochloroacetone with water activity in sulphuric acid, and concluded from their results that two or three water molecules are taken up in going to the transition-state.

Examination of the entropy of activation for the water-catalysed hydration of acetaldehyde suggests that the transition-state has a highly ordered structure. Calculations based on the first-order composite rate constants of Bell and Darwent (18) at 0°C. and of Bell, Rand, and Wynne-Jones (19) at 25°C., using the corrected equilibrium constants of Bell and Clunie (4), gives $\Delta S^{\ddagger} = -41.3$ e.u., which may be compared with the value $\Delta S = -16.6$ e.u. calculated from

Bell and Clunie's measurements for the equilibrium hydration process. The data for the hydroxide- and hydronium ion-catalysed reactions are subject to larger uncertainties, but undoubtedly lie much closer to zero, a fact which has led Kurtz and Coburn (20) to conclude that there is a large difference in the degree of hydration of the transition-states. However, calculation of the entropy of ionization of water from the ionic product data of Harned and Robinson (41) gives $\Delta S = -26.8$ e.u., showing that a considerable part of this difference is attributable to the ground states.

It is interesting to inquire whether any limitations can be placed on the allowed configuration of a cyclic transition-state as a result of considering the most likely cyclic intermediates involved. Albery (42) presents an argument that would exclude configurations in which some of the bond changes are completed, since these would be expected to be formed from cyclic systems made up partly of ionized species. Albery states that if, for example, the reaction scheme for dehydration:



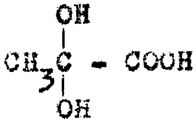
ROH is a general acid catalyst.

is not to degenerate into the previous mechanism passing through a non-cyclic transition-state, the slow step k_2 must be faster than the rate of break-up of the ionized complex II, while it must also necessarily be slower than the re-conversion of II to I by proton transfers along the hydrogen bonds; these two rates are put at 10^{11} sec.$^{-1}$ and 10^{14} sec.$^{-1}$, respectively, to produce a rather tight restriction on the value of k_2 and thereby to dismiss the mechanism. Bell (6) has countered this by arguing that the rate of break-up of II by collisions with solvent molecules must be considerably less than 10^{11} sec.$^{-1}$, which is calculated for the separation of two species not bound by any specific chemical forces. It may also be pointed out that the premature diversion of the complexes II into ionized fragments is of little consequence provided that these complexes exist in sufficiently high stationary concentration for some to undergo the relatively slow dehydration step; wastage of the intermediate by solvent collisions merely represents one mechanism for the reaction:

$$R_1R_2C(OH)_2 + ROH \rightleftharpoons R_1R_2C(OH)_2H^+ + RO^-.$$

On a rather different line of argument, it is quite probable that Swain's objections to the above considerations are valid in this case, since whereas the previous linear transition-states could not be approached from ionized molecules except either through the intermediates specified or by means of a cyclic process (in which case the transition-states should be regarded as cyclic), in the present case any configuration can be reached by entirely reasonable simultaneous motions of the hydrogen atoms. Configurations in which no atom transfer is complete are referred to as belonging to a synchronous mechanism and others are given the label step-wise; any one of the infinite number of possible configurations is described as more or less synchronous or step-wise (to use the familiar terms) without implying that at some stage in the whole range of mechanisms from one extreme to the other the reaction path necessarily starts to pass through one or more stable cyclic ionized intermediates such as II.

Mention should be made briefly of two investigations relating to possible special mechanisms in which catalysis may be provided by a neighbouring group in the substrate through a cyclic transition-state. Eigen and co-workers (27) observed that the dehydration of the hydrate of pyruvic acid,



$$CH_3C(OH)_2 - COOH$$

proceeded almost 100 times more rapidly than that of acetaldehyde, and suggested that intramolecular catalysis by the carboxyl group could be responsible, and recent measurements by Ahrens (13) have shown that the ethyl ester undergoes the reaction about 20 times more slowly than the acid, thus providing a better comparison. On the other hand, Pocker and Meany (23) found that 2-pyridine aldehyde undergoes hydration more slowly than the 4-isomer in spite of the possibility of basic catalysis by the neighbouring nitrogen atom in the former case. It may be that the stereo-electronic preference for co-planarity of the N-H bond and C=O group with the aromatic ring, linearity of hydrogen-bonds, and attack on the π-system of the carbonyl group may be responsible for the apparent lack of intramolecular catalysis in this case.

As shown above, Eigen's postulate of a cyclic transition-state is strongly supported by the catalytic behaviour and the magnitude of the rates of these reactions as well as by evidence for the inclusion of several water molecules. Part of the object of the present work has been to extend the investigations of Bell, Millington, and Pink into the latter point by studying kinetic orders with respect to water in the presence of a number of other acid catalysts. Practically nothing has yet been concluded concerning the configuration of the transition-state, wherein lies an understanding of the relative reactivities of different aldehydes and ketones and the magnitudes of their Brönsted coefficients, and with this end in mind measurements of solvent deuterium isotope effects on the rates of the reaction have been undertaken.

[illegible] the configuration [illegible]

[illegible] and.

[illegible]

[illegible] expression

$$K = \frac{\prod Q^0 (\text{products})}{\prod Q^0 (\text{reactants})} \times \exp\left(-\frac{\Delta E}{kT}\right),$$

[illegible] the difference in potential energy per molecule between products and reactants, and Q^0 is the total partition function [illegible] species.

$$Q^0 = Q_{trans} \times Q_{rot} \times Q_{vib}$$

$$Q_{trans} = \frac{(2\pi mkT)^{3/2}}{h^3},$$

$$Q_{rot} = [illegible]^{3/2} \cdot \pi^{1/2} \cdot (I_x I_y I_z)^{\frac{1}{2}}$$ for a non-linear molecule

$$Q_{vib} = \prod \frac{\exp(-h\nu_i/2kT)}{1-\exp(-h\nu_i/kT)} = \prod \frac{1}{2\sinh u_i}$$

[illegible]

CHAPTER II

Hydrogen Isotope Effects

The theory of the origin of kinetic isotope effects has been discussed in detail by Bigeleisen and Wolfsberg (43), Bell (44), and Melander (45), and only a brief summary is presented here. Particular attention is devoted instead to more recent studies designed to relate the magnitude of the effect to the configuration of the transition-state.

1. General theory of isotope effects

Statistical mechanics relates the equilibrium constant for a reaction to the molecular properties of the species involved through the general expression

$$K = \frac{\prod Q^{o}(\text{products})}{\prod Q^{o}(\text{reactants})} \times \exp\left(-\frac{\Delta\epsilon}{kT}\right),$$

where $\Delta\epsilon$ is the difference in potential energy per molecule between the products and reactants, and Q^{o} is the total partition function for each species.

$$Q^{o} = Q_{trans} \times Q_{rot} \times Q_{vib}$$

$$Q_{trans} = \frac{(2\pi MkT)^{3/2}}{h^{3}}.V$$

$$Q_{rot} = \frac{(8kT)^{3/2}}{sh^{3}}.\pi^{7/2}.(I_{x}I_{y}I_{z})^{\frac{1}{2}} \quad \text{for a non-linear molecule}$$

$$Q_{vib} = \prod_{i} \frac{\exp(-h\nu_{i}/2kT)}{1-\exp(-h\nu_{i}/kT)} = \prod_{i} \frac{1}{2\sinh\frac{1}{2}u_{i}}$$

where $u_{i} = \frac{h\nu_{i}}{kT}$, M is the mass of the molecule, the I's are the principal moments of inertia, s is the symmetry number, and the ν_{i}'s are the frequencies of the normal modes of vibration. The problem of assessing the effect of isotopic substitution on the equilibrium through its effect on all three factors of Q^{o} is simplified by the use of the Redlich-Teller product rule, which interrelates ratios of the above molecular quantities for two isotopic species

$$\left(\frac{M_1}{M_2}\right)^{3/2} \cdot \frac{(I_xI_yI_z)_1^{\frac{1}{2}}}{(I_xI_yI_z)_2^{\frac{1}{2}}} = \prod_j \frac{(m_j)_1^{3/2}}{(m_j)_2^{3/2}} \cdot \prod_i \frac{(\nu_i)_1}{(\nu_i)_2} \quad ,$$

where the m's are the masses of the j atoms in the molecule, and the subscripts 1 and 2 refer to the two isotopes. The second factor, containing the moments of inertia, is modified for a linear molecule in the same way as in the expression for Q_{rot}. On writing the expression for the ratio of the two isotopic equilibrium constants, the ratios of molecular masses and moments of inertia are replaced by the ratios of atomic masses and molecular vibration frequencies; moreover the atomic mass ratios cancel between the two sides of each reaction, leaving

$$\frac{K_1}{K_2} = \prod\left[\left(\frac{s_1}{s_2}\right)_{react.} \left(\frac{s_2}{s_1}\right)_{prod.}\right]\prod_{k,i}\left[\left(\frac{\frac{\frac{1}{2}u_2}{\sinh \frac{1}{2}u_2}}{\frac{\frac{1}{2}u_1}{\sinh \frac{1}{2}u_1}}\right)_{react.} \left(\frac{\frac{\frac{1}{2}u_1}{\sinh \frac{1}{2}u_1}}{\frac{\frac{1}{2}u_2}{\sinh \frac{1}{2}u_2}}\right)_{prod.}\right] \qquad (1)$$

The Born-Oppenheimer principle has allowed cancellation of the potential energy terms between the two reactions. Ratios in the above expression involving frequencies which are unaffected by the substitution of isotopes in one or more positions of the molecule become unity, so that the problem reduces to that of assessing the k frequencies of the reactants and i frequencies of the products which remain.

The rate of a reaction in which the activated complex $M^{\ddagger}$ is considered to be formed in the activation equilibrium

$$A + B + . \quad . \rightleftharpoons M^{\ddagger} + N + . \quad .$$

is given by the expression

$$\text{rate constant} = \alpha \left(\frac{kT}{h}\right) K^{\ddagger} . \frac{\gamma_A \gamma_B}{\gamma_{M^{\ddagger}} . \gamma_N} \cdot e_{qmt} \qquad (2)$$

where k and h are Boltzmann's and Planck's constants, respectively, T is the absolute temperature, and the γ's are the activity coefficients. $K^{\ddagger}$ differs from the constant volume equilibrium constant for the above process by the omission of any contribution from the reaction co-ordinate mode to the vibrational partition function for $M^{\ddagger}$, α is the transmission coefficient, and e_{qmt} is the quantum mechanical tunnel correction. Provided that the medium is the same in both cases, the effects of the γ's for two isotopic species will cancel to a very good approximation, so that the ratio of the rate constants k_1 and k_2 for the two reactions becomes

$$\frac{k_1}{k_2} = \frac{\alpha_1}{\alpha_2} \times \frac{e_{1\ qmt}}{e_{2\ qmt}} \times \prod \left[\left(\frac{s_1}{s_2}\right)_{react.} \left(\frac{s_2}{s_1}\right)_{rhs.} \right] \times \left(\frac{u_1}{u_2}\right)_L$$

$$\times \prod_{k,i} \left[\left(\frac{\dfrac{\frac{1}{2}u_2}{\sinh \frac{1}{2}u_2}}{\dfrac{\frac{1}{2}u_1}{\sinh \frac{1}{2}u_1}} \right)_{react.} \left(\frac{\dfrac{\frac{1}{2}u_1}{\sinh \frac{1}{2}u_1}}{\dfrac{\frac{1}{2}u_2}{\sinh \frac{1}{2}u_2}} \right)_{rhs.} \right] \qquad (3)$$

(The subscript 'rhs' refers to all the species on the right-hand side of the activation equilibrium). In this expression the imaginary frequencies ν_L of the reaction coordinate modes only appear in the terms representing the rotational and translational partition functions, and the i frequencies of the continued product refer only to real isotopically sensitive modes on the right-hand side of the above pseudo-equilibrium of activation.

The transmission coefficient α is a purely classical factor which takes account of the fact that some systems will be reflected back to reactants in spite of having enough energy to surmount the barrier; its magnitude depends on the exact shape of the potential energy surface but is not considered to be particularly sensitive to isotopic substitution. On the other hand, the tunnel correction c_{qmt} for hydrogen transfer may depend considerably on the nature of the isotope taking part. This follows qualitatively from the observation that the de Broglie wavelength, $\lambda = h/mv$, for hydrogen atoms of normal thermal energies is of the same order of magnitude as the width of the energy barrier to reaction, and for a given energy is inversely proportional to the square root of the atomic mass. A full discussion is to be found in a recent review by Caldin (93). Bell has shown that for a symmetrical one-dimensional parabolic barrier, if

$$u_L i = \frac{h\nu_L i}{kT} < 2\Pi ,$$

the magnitude of the correction is given by the expression

$$c_{qmt} = \frac{\frac{1}{2}u_L i}{\sin \frac{1}{2}u_L i} = \frac{\frac{1}{2}u_L}{\sinh \frac{1}{2}u_L} \quad \text{where } u_L \text{ is imaginary.} \qquad (4)$$

It is interesting to note t[illegible] continued product of Eq.(3) have identical forms, and in fact they each represent the quantum effect associated with one normal co-ordinate. In the classical or high temperature limits,

$$\text{where } h \longrightarrow 0 \text{ or } T \longrightarrow \infty \text{ , and } \frac{\frac{1}{2}u}{\sinh \frac{1}{2}u} \longrightarrow 1,$$

the expression for the kinetic isotope effect becomes

$$\frac{k_1}{k_2} = \left(\frac{\nu_1}{\nu_2}\right)_L \times \prod \left[\left(\frac{s_1}{s_2}\right)_{react.} \times \left(\frac{s_2}{s_1}\right)_{rhs.}\right] ,$$

whereas for equilibria,

$$\frac{K_1}{K_2} = \prod \left[\left(\frac{s_1}{s_2}\right)_{react.} \times \left(\frac{s_2}{s_1}\right)_{prod.} \right]$$

The equilibrium isotope effect is therefore purely quantal, in contrast to that on reaction rates which is partly classical in origin.

It has recently been suggested that kinetic isotope effects may be affected by a failure of transition-state theory, as a result of the very short life-time of the activated state. As pointed out by Bell (47), transfer of a proton across the hydrogen-bond between AH and B at a rate greater than the rate of orientation of the solvent will lead to a greater departure from equilibrium solvation of the transition-state for transfer of protium than in the case of the more slowly moving deuterium, and hence to an inverse contribution to the isotope effect. However, if the reacting system exchanges energy with the solvent in small amounts only, such non-adiabatic transfer of a proton between two stable hydrogen-bonded states should only be possible where the total energy change is small and the process is not appreciably activated.

2. The magnitude of primary kinetic hydrogen isotope effects

The assessment of the influence on reaction rate of isotopic variation of the proton transferred is important in the present work and is therefore discussed here. Theoretical treatments all assume that both in the ground- and transition-state only a small number of normal modes involve appreciable motion of the proton and that they can all be described by the distortions of a few bonds lying close to the reaction centre. For the ground-state the small mass of the hydrogen atom and the fairly large force constants opposing its motion make this a very good approximation, and experimental justification for it is provided by the observation of characteristic absorption peaks in the infra-red for bonds involving hydrogen. For example, for aliphatic C-H bonds in saturated systems these occur typically at:

$$\text{C-H stretch} = \sim 3000\ \text{cm.}^{-1}\ , \quad \text{C-H bend} = \sim 1000\ \text{cm.}^{-1}\ ,$$

frequencies which are high enough to justify the approximation of no vibrational excitation above the zero-point level,

$$\text{i.e. } h\nu \gg kT, \text{ therefore } \sinh \tfrac{1}{2}u = \tfrac{1}{2}\exp(\tfrac{1}{2}u)\ .$$

Moreover these frequencies are to a good approximation inversely proportional to the square root of the mass of the hydrogen isotope, so that

$$u_2 = u_1\left(\frac{m_1}{m_2}\right)^{\frac{1}{2}}$$

Therefore for the activation equilibrium

$$AH + B \rightleftharpoons (A\text{-----}H\text{-----}B)^{\ddagger} \qquad \text{(leaving charges unspecified),}$$

the term relating to the reactants in the continued product of Eq. (3) may now be written as

$$\prod_{3}\left(\frac{m_1}{m_2}\right)^{\frac{1}{2}} \times \exp\left[\frac{u_1}{2}\left(1-\sqrt{\frac{m_1}{m_2}}\right)\right]$$

where the three frequencies belong to the single stretching and doubly degenerate bending modes of the polyatomic molecule AH. In the particular case where AH is a hydrogen halide, the bending frequencies are replaced by weak vibrations of the molecule in its solvent cage, for which

$$h\nu \ll kT, \text{ and therefore } \sinh \tfrac{1}{2}u = \tfrac{1}{2}u\ ,$$

leaving in place of the above product just the one factor relating to the stretching vibration. This should give rise to smaller isotope effects in transfers from halogen acids, as has recently been demonstrated experimentally by Kresge and Chiang (60).

The theoretical problem arises in the assessment of the relevant transition-state frequencies. A number of models have been proposed for their calculation, all implicitly assuming the separability of hydrogenic vibrations by restricting their consideration to a small number of atoms. For a linear three-centre model the following frequencies must be considered:

$\overset{\leftarrow}{A} \quad H \quad \vec{B} \quad \nu_1$ symmetric stretch (motion of H indeterminate)

$\overset{\uparrow}{A} \quad \underset{\downarrow}{H} \quad \overset{\uparrow}{B} \quad \nu_2$ bending (doubly degenerate)

$\overset{\leftarrow}{A} \quad \vec{H} \quad \overset{\leftarrow}{B} \quad \nu_3$ anti-symmetric stretch ($i\nu_3'$) .

For all but the most unsymmetrical transition-states ν_3 represents the reaction coordinate, and since its frequency is then imaginary it is often written $i\nu_3'$, where ν_3' is a real quantity.

Bell (46) considered a model of the above type, assuming central forces arising from coulombic interactions between point charges balanced by a steep repulsive potential between A and B. For any reasonable symmetry both the magnitude of and isotope effect on ν_1 were found to be negligible, while in contrast both ν_3 and ν_2 were of the same order of magnitude as ground-state frequencies and lay approximately in the ratio $\sqrt{2}:1$. From this it follows that the effect of the tunnel correction should outweigh that of the zero-point energy residing in the bending vibrations, to give an isotope effect which should be almost constant and larger than the value calculated for complete loss of the reactant stretching frequency; this minimum isotope effect has the approximate values C–H 6.9, N–H 8.5, O–H 10.6.

A somewhat different electrostatic treatment has been presented by Bader (48), based on Platt's model for diatomic hydrides.

The basic centres A and B are regarded as nuclei surrounded by rigid spherical charge distributions which are defined by Slater atomic orbitals, and the forces are entirely coulombic in origin; A and B are moreover held immobile, so that only approximate values of ν_2 and ν_3 may be calculated, and the neglect of ν_1 is held to be justified by the low values of this frequency in hydrogen-bonded systems. For a given reaction the transition-state is defined by the conditions of zero net force on the proton and a zero value for ν_3, leaving the bending frequencies to account for any variation in the isotope effect as A and B are changed. With these assumptions Bader predicts a minimum in the isotope effect as the transition-state passes through a symmetrical configuration.

Turning to experimental values of the kinetic isotope effect in proton transfers, little agreement is found with the above predictions. Bell and co-workers (49-51) have studied the abstraction of hydrogen and deuterium from a large number of carbon acids by water, hydroxide and carboxylate anions, and pyridines, and when plotted against the statistically corrected quantity

$$\Delta pK = pK_a \text{ of carbon acid} - pk_a \text{ of conjugate acid of catalyst}$$

these show a clear maximum around $\Delta pK = 0$. If, on the basis of the Hammond postulate (52), ΔpK is taken as a measure of transition-state symmetry, a maximum isotope effect of about 10 is indicated when the proton is shared equally between A and B, falling to less than 3 for a reaction with the least symmetrical transition-state. A similar conclusion is reached from the work of Longridge and Long (53) on acid catalysed hydrogen exchange in a series of azulenes. For the abstraction of a proton by the same base from a series of substrates Bell and Crooks (49) found that the isotope effect varied fairly uniformly with the Brönsted coefficient β, which can also be interpreted as a measure of transition-state configuration (ref. 16, Chapter 7), but a rather poor correlation has been found by

Barnes and Bell (51) if a wider range of reactions is included. Similar remarks apply to the use of reactivity, as has been demonstrated by Kresge (54) for a wide spectrum of A-S_E2 reactions, (although these also include a secondary isotope and a medium effect). The reason why some measures of transition-state symmetry are better able than others to correlate the observed primary isotope effects is no more understood than the more general problem of the relation between rates and equilibria.

Returning to the theoretical problem, Bell (47) has suggested two reasons for the failure of the above electrostatic three-centre models to predict the observed variation in the isotope effect. Within the three-centre approximation smaller isotope effects for unsymmetrical transition-states would result by recognising that the analytical expressions for the degree of quantum mechanical tunnelling overestimate its magnitude when the barrier is unsymmetrical and the reaction co-ordinate involves motion of the heavy atoms. Secondly, and perhaps more importantly, it may not be correct to assume the hydrogenic frequencies to be essentially localised in three atoms.

A number of attempts have been made to account for the observed variation in the primary isotope effect by using a valency force field description; this approach requires fairly arbitrary assumptions of values for the force constants and therefore tends to be 'a posteriori' in nature, but it has the advantage of appearing physically convincing and can more easily be extended to include more atoms. For a three-centre system with bond force constants k_1 and k_2 and an interaction force constant k_{12}

$$\underset{k_{12}}{A \longleftarrow k_1 \longrightarrow H \longleftarrow k_2 \longrightarrow B}$$

the usual treatment gives expressions for the two stretching frequencies ν_1 and ν_3. The nature of the solutions obtained depends upon the value of $(k_1k_2-k_{12}^2)$ assumed. Westheimer (55) put this quantity and hence the value of ν_3 equal to zero, and thereby obtained an expression for ν_1 which made this responsible for the observed maximum in the isotope effect, bending frequencies having been assumed to cancel between reactants and transition-state. Bell (47), however, pointed out that if the above term is given a magnitude sufficiently large and negative to produce a similar curvature of the potential energy surface in the direction of the reaction co-ordinate as in other directions, ν_1 becomes considerably less sensitive either to configuration or to isotopic substitution, and Albery has generalised this relationship to all relative values of k_{12}^2 and k_1k_2 (56). More O'Ferrall (57) has given a fairly detailed treatment based on a linear five-centre model of the isotope effects to be expected for the abstraction of protons bonded to different atoms. The values assumed for the force constants and for the manner of their variation with bond order give rise to bending frequencies for all configurations which cancel approximately with those in the reactants (except when the base is a halide ion), and the choice of values of the ratio k_{12}^2/k_1k_2 not very much greater than unity again makes ν_1 chiefly responsible for the variation in isotope effect.

The theoretical situation with regard to primary isotope effects must therefore be regarded as fairly unresolved. The view that their variation is caused essentially by changes in transition-state bending frequencies can be supported by an electrostatic model, provided certain assumptions are made regarding the magnitude of the tunnel effect, but it is difficult to include in this treatment the effect of the adjacent bonds on the bending frequencies in a non-arbitrary way. On the other hand, the explanation in terms of the symmetric stretching mode demands extreme values of k_1/k_2, together with a curvature in the direction of the reaction co-ordinate which is much smaller than that in other directions.

Brief mention of experimental work relating to the tunnel correction is required, since in principle this is capable of giving an independent measure of ν_3. Two routes have been followed, the investigation of Arrhenius curvature and the measurement of the ratio of the pre-exponential factors from the temperature variation of the kinetic isotope effect; concordant application of both by Caldin and co-workers (58) to the reaction between 4-nitrobenzyl cyanide and ethoxide ion in an ethanol-ether mixture must be regarded as justifying their analyses in terms of Bell's equations. Caldin and Tomalin (59) have recently summarised the results for twelve reactions in which barrier curvatures have been deduced, (in all of which steric hindrance to reaction may be recognised), and have calculated the activation energy difference E^H-E^D from which the tunnelling contribution has been removed for the six reactions in which proton abstraction is brought about by oxygen or nitrogen bases in aqueous media. When plotted against ΔpK, these show a very similar curve to that obtained by Bell's group if it is assumed that their isotope effects are due entirely to the zero-point energy difference between proton and deuteron transfers, from which it may tentatively be concluded that quantum mechanical tunnelling makes only a small contribution to the majority of these isotope effects. Unfortunately this does not settle the controversy over the value of ν_3, since it may conceivably be the applicability of Bell's equations rather than the value of ν_3 which is increased by the influence of steric factors.

3. General theory of solvent isotope effects

The above results have all been obtained for proton transfers from carbon in H_2O as solvent, and were made possible by the negligibly slow rates at which these substrates exchange protons with the aqueous solvent. In such cases the effect of isotopic substitution of protons not transferred in the reaction may similarly be investigated by simply determining the appropriate rate constant ratio, provided that the required isotopic labelling can be achieved. In the present work, however, as in all transfers between oxygen or nitrogen atoms, the lability of the transferred proton makes it necessary to study the deuterium exchange in D_2O. This automatically introduces secondary and medium isotope effects, the unravelling of which is aided by additional measurements of the equilibrium or rate in mixtures of light and heavy water; the problem of organic synthesis is now one of kinetic analysis. Purlee (61) revived interest in this subject by showing that the original treatments of Gross and Butler were considerably simplified by taking the disproportionation constant

$$K = \frac{[HOD]^2}{[H_2O][D_2O]}$$

to be closely equal to 4, for which more recent experimental support was produced. This was followed by the important work of Gold (62), who showed for the first time how the theory could be applied to the kinetics of reactions proceeding by different mechanisms, and further extensions were worked out by Swain and Thornton (63). General treatments applicable to both equilibria and kinetics have been given by Long and co-workers (64) and by Kresge (65), and the subject has been critically reviewed by Gold (92); a summary of the theory is presented below.

In order to formulate an expression for the ratio of concentrations in any proton exchange equilibrium at a given atom fraction (n) of deuterium in the solvent, it is necessary to obtain relations between the concentrations of the various isotopic homologues of each chemical species. This is achieved through the rule of the geometric mean, according to which the equilibrium constant for any isotopic disproportionation reaction is given by the quotient of the symmetry numbers raised to the appropriate powers. Bigeleisen has shown this to be exact for small quantum corrections (66) and approximately true for larger ones (67); it can readily be seen from equations (1) and (3) to be true for large quantum corrections provided that the vibrations of chemically equivalent hydrogen atoms can be treated as separable from each other, just as single hydrogenic vibrations were taken as separable from those of the rest of the molecule in the above discussion of primary isotope effects.

For the general case of a molecule AH_i with i equivalent exchangeable hydrogen atoms, an equilibrium constant ϕ is defined for the reaction

$$\frac{1}{i}\,AH_i + \frac{1}{2}\,D_2O \rightleftharpoons \frac{1}{i}\,AD_i + \frac{1}{2}\,H_2O \quad \phi \tag{5}$$

This is independent of n provided that the protons of AH_i are vibrationally independent of those of the solvent. It may be combined with the disproportionation equilibrium

$$\frac{1}{i(i-j)}\,AH_i + \frac{1}{i}\,AD_i \rightleftharpoons \frac{1}{i-j}\,AH_jD_{i-j} \qquad K_{dis}$$

to give the equation

$$\frac{1}{i-j}\,AH_i + \frac{1}{2}\,D_2O \rightleftharpoons \frac{1}{i-j}\,AH_jD_{i-j} + \frac{1}{2}\,H_2O \quad \phi.K_{dis}$$

from which

$$\frac{[AH_jD_{i-j}][H_2O]^{(i-j)/2}}{[AH_i][D_2O]^{(i-j)/2}} = \phi^{i-j} \cdot K_{dis}^{i-j} \; .$$

Now ϕ contains no symmetry factors and by the rule of the geometric mean K_{dis} contains only symmetry factors, so that

$$K_{dis}^{i-j} = \frac{s_{AH_i}}{s_{AH_jD_{i-j}}}\left(\frac{s_{D_2O}}{s_{H_2O}}\right)^{(i-j)/2}$$

This may be evaluated without knowing the symmetry of AH_i if use is made of a theorem proposed by Bishop and Laidler (68), namely that the ratio of the symmetry factors for a reaction is equal to the ratio of statistical factors, where these are defined as the number of different sets on one side of the reaction which can be formed if identical atoms on the other side are separately labelled. Since AH_i and AH_jD_{i-j} have the same geometrical shape, the number of different sets that can be formed without regard to isotopic differences must obviously be equal, but for each of these there are ${}^iC_j$ ways of putting in the i-j deuteriums. The two waters make equal contributions, so that

$$[AH_jD_{i-j}] = [AH_i] \frac{[D_2O]}{[H_2O]}^{(i-j)/2} \cdot \phi^{i-j} \cdot {}^iC_j$$

From this it follows that

$$[AL_i] = [AH_i] \left[1 + \phi \left(\frac{[D_2O]}{[H_2O]} \right)^{\frac{1}{2}} \right]^i$$

where $[AL_i]$ stands for the total concentration of all the isotopic homologues.

The ratio $\frac{[D_2O]}{[H_2O]}$ can be evaluated from the disproportionation constant predicted for water by the rule of the geometric mean, K = 4. If HOD has mole fraction 2y, so that its deuterium and protium each constitute an atom fraction y of the total number of lyons, the mole fractions of H_2O and D_2O will be (1-n-y) and (n-y), respectively, provided that the solvent is present in large excess. Thus

$$\frac{4y^2}{(1-n-y)(n-y)} = 4$$

from which $[H_2O] = (1-n)^2$, $[D_2O] = n^2$, and $[HOD] = 2n(1-n)$.

Therefore

$$[AL_i] = [AH_i]\left(\frac{1-n+n\phi}{1-n}\right)^i \qquad (6)$$

Since it can now be shown that

$$\frac{\text{number of H atoms in } AL_i}{\text{number of D atoms in } AL_i} = \frac{1-n}{n\phi} \quad ,$$

i.e.
$$\frac{(H/D)_{\text{solvent}}}{(H/D)_{\text{substrate}}} = \phi \quad , \qquad (7)$$

ϕ acquires a readily understood physical significance, and is usually referred to as the fractionation factor for the i protons of AH_i. For a molecule containing more than one set of equivalent exchangeable protons, the above treatment leads to a relation such as

$$[AH_3DL'_2] = [AH_3DH'_2] + [AH_3DH'D'] + [AH_3DD'_2]$$

$$= [AH_3DH'_2]\left(\frac{1-n+n\phi'}{1-n}\right)^2$$

from which

$$[AL_4L'_2] = [AH_4H'_2]\frac{(1-n+n\phi)^4(1-n+n\phi')^2}{(1-n)^6}$$

For a reaction involving proton exchange between chemically different species,

$$\text{e.g.} \qquad AL_i + L_2O \rightleftharpoons AL^-_{i-1} + L_3O^+ ,$$

the effective equilibrium constant may now be written,

$$K_n = \frac{[AL^-_{i-1}]_n[L_3O^+]_n}{[AL_i]_n} = \frac{[AH^-_{i-1}]_n[H_3O^+]_n}{[AH_i]_n} \times \frac{(1-n+n\phi_2)^{i-1}(1-n+n\ell)^3}{(1-n+n\phi_1)^i(1-n)^2} \qquad (8)$$

where the concentration of solvent is expressed in mole fraction units, and the fractionation factors are assigned as follows:

$$\phi_1 \text{ for } AH_i, \quad \phi_2 \text{ for } AH^-_{i-1}, \text{ and } \ell \text{ for } H_3O^+.$$

This may be related to the effective equilibrium constant in light water,

$$K_H = \frac{[AH^-_{i-1}]_H [H_3O^+]_H}{[AH_i]_H} \quad ,$$

through the thermodynamic equilibrium constant K_T and the activity coefficients referred to infinite dilution,

$$K_T = \frac{[AH^-_{i-1}]_n [H_3O^+]_n}{[AH_i]_n (1-n)^2} \times \frac{\gamma_{AH^-_{i-1}} \, \gamma_{H_3O^+}}{\gamma_{AH_i}} \quad .$$

Following Halevi, Long, and Paul (69), the free energy of each chemical species is taken to vary linearly with n,

$$\text{i.e.} \quad \frac{\gamma_n}{\gamma_H} = \left(\frac{\gamma_D}{\gamma_H}\right)^n \quad ,$$

$$\text{so that} \quad \frac{K_n}{K_H} = \frac{(1-n+n\phi_2)^{i-1}(1-n+n\ell)^3}{(1-n+n\phi_1)^i} \times \left[\frac{(\gamma_H/\gamma_D)_{AH^-_{i-1}} (\gamma_H/\gamma_D)_{H_3O^+}}{(\gamma_H/\gamma_D)_{AH_i}}\right]^n \qquad (9)$$

The ratio γ_H/γ_D for each species may be referred to as its degenerate activity coefficient of transfer between light and heavy water, and would be expected to vary little with concentration (92). The variation of the position of equilibrium with the deuterium atom fraction of the solvent can thus be seen to be a product of both exchange and medium (or transfer) effects. In the special case where n is unity, equation (9) reduces to

$$\frac{K_D}{K_H} = \frac{\phi_2^{i-1} \cdot \ell^3}{\phi_1^{i}} \prod \left(\frac{\gamma_H}{\gamma_D}\right) \qquad (10)$$

where the continued product stands for the activity coefficient term in square brackets in equation (9), raised to the power unity.

Expressions analogous to equation (9) may be written for any equilibrium, the exchange term being formed from the product of the factors (1-n+nϕ) for each set of equivalent exchangeable hydrogens and raised to a power equal to the number in the set, and the medium effect being accounted for by the degenerate activity coefficient of transfer for each chemical species. Factors relating to the right-hand side of the equilibrium appear in the numerator, and the others in the denominator.

For kinetics the basic equation of absolute reaction rate theory (eq. 2) may be rewritten

$$\text{rate constant} = \alpha\left(\frac{kT}{h}\right)K^{\ddagger}_{eff} \cdot c_{qmt} \quad , \qquad (11)$$

where $K^{\ddagger}_{eff}$ is an effective non-thermodynamic equilibrium constant, equal like K_n and K_H of equation (9) to a ratio of concentrations. When isotopic substitution occurs other than in a proton undergoing transfer and affects neither α nor c_{qmt}, the variation in the rate constant k_n from its value k_H in light water therefore becomes for the activation equilibrium

$$A + B \quad \cdot \; \cdot \; \cdot \rightleftharpoons M^{\ddagger} \; + N \quad \cdot \; \cdot \; \cdot$$

$$\frac{k_n}{k_H} = \frac{\prod_{M^{\ddagger},N}(1-n+n\phi)}{\prod_{A,B}(1-n+n\phi)} \times \frac{\prod_{M^{\ddagger},N}(\gamma_H/\gamma_D)^n}{\prod_{A,B}(\gamma_H/\gamma_D)^n} \quad , \qquad (12)$$

an expression completely analogous with equation (9).

When on the other hand the proton transferred in the rate-determining step is in labile equilibrium with the solvent, a little more consideration is required to make clear the meaning of ϕ for the transferred proton and to express α_n and $c_{qmt,n}$ in terms of their values for the two isotopic species. The measured rate constant k_n can be written as the sum of two expressions, each referring to a transition-state containing one of the isotopes, and this is transformed by the treatment of the above section into the kinetic equivalent of equation (8) in which the transferred proton is represented by the term

$$[(1-n).\alpha_H.c_{qmt,H} + n.\phi_{eq}.\alpha_D.c_{qmt,D}] \quad .$$

On division by the expression for k_H, this becomes in the kinetic equivalent of equation (9)

$$\left[(1-n) + n.\phi_{eq}.\frac{\alpha_D}{\alpha_H} . \frac{c_{qmt,D}}{c_{qmt,H}}\right] \quad \text{or} \quad (1-n+n\phi_T) \quad .$$

Such reactions may therefore be represented by the general equation (eq. 12), but the fractionation factor ϕ_T for the transferred proton has a different physical significance from those for protons in stable potentials. Whereas the latter consists merely of a partition function product, ϕ_T contains contributions relating to the tunnel effect and the transmission coefficient, and in its partition function product ν_L occurs only in the terms representing translation and rotation. The ratio of the rate of abstraction from an oxygen or nitrogen atom in H_2O to the rate of deuteron abstraction in D_2O is now given by

$$\frac{k_H}{k_D} = \frac{\phi_1}{\phi_T} \Big/ \prod(\gamma_H/\gamma_D)$$

where ϕ_1 is the ground-state fractionation factor. Since ϕ_1 and the medium effect factor are both normally fairly close to unity, the quantity $1/\phi_T$ should have similar values to those of the primary isotope effects described above for proton abstraction from carbon.

A similar division of the term $(1-n+n\phi_T)$ into the separate contributions to the rate from the proto and deutero transition-states is required to derive an expression for the product isotope effect, i.e. the ratio of hydrogen to deuterium appearing in the product when this is sufficiently non-labile to be kinetically rather than thermodynamically determined. If m is the fraction of deuterium in the product when the reaction is conducted in a solvent of deuterium atom fraction n,

$$\frac{1-m}{m} = \frac{1-n}{n\phi_T}$$

4. The magnitudes of hydrogen fractionation factors in stable species

Measurement of the solvent deuterium isotope effect on the rate of a reaction gives information regarding the transition-state to the extent that values can be obtained for the fractionation factors of its protons. Knowledge of the fractionation factors of the stable species involved is required to obtain these quantities, while to interpret those relating to protons not transferred in the reaction in terms of their chemical environment a general understanding of the magnitude of such factors is very useful; the solvent isotope effect on equilibria is therefore discussed first.

It is of prime importance to determine the contribution of the medium effect in equation (12). The existence of such an effect is evident from the differences in the heats of solution and in the solubilities of simple salts in light and heavy water, as summarised by Swain and Bader (71), and from the examples given by Bell (ref. 44, p.199) of reactions which, although not formally involving exchangeable protons, proceed 20 - 40% faster in light than in heavy water.

Salomaa and Aalto (94) found that the transfer free energies of lithium, sodium, potassium, and cadmium chlorides between their dilute solutions in the two waters varied only over a 5% range, from which they concluded that almost all the effect could be attributed to the anion. Gold (72) and Goodall and Long (70) have pointed out that lithium fluoride and small non-electrolyte molecules such as argon and propane, which are usually regarded as structure-forming, dissolve more readily in heavy water, whereas for other salts and larger organic molecules the reverse is true, and have interpreted this qualitatively by postulating that the disordered solvent molecules in the vicinity of the solute species have more loosely vibrating hydrogen atoms than those in the bulk of the solvent. Swain and Bader (71) achieved moderate success in explaining these trends semi-quantitatively by attributing the medium effect for the alkali metal halides entirely to the different librational frequencies associated with aqueous solutions of the salts. They also observed that the presence of hydronium or hydroxide ions caused little change in the librational frequencies of water, which was attributed to the hydrogen-bonding ability of these ions, and for this reason the medium effect associated with these species is often assumed to be small. Rather less work has been done regarding organic molecules; one example is the 6% greater solubility of nitromethane in light than in heavy water (referred to in ref. 70).

Gold has recently pointed out that the medium effect may be formally represented by additional terms of type $(1-n+n\phi)$ to take account of fractionation in the solvent molecules surrounding each molecule of solute(72). Use of an approximation introduced by Goodall and Long

$$1-n+n\phi \simeq \phi^n \quad ,$$

relates this treatment of the medium effect to that assumed by Halevi, Long, and Paul (69) in their use of the equation

$$\frac{\gamma_n}{\gamma_H} = \left(\frac{\gamma_D}{\gamma_H}\right)^n \quad .$$

Most of the work designed to measure the fractionation factors of stable species has been concerned with acid dissociation equilibria, since these reactions are subject to well-established and accurate techniques of measurement. The behaviour of such systems in H_2O-D_2O mixtures is governed by the fractionation factor for the solvated proton (usually given the symbol l), the number of water molecules (p) whose solvation of the proton causes their own hydrogens to be subject to fractionation, at least one other fractionation factor, and the medium effect. Since the equilibrium constant data as a function of n are only accurate enough to allow two of these parameters to be obtained, the independent determination of l and p by a number of physical measurements is of crucial importance for a large part of isotopic solvent mixture work.

A review of these methods for determining l and p has been given by Gold and Kessick (73). The hypothetical equilibrium constant L for the reaction

$$2D^+(D_2O)_p^{\;D_2O} + (2p+1)H_2O^{\;H_2O} \rightleftharpoons 2H^+(H_2O)_p^{\;H_2O} + (2p+1)D_2O^{\;D_2O} \qquad L$$

can be obtained from the e.m.f. of a suitable electrochemical cell combined with the free energy change for the reaction

$$D_2(g) + H_2O(l) \rightleftharpoons H_2(g) + D_2O(l)$$

provided that some allowance is made for the free energy of transfer of an anion between the two waters. Purlee (61) considered that the use of the cells with transference:

$$\mathrm{Pt}\ (H_2)\,|\ \mathrm{HCl\ in}\ H_2O\ \vdots\ \mathrm{KCl(sat)\ in}\ H_2O\ |\ Hg_2Cl_2, Hg$$

$$\mathrm{Pt}\ (D_2)\,|\ \mathrm{DCl\ in}\ D_2O\ \vdots\ \mathrm{KCl(sat)\ in}\ H_2O\ |\ Hg_2Cl_2, Hg$$

eliminated the need for the latter correction, but Heinzinger and Weston (74) have shown that this is wrong and that Purlee's value of L = 11.0 must therefore be regarded as an upper limit. Swain and

Bader (71) used instead the e.m.f.'s of the cells without transference:

$$\mathrm{Pt}\ (H_2)\ |\ \mathrm{HCl\ in\ } H_2O\ |\ \mathrm{AgCl, Ag}$$

$$\mathrm{Pt}\ (D_2)\ |\ \mathrm{DCl\ in\ } D_2O\ |\ \mathrm{AgCl, Ag}$$

and the value for the free energy of transfer of the chloride ion calculated by their libration frequencies theory; this leads to the value L = 8.25 at 25°C. The alternative use of Salomaa and Aalto's determination of the transfer free energy of the chloride ion, obtained with the assumption that the cations made a negligible contribution to their measured free energies, gives L = 9.0 ± 0.3 (94). No estimate of the value of l is possible, however, from these essentially thermodynamic measurements without assuming a structure for the hydronium ion.

Proton magnetic resonance studies have been employed to obtain a direct measure of l by comparing the chemical shift obtained on adding acid to a mixture of light and heavy water with that obtained on adding the same concentration of acid to light water. If the atom fractions of protons in the hydronium ion and in the water are a and w, respectively, the corresponding quantities for the deuterons are a' and w', and the chemical shifts associated with these sites are δ_1 and δ_2 relative to some fixed reference signal, the chemical shift Δ for a stoichiometric atom fraction A of added acid in a solution of deuterium atom fraction n is given by

$$\Delta = \frac{a\,\delta_1}{a + w} + \frac{w\,\delta_2}{a + w} \quad .$$

By making use of the relations

$$l = \frac{a'w}{aw'} \text{ from eq. (7),} \qquad a + a' + w + w' = 1$$

$$a' + w' = n$$

$$\frac{w'}{w} = \frac{n}{1-n} \left(\text{provided } A \ll w + w'\right), \quad a + a' = A(2p + 1)$$

this may be transformed into

$$\Delta = \frac{A(2p+1)(\delta_1 - \delta_2)}{(1 - n + n\ell)} + \delta_2 \quad .$$

If Δ' is the chemical shift relative to pure water, the ratio of its value in light water to that in the solvent mixture with the same acid concentration is given by

$$\frac{\Delta'_H}{\Delta'_n} = 1-n+n\ell \qquad (13)$$

Using this method Gold (75) has obtained values of ℓ of 0.69 in perchloric and 0.70 in hydrochloric acid, both ± 0.02, while Kresge and Allred (76) found that in perchloric acid $\ell = 0.67 \pm 0.01$.

The virtual independence of the above results of the acid used suggests that the anions are responsible for only a very small part of the observed chemical shift, but some uncertainty arising from the neglect of this contribution is nevertheless present. In addition the value of ℓ measured by the p.m.r. method is only identifiable with a fractionation factor if all the protons making up the hydronium ion are describable by this same factor and no other fractionation effects associated with different chemical shifts are caused in the surrounding solvent, i.e. it assumes no medium effect. These assumptions, if valid, also allow combination of the results with those of the electrochemical measurements to permit calculation of the number of protons whose involvement in the hydronium ion causes fractionation, since L and ℓ are then related by $L = \ell^{-2(2p+1)}$. The best integral value of p thus obtained is unity, which gives values of L ranging from 8.5 to 11.1 as ℓ is varied from 0.70 to 0.67; this supports the model H_3O^+ over that of unspecified solvation, although it does not rule out larger structures in which fractionation is confined to the inner three protons. Further support for both the monosolvated proton model and the above range of values for ℓ is obtained from the work of Heinsinger and Weston (74) on the fractionation of hydrogen isotopes between aqueous solutions of perchloric acid and the vapour phase. Since their results were obtained at low n they are related to ℓ through a factor dependent on p, and the choice of p = 1 results in $\ell = 0.65$ at 13.5°C; a small uncertainty is introduced in assessing the effect of the perchlorate anions on the isotopic equilibrium between the two phases, and assumptions identical with those made in interpreting the p.m.r. results are involved in identifying this result with the fractionation factor for exchange. It is now generally agreed (92) that the best value of ℓ can be put at 0.69 ± 0.02 at 25°C, since this not only falls within the range of the p.m.r. values but also agrees with the result of Salomaa and Aalto for L and with the temperature-corrected results of Heinsinger and Weston if p is taken to be unity in both cases.

Having now a fairly close estimate of the contribution of the hydronium ion to the equilibrium isotope effect at any solvent composition, useful conclusions may be drawn from the measurement of acid dissociation equilibria. The isotope effect on the ionic product of water over a range of deuterium atom fractions has been investigated by Salomaa, Schaleger, and Long (64), who used a glass electrode in a cell with transference, and by Gold and Lowe (77), who dispensed with the liquid junction by the use of a silver-silver chloride electrode. The results of the latter workers are systematically the higher of the two ($K_{H_2O}/K_{D_2O} = 7.28$ at 25°C.), and may be preferred since most sources of error tend to decrease an isotope effect, but in both cases a very similar type of variation with n is found. Taking $\ell = 0.69$ and p = 1, Gold and Lowe were able to calculate a fractionation factor $\phi_{\bar{O}H}$ of 0.53 for the hydroxide ion and a medium effect contribution of 0.79 to the ratio K_D/K_H. The latter value would appear to indicate that the sum of the free energies of transfer of the hydronium and hydroxide ions is not negligible, in contrast to the conclusions reached by Swain and Bader from their spectroscopic measurements, and similar doubts are raised by the inability of the p.m.r. method to confirm this value for $\phi_{\bar{OH}}$ (92).

The ratios of the dissociation constants in light to those in heavy water for a fairly large number of organic acids, particularly carboxylic acids and phenols, have been determined, and these can yield approximate values for their fractionation factors if l is taken from the above work and the total medium effect is either neglected or assessed. Conductimetric (78) and potentiometric (64,79) methods have been used, and in the most intensively studied case, that of acetic acid, a number of independent determinations agree within 1% with the value K_H/K_D 3.30 (see refs. 70,79 for sources). Bell and Kuhn (80) employed a spectrophotometric indicator method in which this result for acetic acid was used as a standard, and Högfeldt and Bigeleisen (81) obtained direct spectrophotometric measurements for the basic ionisation equilibria of a series of aromatic amines; the latter values do not allow estimation of the fractionation factors since both the acid and basic species carry exchangeable hydrogen atoms.

The values of K_H/K_D obtained for the oxygen acids from the above measurements (and hence probably also the fractionation factors) decrease in general with the pK_A of the acid, although Bell and Kuhn have pointed out that a good correlation is obtained only for the phenols and haloalcohols. Bellamy, Osborn, and Pace (82) have shown that, although the O-H stretching frequencies of a series of carboxylic acids are almost identical in the vapour phase, they are lowered on solution in organic solvents, the more so the greater the electron-donor power of the solvent and the strength of the acid. Bunton and Shiner (83) attempted to use such a trend in the hydrogen-bond stretching frequencies in aqueous solution to explain quantitatively the K_H/K_D ratios; it was postulated that the frequency of a hydrogen-bond between the acid and water should decrease with pK_A

and that that of a hydrogen-bond donated by water to the conjugate base should vary in the opposite direction, and these frequencies were obtained by linear interpolation between the measured values for H_3O^+, H_2O, and $\bar{O}H$. By making further assumptions concerning the number of such hydrogen-bonds formed, predictions of K_H/K_D were made in reasonable agreement with experiment, for example 3.1 for acetic acid. It is interesting to note that their consideration of the hydrogen-bonds formed between the solvent and the conjugate base is equivalent to the inclusion of a medium effect, although their approach does not allow a complete division of the dissociation constant ratio into medium and exchange contributions. This treatment of the medium effect in terms of the hydrogen-bond stretching frequencies between the solute and the solvating water molecules is quite different from that given by Swain and Bader (71) based on the change in libration frequencies resulting from the structure-making or breaking effect of the solute; in reality both effects might be expected to operate.

Since determination of the fractionation factor of an acid from its dissociation constant ratio K_H/K_D is subject to uncertainties arising from the medium effect, use of the p.m.r. method for the acid would provide a useful check. Such a strategy has been adopted by Gold and Lowe (79), who combined a p.m.r. study of acetic acid (suppressing the ionisation by the addition of 0.01 M. sodium acetate) with potentiometric measurements of the acid dissociation constant over a range of deuterium atom fractions. The p.m.r. results for acetic acid gave $\phi = 0.96 \pm 0.02$, leading to a total medium effect on the reaction of 0.89 when $l = 0.69$. Values of ϕ determined merely from K_H/K_D may therefore be around 10% too high, although relative values are likely to be better than this. In their p.m.r. study Gold and Lowe considered the small contributions made to the chemical shift by protons fractionated in the solvent sphere of the acid and by deuterium substitution in water. By assuming the two to be equal they were able to deduce a value for the latter effect in good agreement with independent measurements and hence to obtain a refined value of ϕ, but this treatment was not carried out in the previously described experiments on the hydronium ion in which the effect may well be greater.

Recent direct mass-spectrometric determination of the equilibrium constant K for the reaction

$$H_2O + D_2O \rightleftharpoons 2HOD$$

has led to a value K = 3.76 ± 0.02 (84,85), which is appreciably lower than the previously accepted estimate based on spectroscopic measurements. This significant deviation from the rule of the geometric mean makes less accurate the relation

$$\frac{[D_2O]}{[H_2O]} = \frac{n^2}{(1-n)^2}$$

which was used to derive equation (6), and the consequent effect of this on solvent mixture theory has been investigated by Gold (86), Kresge and Chiang (87), and Albery and Davies (95). All three treatments show that the fractionation factor for a single exchangeable proton, regarded as defined operationally by any expression derived from equations (6) or (7), should vary over the full range of solvent composition by an amount closely equal to the fractional difference between K and 4.00 . This prediction has been at least partly confirmed by Gold for the fractionation factor of t-butyl alcohol (86), by Kresge and Chiang (87) for 1,3,5-trimethoxybenzene, and by Albery and Davies (104) for the product isotope effect in the acid catalysed decomposition of ethyl diazoacetate, all of which involved direct determination of H/D ratios by mass-spectrometry or p.m.r. integration and therefore avoided any medium effect. The above authors also point out that the effects of deviations from the rule of the geometric mean by substances on different sides of an equilibrium should partly cancel, and that in particular the position of equilibria involving the interconversion of H_2O and H_3O^+ should deviate little from the predictions of the simple theory outlined above. Nevertheless these considerations place a limit on the interpretation of the data from solvent mixture work irrespective of their experimental accuracy.

5. The magnitude of hydrogen fractionation factors in transition-states

Having discussed the application of isotopic solvent mixture theory to equilibria, it is now possible to consider its use in kinetic studies through equation (12). It was an early hope of the Gross-Butler theory to be able to distinguish between rival mechanisms from the shape of the curve of k_n/k_H plotted against n, but the more recent development of the general theory has shown that this will nearly always be prevented by the number of adjustable parameters required to specify the assumed transition-state. On the other hand distinction between mechanisms may be possible if use is also made of the value of k_D/k_H, and in fact most studies of kinetics in isotopically mixed solvents are now carried out with the aim of obtaining detailed information as to the configuration of the transition-state, its constitution and general structure having been inferred from k_D/k_H and other kinetic evidence.

The reactions for which solvent isotope effects have been most often measured are those involving proton transfer from a hydronium ion to a carbon atom of an organic substrate. The expected values of k_D/k_H have been summarised by Albery as follows (42):

	reactants	approximate k_D/k_H range
A1	$H_3O^+ + S \rightleftharpoons H_2O + [HS^{\prime +}]^{\ddagger}$	> 2.5
A2	$H_3O^+ + S + H_2O \rightleftharpoons H_2O + [HS^{\prime}{-}{-}{-}{-}OH_2^{+}]^{\ddagger}$	1.5-2.5
AS_E2	$H_3O^+ + S \rightleftharpoons [H_2O{-}{-}{-}H{-}{-}{-}S^{\prime +}]^{\ddagger}$	< 1.5 ,

in which the transition-states are enclosed in square brackets. The expected value for an A1 reaction is equal to the ratio K_H/K_D for the dissociation of the fairly strong acid $[HS'^{+}]^{\ddagger}$, while the figure for an A2 reaction is lower than this by the degree to which partial positive charge on the participating water molecule decreases the fractionation factors of the two hydrogen atoms. The $A S_E 2$ transition-state has the same composition as the A2, and its water molecule similarly carries a partial positive charge, but in this case the single proton is undergoing transfer and therefore has a smaller fractionation factor, which may often lead to a rate faster in light than in heavy water; catalysis of these latter reactions by general acids is accompanied by even larger values of k_H/k_D as a result of the absence of the secondary isotope effect associated with the residual water molecule.

The equation for an $A S_E 2$ reaction, first worked out by Gold (62), contains two fractionation factors characteristic of the transition-state (ϕ_1 for the primary and ϕ_2 for the secondary protons), and these may be obtained from measurements over a range of solvent composition if a value is taken for ℓ, p is put equal to unity, and the medium effect is neglected. Gold further suggested that the fractionation factor ϕ_2 for the protons which form the incipient water molecule may be written $\phi_2 = \ell^{1-\alpha'}$, where the coefficient α' may be fairly closely identified with the Brönsted coefficient α for general acid catalysis of the reaction, and this can be used as a check on the analysis. This procedure has been followed by Kresge (65) for the $A S_E 2$ reaction of 1,3,5-trimethoxybenzene in dilute perchloric acid solution, and yields $\alpha' = 0.6$ and $\phi_1 = 0.15$; the Brönsted coefficient obtained from carboxylic acid catalysis is concordant with both these values. Kresge, Onwood, and Slae (88) have confirmed and refined the value of α' for this reaction by measuring the rate of incorporation of tritium into the substrate from tritiated light and heavy waters, a method which eliminates the primary isotope effect, but surprisingly an identical value was found for 1,3-dimethoxybenzene in spite of the fact that the rate is 10^3 times less. Before drawing firm conclusions as to the change in transition-state configuration with reactivity in these latter experiments, it would be preferable to eliminate the medium effect, which may be achieved in this case by carrying out the measurements over a range of solvent composition.

For proton transfers to carbon in which the proton once transferred is no longer labile it is possible to measure the primary effect ϕ_1 separately by subjecting the product to isotopic analysis; the result should be independent of any medium effect. Such a strategy was adopted by Gold and Kessick (73) in the perchloric acid catalysed $A\text{-}S_E2$ hydration of isobutene, giving $\phi_1 = 0.25$ and $\alpha' = 0.85$. The latter value is consistent with the apparent absence of general acid catalysis and completely describes the experimental curve of k_n/k_H against n, but on the grounds that the shape of the curve is not particularly sensitive to the number of parameters describing it the authors declined to deduce either that proton transfer cannot occur through a solvent bridge or that medium effects are absent. Similar remarks apply to the recent study by Gold and Waterman (89) on the hydronium ion catalysed hydrolysis of 2-dichloro-methylene-1,3-dioxolane, in which a product isotope effect was also determined, and the analogous reaction of cyanoketen dimethyl acetal (90). In these cases the secondary fractionation factors ϕ_2 could be defined within a range compatible with the measured Brönsted coefficients of 0.49 and 0.62, respectively, but neither the absolute nor the relative values of the primary factors ϕ_1 (0.27 and 0.20, respectively) can be interpreted if the Brönsted coefficients derived from the rates of catalysis by carboxylic acids are identified rigidly with the extent of proton transfer in the transition-state for the reaction with the hydronium ion. This parallels the findings of Bell and co-workers (51) in proton abstraction from carbon acids by water and carboxylate anions, reactions which are similar to the reverse of those studied above.

Since the above work by Gold's and Kresge's schools has shown that the secondary isotope effect in $A S_E 2$ reactions varies at least qualitatively in a way which is understandable from the expected configuration of the transition-state, it is possible to obtain further information as to the magnitude of the primary isotope effect in reactions for which only $k_{H_3O^+}/k_{D_3O^+}$ has been measured. Kresge, Sagatys, and Chen (54) show that in the dilute acid catalysed hydrolysis of 14 vinyl ethers $k_{H_3O^+}/k_{D_3O^+}$ increases with reactivity from 1.7 to 3.5, excluding a few higher figures for which quantum mechanical tunnelling was held partly responsible; if these reactions are all energetically 'uphill', the maximum correction for the secondary effect (on the assumption that the transition-state varies from completely product-like to symmetrical) leads to the rather smaller trend of 0.19 to 0.14 in the primary fractionation factor ϕ_1. A similar treatment on the variation in $k_{H_3O^+}/k_{D_3O^+}$ from 2.5 to 6.0 observed by Noyce, Hartter, and Miles (91) in the concentrated sulphuric acid catalysed isomerisation of a series of p-substituted cis-stilbenes gives a trend in ϕ_1 of 0.13 to 0.08. The observation of lower values of ϕ_1 in the latter case in spite of lower reactivity is a further indication of the difficulty of obtaining more than a qualitative understanding of primary hydrogen isotope effects.

In rate-determining proton transfers from weaker acids to carbon the reduction in the number of protons concerned in the transition-state makes it easier to determine the contribution from the medium effect or from the intervention of solvent bridges. In the above-mentioned studies of Gold and Waterman it was found that the rate of the acetic acid catalysed reactions in both cases varied almost linearly with solvent composition, which, when combined with the known value of near unity for the fractionation factor of the acid, indicates that the transition-state is adequately described by a single fractionation factor. In contrast to this the work of Goodall and Long (70) on the reaction of acetic acid with nitromethane anion gave rise to a curved plot of k_n/k_H against n, from which it was concluded that medium effects must be present. Conclusions as to the validity of a solvent bridge mechanism from this work, and also from the comparisons between rate and product isotope effects carried out by Kreevoy's school (96), depend on the assessment of the degenerate activity coefficient of transfer for the transition-state, a quantity about whose magnitude no information yet exists; nevertheless reasonable estimates of this based on stable systems suggest that such solvent bridges are probably absent in the carboxylic and related acid catalysed reactions studied. The finding of a significant medium effect in the work of Goodall and Long but not in that of Gold and Waterman may be compared with the conclusions based on the experiments of Salomaa and Aalto (94) that anions are associated with much larger effects than cations.

Comparatively little work has been done on the effect of isotopically mixed solvents on the rates of water catalysed (or spontaneous) reactions, and Gold (92) has indicated the need for more work in this field. Batts and Gold (97) have interpreted previously obtained data on the decomposition of nitramide and their own measurements for the hydrolysis of acetic anhydride on the basis of reasonable transition-states and measured values of the Brønsted coefficients, (although the latter reaction requires a more complex transition-state than that adopted, if a rate-determining step faster than diffusion control is to be avoided). Huang, Robinson, and Long (98) have studied the spontaneous mutarotation of α-D-tetramethyl glucose, and this is considered in the Discussion along with analogous experiments performed in the present work.

EXPERIMENTAL SECTION

CHAPTER III

GENERAL PRELIMINARIES

1. Kinetics of parallel reversible first order reactions

The kinetic measurements performed in the present work consisted largely in following the net rate of disappearance of the ketone sym-dichloroacetone in a solution containing an excess of water and sometimes also an excess of an acid catalyst. It is therefore of interest to examine the possible kinetic behaviour of the system, as this determines the manner in which the primary data are treated.

The reactions considered are the parallel reversible additions of catalyst or water to give the adducts A_1 and A_3, respectively, from the ketone A_2. The stoichiometry is assumed to be 1:1 in ketone, and the interconversions to be kinetically of the first order with respect to A_1, A_2, and A_3.

$$A_1 \underset{k_{21}}{\overset{k_{12}}{\rightleftharpoons}} A_2 \underset{k_{32}}{\overset{k_{23}}{\rightleftharpoons}} A_3$$

The general solution for each concentration as a function of the time t may be written (99) as a linear combination of the three particular solutions

$$[A_1] = \sum_r Q_r \cdot \exp(-\lambda_r t)$$

$$[A_2] = \sum_r Q_r \cdot \frac{(k_{12} - \lambda_r)}{k_{21}} \cdot \exp(-\lambda_r t)$$

$$[A_3] = \sum_r Q_r \cdot \frac{k_{23}(k_{12} - \lambda_r)}{k_{21}(k_{32} - \lambda_r)} \cdot \exp(-\lambda_r t) \quad ,$$

where square brackets denote concentrations. The λ_r's are the solutions of the secular determinant and are given by

$$\lambda_1 = 0, \quad \lambda_2 = \tfrac{1}{2}(p + q), \quad \lambda_3 = \tfrac{1}{2}(p - q),$$

$$p = (k_{12}+k_{21}+k_{23}+k_{32}), \quad \text{and} \quad q = [p^2-4(k_{12}k_{23}+k_{21}k_{32}+k_{12}k_{32})]^{\frac{1}{2}},$$

and the Q_r's are the coefficients to be determined from the boundary conditions. In the present case these are the initial conditions

$$[A_2] = [A_2^{o}], \quad [A_1] = [A_3] = 0 \quad \text{at time } t = 0,$$

insertion of which into the above equations allows solution for the Q_r's in terms of the k's. Substitution of these relations into the general equations allows them to be expressed in their final form:

$$[A_1] = [A_2^{o}]\left[\frac{k_{21}k_{32}}{\lambda_2\lambda_3} + \frac{k_{21}(k_{32}-\lambda_2)}{\lambda_2(\lambda_2-\lambda_3)}\cdot\exp(-\lambda_2 t) + \frac{k_{21}(k_{32}-\lambda_3)}{\lambda_3(\lambda_3-\lambda_2)}\cdot\exp(-\lambda_3 t)\right] \quad ..(17)$$

$$[A_2] = [A_2^{o}]\left[\frac{k_{12}k_{32}}{\lambda_2\lambda_3} + \frac{(k_{32}-\lambda_2)(k_{12}-\lambda_2)}{\lambda_2(\lambda_2-\lambda_3)}\cdot\exp(-\lambda_2 t) + \frac{(k_{32}-\lambda_3)(k_{12}-\lambda_3)}{\lambda_3(\lambda_3-\lambda_2)}\cdot\exp(-\lambda_3 t)\right] \quad ..(18)$$

$$[A_3] = [A_2^{o}]\left[\frac{k_{12}k_{23}}{\lambda_2\lambda_3} + \frac{k_{23}(k_{12}-\lambda_2)}{\lambda_2(\lambda_2-\lambda_3)}\cdot\exp(-\lambda_2 t) + \frac{k_{23}(k_{12}-\lambda_3)}{\lambda_3(\lambda_3-\lambda_2)}\cdot\exp(-\lambda_3 t)\right] \quad ..(19)$$

These may be checked by their symmetry and by their ability to reduce both to the initial conditions and to the relation $[A_2^{o}] = [A_1] + [A_2] + [A_3]$ for all t.

The above equations predict that, if the reaction is monitored spectrophotometrically and each substance separately obeys Beer's law, the decrease in the optical density with time is expressed in the general case by the sum of two exponential decay curves; the final reading and the two amplitudes and time constants are each dependent on all four rate constants. Total first order kinetics will only be observed under one of the following conditions:

(i) $k_{12}, k_{21} \ll k_{32}, k_{23}$, or vice versa.

In this situation λ_2 and λ_3 will be very different, leading to apparent first order behaviour. However, either the reaction will be preceded by a rapid change in optical density or the final reading will show a drift with time.

(ii) $k_{12} = k_{32} = 0$, i.e. both reactions are irreversible.

In this case $\lambda_2 = k_{23}+k_{21}$ and $\lambda_3 = 0$, so that, if the reaction is followed at a wavelength at which only the ketone absorbs, the final optical density will be zero.

(iii) $\lambda_2 = \lambda_3$.

This requires a particular relation between the rate constants and can therefore only be satisfied at a particular catalyst concentration.

(iv) $k_{21} = 0$.

In this case $\lambda_2 = k_{12}$ and $\lambda_3 = k_{23}+k_{32}$, so that equation (18) becomes

$$[A_2] = [A_2^{\circ}]\left[\frac{k_{32}}{k_{23}+k_{32}} + \frac{k_{23}}{k_{23}+k_{32}} \exp[-(k_{23}+k_{32})t]\right]$$

If only A_2 absorbs, and the optical densities initially, at time t, and finally are D°, D, and D^{∞}, respectively, this may be written

$$D - D^{\infty} = (D^{0} - D^{\infty})\exp(-k_1 t) \qquad (20)$$

and

$$\frac{D^{\infty}}{D^{0} - D^{\infty}} = \frac{k_{32}}{k_{23}} = \frac{k_d}{k_h} = K_d \qquad (21).$$

Equation (20) is valid for the relaxation of an equilibrium between two species with kinetic orders higher than unity, provided that the displacement is sufficiently small (100). In the above expressions k_h and k_d are the first order rate constants for hydration and dehydration, respectively, and $k_1 = k_h + k_d$ is the composite first order rate constant which defines the exponential. In the following work each kinetic run is found to be described by equation (20), from which k_1 is obtained, while the ratio k_d/k_h is obtained from equation (21).

The kinetics of the approach to equilibrium of a solution containing a mixture of light and heavy water are not included in the above reaction scheme, since the various isotopically different hydrates are rapidly interconvertible. In this case the kinetics have the same form as in an isotopically pure solvent, but the separate first order rate constants k_h and k_d are functions of the deuterium atom fraction as explained in the previous chapter.

2. The purity of substrate and solvents

The use of sym-dichloroacetone as substrate in a solvent mixture of dioxan with light or heavy water is common to all the kinetic experiments of the present work, and operations and tests relating to the purity of these substances are described here. The various catalysts used are dealt with separately later.

DIOXAN (1,4-dioxan).

Dioxan was required to be completely free of the diethyl acetal normally present in amounts of up to 1%, since the liberation of acetaldehyde in the acid-catalysed hydrolysis of this impurity would interfere with spectrophotometric measurement of the hydration reaction. A quantity of Analar material obtained from B.D.H. (0.8% acetal content specified) was purified as recommended by Weissberger (101) by refluxing with aqueous hydrochloric acid in a current of nitrogen, neutralising and drying over potassium hydroxide, and finally refluxing over sodium and then distilling, b.p. 101°C. (lit. 101°C. (102,103)). A sample of B.D.H. dioxan of grade "special for spectroscopy" was refluxed over sodium for four hours, and then distilled from the mixture, b.p. 101°C. The distillation of both materials was carried out through a 20-plate Oldershaw fractionating column, fitted with a device to control the reflux ratio.

These substances were then compared by means of the following tests:

(i) Proton magnetic resonance spectra were run on a Perkin-Elmer model R10 60 Mc/s. spectrometer* (in common with all other p.m.r. spectra recorded in this thesis), and showed no impurities. By comparison with the ^{13}C satellites it was concluded that the proportion of acetal present could not exceed a small fraction of a percent by weight.

(ii) Samples of both materials and of the unpurified Analar dioxan were analysed by gas-liquid chromatography, using a Perkin-Elmer F11 instrument with a fluorinated silicon oil column. At 75°C. and a nitrogen pressure of 10 lb/sq.in. the unpurified dioxan exhibited a main peak of retention time $7\frac{1}{2}$ minutes preceded by a close group of peaks at 6 minutes, the intensity of which corresponded to a relative concentration of around 0.5%. The latter peaks were absent in the chromatographs obtained from the two purified samples, and no further resolution of the single peak could be obtained on doubling the retention time by lowering the temperature to 50°C. It was therefore concluded that these each contained no more than 0.05% impurity.

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* I am grateful to Drs. D. J. Barnes and B. G. Cox for instruction and help in the use of this instrument.

(iii) The most sensitive and relevant test for acetal was considered to be any increase in spectrophotometric absorption in the neighbourhood of 285 mμ on addition of aqueous acid to the dioxan. When an equal volume of 2N. hydrochloric acid was added to the unpurified material the initial optical density of 0.140 (mersured with respect to water in a 1 cm. cell) rose to 0.275, and acetaldehyde could be clearly smelt. On the other hand the two purified solvents showed a slight decrease from their initial values of about 0.035 to 0.025, from which it was concluded that any of the impurity which they contained should be negligible for the purpose of the present work.

As a result of the above tests exclusive use was made of the spectroscopic grade solvent, dried and freed from peroxides and small quantities of acetal by refluxing over sodium and then distilling as described above. The distillate was guarded from atmospheric moisture by sealing with 'Parafilm', and was stored in the dark to minimise the formation of peroxides; no sample was kept for longer than ten days. A few batches were purified by the alternative use of lithium aluminium hydride, which was shown to give material of identical purity.

A kinetic test of the dryness of the dioxan is reported in Chapter V, section A4.

SYM-DICHLOROACETONE (1,3-dichloro-propan-2-one)

Sym-dichloroacetone of unspecified purity was obtained from B.D.H. It was found to have m.p. 42-43°C. (lit. 45°C. (102,103)), with some signs of pre-melting at 41°C. This and other melting points were determined on a Gallenkamp melting point apparatus (MF-370), and are uncorrected. Previous workers report an identical result (2,3,6,21), in view of which their chlorine analysis by hydrolysis and titration (2,6,21), indicating 99.2% purity by weight, was accepted as applying approximately in the present case. The isomeric purity in the present work was checked by running the p.m.r. spectrum of a 2M. solution in dioxan, in which a single peak attributable to the ketone was observed at 0.8 p.p.m. downfield from that of the solvent.

At a sensitivity high enough for any peaks several times smaller than the ^{13}C satellites of the solute to be readily distinguished no spurious peaks could be detected, which indicated maximum impurity limits of $\frac{1}{2}$% for CCl_2H and $\frac{1}{4}$% for CH_3.

The most likely impurity was considered to be the carbonyl hydrate, which, since dehydration is exceedingly slow in the absence of water, was checked for by measuring the molar extinction coefficients (ϵ) in carbon tetrachloride and in dioxan. The former solvent (spectroscopic grade) was dried over successive amounts of anhydrous sodium sulphate for two 12 hour periods; separate solutions gave

$$\epsilon = 41.7,\ 41.1 \quad \text{at} \quad \lambda = 298\ m\mu ,$$

which may be compared with the value $\epsilon = 40.7 \pm 0.1$ obtained by Greenzaid, Rappoport, and Samuel at the same wavelength (3). The extinction coefficient in dioxan, purified as described above, was determined eight times at intervals during the course of the experimental work. The results at the wavelength of maximum absorption (285 $m\mu$) in chronological order were

$$\epsilon = 29.4, 28.4, 29.1, 28.1, 29.6, 28.5, 28.9, 29.3, \quad \text{mean} = 29.0 \pm 0.6,$$

which may be compared with 29.3 ± 0.2 found by Greenzaid et al. (3) using ketone purified by distillation and 28.0 ± 0.2 obtained by Bell, Millington, and Pink (6) with unpurified material. Bell and McDougall (2) were unable to obtain reproducible values, and no figure is reported by Bell and Jensen (21). The fairly high standard deviation in the present case may be attributed partly to varying degrees of hydration from one portion of the solid to another, but it is clear that no sample is likely to be more than 3% hydrated and that the average degree of hydration is no greater than 1%.

In view of the above results and the fact that kinetic measurements were to be taken over a number of half-lives, sym-dichloroacetone was used as supplied without further purification. No corrections have been made to the equilibrium data for any small degree of hydration of the solid ketone.

WATER

Water was passed through a Permutit de-ionising column, and was then distilled once from potassium permanganate solution.

DEUTERIUM OXIDE

Deuterium oxide was supplied in 50g. lots by B.D.H. in sealed plastic containers, and had a stated protium content of 0.3%. This figure was checked by measuring the relative intensities of the water and methylene peaks in the p.m.r. spectrum of a 0.223M. solution of potassium acetone sulphonate* in the heavy water. The results indicated an isotopic purity of 99.2%, which has been confirmed for different samples of the same material by other workers in these laboratories.

Deuterium oxide was used in the present work without further purification.

3. Spectrophotometry: instruments and thermostatting

Kinetic and equilibrium measurements were made spectrophotometrically, using the weak absorption band of the ketone in the near ultra-violet. The wavelength of maximum absorption in dry dioxan was found to be 285 $m\mu$, in agreement with the work of Bell, Millington, and Pink (6); these latter workers report that λ_{max} decreases by 3 $m\mu$ in going to a solution containing 17% of water by weight, but the use of initial optical densities obtained in the present work (unless otherwise stated) by back extrapolation of the kinetic data in each experiment avoided the need to consider any small variation of λ_{max} with solvent composition. The broad nature of the absorption allowed the use of higher wavelengths when required to minimise absorption by the catalyst, and equilibrium measurements in all cases are only quoted when a solvent blank was used. Unmatched 1 cm. quartz cells were employed, and a zero correction made from measurements with distilled water before and after each experiment.

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* I am grateful to Dr. D. J. Barnes for supplying this substance.

These measurements also provided a check that the cells had been properly cleaned, after which they were rinsed several times with Analar acetone and dried over a smooth glass tube connected to the service vacuum line. The cells were fitted with Teflon stoppers, which were washed only with water.

Two Unicam spectrophotometers were employed, an SP700A double beam recording instrument, and an SP500 Series 2 single beam instrument used exclusively in the manual, null balance mode. Measurements in both cases were restricted to the optical density range 0.0-1.0, over which range the ketone was found to obey Beer's law. The cell compartments provided space for two and four cells, respectively, and movement of different cells into the light path of the SP500 was achieved automatically and with minimum chance of disturbance by means of an SP505 control unit. In both cases a deuterium lamp served as the light source. Because of its greater accuracy, which was particularly important in deriving equilibrium data from the initial and final absorptions in a kinetic run, the SP500 instrument in the null balance mode was used for the majority of the experiments recorded here.

Both instruments were thermostatted to 25.00 ± 0.02°C. by means of water flowing through the metal cell-block from a Grant thermostatic bath, the temperature of which was controlled by a mercury contact unit. An attempt was made to draw water through the cell-block by means of a pump situated between it and the point at which the water returned to the bath, but this was abandoned because of the tendency of the pump to become blocked with air. Instead water was pumped by means of a rotating blade and shaft from a compartment submerged in the bath, a technique which caused minimal heating of the water.

The temperature difference between the bath and a cell filled with liquid in the spectrophotometer was measured by means of a single-junction thermocouple made from copper (s.w.g. 36, 522 ohms/ 1000 yds.) and constantan (s.w.g. 30, 5050 ohms/1000 yds.), fused together in a hot flame, and designed to set up a potential of 0.36 mV. per 10 C°. difference. This gave rise to a deflection of 20 mm. per 1 C°. difference on a Pye Scalamp galvanometer (7901/S) operating at maximum sensitivity, and indicated a temperature difference of 0.05 C°. between the bath and the cell; adjustment of the bath temperature brought that of the cell to 25.00°C. The constancy of the bath temperature was monitored with a mercury thermometer reading to 0.01 C°., and the above determination of the cell temperature was repeated after nine months and found not to have changed. Since it can be shown that for a reaction of $\Delta H^{\ddagger} = 18$ kcal/mole a change of temperature of 0.1 C°. causes a 1% change in the rate at 25°C., the temperature control was considered adequate.

4. Preparation of solvent mixtures

The solvent mixtures used in the present work, consisting of dioxan containing 2-10% of water by volume, were prepared volumetrically; when checked by weight this is stated explicitly. The small volumes of water or deuterium oxide required were dispensed by means of an "Agla" hypodermic syringe, which was attached by a rigid holder to a micrometer screw gauge which operated the plunger. The barrel and plunger were made of glass, the needle was of stainless steel, and 0.01 ml. of the total capacity of 0.50 ml. was ejected by one revolution of the micrometer head.

It was found that reproducible amounts were delivered by the syringe provided that the tip of the needle was made to touch the surface of both the stock solution after filling and the liquid dispensed after ejection. The accuracy and reproducibility were tested by weight in the course of making up some of the reaction solutions, and the results are given in table (3) for H_2O and in table (4) for D_2O.

TABLE 3

Calibration of syringe (H_2O)

Volume intended to be delivered. (ml.)	Mass delivered per unit volume intended (g/ml.)		
	number of experiments	mean	standard deviation. (%)
0.50	6	0.991	0.3
0.45	2	0.990	diff. of 0.1%
0.40	6	0.986	0.6
0.35	2	0.991	both agreed
0.30	5	0.992	0.2
0.20	5	0.991	0.5
0.10	5	0.992	0.3

mean of all values = 0.990

Four trials were conducted with 0.01 ml. of water, a volume ten times smaller than any used in the present work, and yielded the ratio 0.97 ± 0.04 g/ml., but it is possible that some of this error may lie in the weighing.

TABLE 4

Calibration of syringe (D_2O)

Volume intended to be delivered. (ml.)	Mass delivered per unit volume intended (g/ml.)		
	number of experiments	mean	standard deviation. (%)
0.50	6	1.097	0.2
0.45	2	1.098	diff. of 0.1%
0.40	4	1.096	0.2
0.35	2	1.096	diff. of 0.1%
0.30	4	1.101	0.2
0.20	2	1.099	diff. of 0.1%
0.10	2	1.099	diff. of 0.3%

mean of all values = 1.098

The final ratio of the densities of the two waters from these measurements is 1.109 at room temperature, which may be compared with the literature value of 1.107 at 20°C. (102). The reproducibility indicated by the above tests was considered to allow most of the reaction solutions to be made up entirely by volume, applying a correction of 1% to the syringe readings in all cases; the composition was checked by weight only when the rate was a particularly sensitive function of any of the concentrations, a situation which applied in the absence of added catalysts.

To ensure that no unwanted traces of moisture entered the reaction solutions, the parts of the syringe and the containing flask to be used were rinsed with Analar acetone and dried in an oven at ~ 80°C. Dioxan was added from a pipette, which had previously been rinsed with acetone and dried by drawing air into it. The flask was finally closed with a ground glass stopper and sealed with 'Parafilm' until the solution was required for use.

CHAPTER IV

EQUILIBRIUM MEASUREMENTS

1. Influence of equilibrium measurements on rate data

In order to convert the measured isotope effect on the composite rate constant into the desired isotope effects on the individual rates of hydration and dehydration, it is necessary to know the effect of replacing light with heavy water in the solvent on the position of the hydration equilibrium. The manner in which these quantities are related is demonstrated as follows.

At any given solvent composition let k^c be the composite second order rate constant, k^c_h and k^c_d be the second order rate constants for hydration and dehydration, respectively, K_d be the dissociation equilibrium constant of the hydrate, and the subscripts H and D represent reactions in the presence of light and heavy water, respectively. Therefore, for each isotopic solvent, from equations (20) and (21),

$$k^c = k^c_h + k^c_d \quad \text{and} \quad K_d = \frac{k^c_d}{k^c_h}$$

so that

$$k^c_h = \frac{k^c}{(1+K_d)} \quad \text{and} \quad k^c_d = \frac{k^c K_d}{(1+K_d)} \tag{22}$$

These relations allow the kinetic isotope effects for reaction in the two directions to be written

$$\frac{k^c_{hH}}{k^c_{hD}} = \frac{k^c_H(1+K_{dD})}{k^c_D(1+K_{dH})} = \frac{k^c_H(1/K_{dH}+K_{dD}/K_{dH})}{k^c_D(1/K_{dH}+1)} \tag{23}$$

and

$$\frac{k^c_{dH}}{k^c_{dD}} = \frac{k^c_H \cdot K_{dH}(1+K_{dD})}{k^c_D \cdot K_{dD}(1+K_{dH})} = \frac{k^c_{hH} \cdot K_{dH}}{k^c_{hD} \cdot K_{dD}} \tag{24}$$

Identical expressions apply to the first order rate constants appropriate in solutions without added catalyst.

In the reactions investigated K_{dH} is never smaller than 0.7 and the equilibrium isotope effect K_{dD}/K_{dH} is close to unity, so that any uncertainty in the latter quantity is never reduced by more than a factor of $2\frac{1}{2}$ in its effect on the desired rate ratio, (although neither is it ever magnified). It is therefore fairly important to obtain as good a measure of the equilibrium isotope effect as possible.

2. A differential method for the equilibrium isotope effect

It is a general principle that, since the accuracy of measuring a small quantity can only be decreased by measuring it added onto a large one, it is always preferable to observe the difference in two similar quantities directly. In the present case the difference in the position of the hydration equilibrium in the two solvents is manifested in slightly different final optical densities when solutions containing equal concentrations of the ketone are allowed to come to equilibrium, and the following series of experiments was designed to measure this difference directly. The relation between the measured and desired quantities is derived as follows.

Let D° and D^∞ be the optical densities before any hydration has taken place and at equilibrium, respectively. Therefore,

$$K_{dH} = \frac{D_H^\infty}{D_H^\circ - D_H^\infty} \quad \text{and} \quad K_{dD} = \frac{D_D^\infty}{D_D^\circ - D_D^\infty} \quad .$$

If $z = D_H^\infty - D_D^\infty$,

$$z = K_{dH}(D_H^\circ - D_H^\infty) - K_{dD}(D_D^\circ - D_H^\infty + z) \quad .$$

And if $D_H^\circ = D_D^\circ = D^\circ$,

$$z = (K_{..}-K_{..})(D^\circ - D^\infty_{..}) - K_{..}z \quad .$$

Divi

$$z = (K_{dH}-K_{dD})(D^\circ - D_H^\infty) - K_{dD}z \quad .$$

Division by K_{dH} and collection of terms gives

$$1 - \frac{K_{dD}}{K_{dH}} = \frac{1 + K_{dH}}{K_{dH} + D_H^\infty/z} \qquad (25) \quad ,$$

in which the difference between the equilibrium isotope effect and unity is related to the small difference s and quantities referring only to the solution containing light water.

The above derivation is dependent upon the assumption $D_H^\circ = D_D^\circ$, i.e. that there is no isotopic medium effect on the extinction coefficient. Because of its relatively large influence on the ratio K_{dD}/K_{dH} and the fact that Kurtz (7) has reported a 1% change in extinction coefficient when acetone is transferred between the two waters, it seemed desirable to investigate the possibility of such an effect in the present case. Any isotope effect on the transition probability must arise from vibrational anharmonicity in the water molecules solvating the carbonyl group the vibrations of which change between the ground and excited states, and these purely electronic isotope effects are normally very small (105). The change in the vibration frequencies on the other hand will be manifested in an isotopic solvent shift of the wavelength of maximum absorption λ_{max}, the fractional change in λ_{max} being approximately equal to one twentieth of the fractional change in the O-H vibration frequency for every O-H bond involved. The latter effect would be expected to be at least as easy to detect as the former and may in fact give rise to a large part of any change in the extinction coefficient at a fixed wavelength. Experiments were therefore conducted to investigate the possibility of a solvent shift of this type.

3. Experimental method

The measurement of the equilibrium isotope effect by the differential method outlined above requires the preparation of solutions containing the same concentration of ketone as well as of the different isotopic waters. This could be achieved quite simply for the present system by adding light or heavy water, or a 50% mixture of the two, to aliquots of a stock solution of sym-dichloroacetone in dioxan. The solutions were made up by weight, and optical densities were measured on the SP 500 instrument for the highest accuracy.

Since the approach to equilibrium in the solution of lowest deuterium oxide mole fraction studied has a half-life of about three days, it was desirable to use an additional catalyst, which was achieved by adding 0.1 ml of Analar 72% B.D.H. perchloric acid to 20 ml. each of light and heavy water to give the solutions to be added to the dioxan. The extra protium atom fraction thus added to the deuterium oxide was negligibly small. An analogous set of solutions was made up in the absence of ketone in order to establish the absorbance zeros. The concentration of ketone in the dioxan stock solution was chosen to give equilibrium optical densities in the region of 0.5 absorbance units, and for this reason a second solution of lower concentration was prepared for the two lowest water mole fractions. These concentrations gave rise to optical density differences between the light and heavy water solutions of around 0.02.

Equilibration in all cases occurred over-night in the cell block of the spectrophotometer, and the attainment of the infinity reading was checked by re-measuring the small optical density difference between the proto- and deutero-solutions at least an hour after the first measurement. Duplicate measurements were made in the absence of perchloric acid for the two highest water mole fractions, and the equilibrated set of solutions from one of these was used to test for the possibility of an isotopic solvent shift on the spectrum of the ketone.

4. Results

The results of the above measurements of the equilibrium constants in the presence of light water are recorded in Table 5, and are denoted by (EQ). These have been computed on the assumption that ϵ_o at 285 mμ decreases slightly as the solution becomes more aqueous. The evidence for and magnitude of this effect comes from the work on catalysis by trichloroacetic acid recorded in chapter V section (F), on the basis of which the following reductions in ϵ_o have been made:

x_w = 0.320, 0.273: 2%, x_w = 0.220, 0.159: 1%, x_w = 0.0859: 0%.
The largest change effected in K_d by this correction is 4%.

Also collected in Table 5 and denoted by (KIN) are the values provided by the kinetic measurements on catalysis by water, reported in chapter V section (A), and obtained by back-extrapolation of the optical density readings to zero time. Analogous measurements obtained in the presence of other catalysts have not been included here, since for these either the catalyst was considered to influence the results or the use of the SP 700 instrument made them insufficiently accurate; in addition back-extrapolation was more difficult for faster reactions. The fourth column of the table, denoted (BMP), contains the values of Bell, Millington, and Pink (6), as calculated from their smoothed relation

$$K_d = \frac{0.201}{x_w} + 0.15 \quad ,$$

obtained from kinetic measurements by the back-extrapolation technique.

TABLE 5

Dissociation equilibrium constants

x_w	K_{dH}(EQ)	K_{dH}(KIN)	K_{dH}(BMP)	K_{dH}(AVE)
0.320	0.773	0.776	0.778	0.775
0.320	0.781			
0.273	0.870	0.898	0.886	0.884
0.273	0.902			
0.220	1.01	1.04	1.06	1.03
0.159	1.33	1.29	1.41	1.31
0.0859	2.35	2.17	2.49	2.26

(In this and other tables experimental results are quoted to three significant figures without claiming a corresponding degree of accuracy.)

It can be seen that the three sets of values agree well in the more highly aqueous solutions, but that at low x_w the deviations become progressively more pronounced. In the latter region errors arising from the optical density readings or from partial hydration of the solid ketone are magnified in the small difference between the initial and equilibrium optical densities, while traces of water impurity in the dioxan are also more important. It is clear that undue significance cannot be attached to any measurements of K_d at low x_w. For the purpose of dividing the composite rate constants reported in chapter V the results in columns (2) and (3) have been averaged to give the values in column (5). These are correlated by the expression

$$K_d = \frac{0.169}{x_w} + 0.26 \qquad (26)$$

with a maximum deviation of 1½% in K_d.

The variation of optical density with wavelength in the neighbourhood of the absorption maximum is shown in Table 6 for a 0.0436 M. solution of the ketone equilibrated in the presence of each of the two isotopic waters.

TABLE 6

Partial spectrum of equilibrated ketone, x_w = 0.273

λ(mμ)	$D^\infty(H_2O)$	$D^\infty(D_2O)$
280	0.563	0.541
281	0.565	0.545
282	0.566	0.547
283	0.568	0.548
284	0.570	0.549
285	0.570	0.548
286	0.567	0.548
287	0.566	0.547
288	0.565	0.543
289	0.561	0.539
290	0.556	0.536

These results establish that any isotopic solvent shift must be less than 1 mμ, from which it may almost certainly be inferred that the second order effect on the extinction coefficient at λ_{max} is correspondingly negligible. Accordingly it has been assumed in the present treatment that the extinction coefficient at 285 mμ is invariant to isotopic substitution in the solvent.

The equilibrium isotope effects measured in the present work are recorded in Table 7. Corrections have been applied for small differences in composition, for which purpose K_d was assumed to be inversely proportional to x_w; the largest correction required was of 1% in K_d.

TABLE 7

Equilibrium isotope effects

x_w	$1-K_{dD}/K_{dH}$ (%)	$1-K_{dHD}/K_{dH}$ (%)
0.320	6.8	3.6
0.320	9.5	6.1
0.273	7.0	2.9
0.273	10.8	5.2
0.220	7.3	7.0
0.159	10.8	7.2
0.0859	7.2	6.3
	Mean = 8.5 ± 2.0	Mean = 5.5 ± 1.8

The results are fairly scattered, the standard deviations being equivalent to superimposed errors of 0.002 units in the readings of both the optical density readings and the zero, if errors in composition are regarded as completely absent. The two sets of data obtained in the absence of perchloric acid (the first listed for x_w= 0.320 and 0.273) are rather lower than the mean values, but the corresponding K_{dH} values do not support any perturbation of the equilibrium by the acid. In any case these differences would result in variations of less than 1% in any kinetic isotope effect, remarks which apply even more strongly to any uncertainties in the K_{dH} values used.

The equilibrium isotope effects measured here are considerably smaller than the mean value of 27% found by Bell, Millington, and Pink in their more approximate experiments. As explained more fully in the Discussion, the present results are more in line with those for similar systems, but it is difficult to see the origin of the discrepancy.

Greenzaid, Rappoport, and Samuel (3) found by p.m.r. that at 27°C. K_{dD} in undiluted D_2O has the value 0.16. Use of the present equilibrium isotope effect together with their value for the enthalpy of hydration leads to a similar result at 25°C. in H_2O, considerably smaller than would be predicted by equation (26). Combination with measurement of the effective extinction coefficient in water reveals that ϵ_o has fallen to around 26.0 at 273 mμ, the band maximum in water, which supports the application of a downward correction to ϵ_o in going from dioxan to the partly aqueous solutions used in the present work.

CHAPTER V

KINETIC MEASUREMENTS

(A) CATALYSIS BY WATER

(1) Experimental technique

The kinetics of the approach to equilibrium in the absence of added catalysts other than water were followed spectrophotometrically using the SP500 instrument in the null balance mode. The reaction media in this case were all made up by weight, on account of the strong dependence of the rate on the mole fraction of water. A portion of each solution was used as the reference in each run, and measurement of its optical density relative to water before and after the reaction served to check its stability.

In a typical experiment the spectrophotometer and deuterium lamp were switched on at least half an hour before the first measurement, the zero difference between the two cells. 5 ml. of the reaction medium (which had been made up from 10 ml. of dioxan) were transferred by pipette into a round bottomed flask, which was then tightly closed by a ground glass stopper, and left for at least twenty minutes in the thermostat tank which served to maintain the cell-block at 25.00°C. Some of the remaining solution was poured into the previously dried reference cell, and the sample cell was dried and left in the thermostatted cell-block for at least twenty minutes to attain temperature equilibrium. About 20 mg. of solid sym-dichloroacetone were transferred to a weighing bottle fitted with a ground glass top and weighed.

The reaction was initiated by allowing the solid ketone to drop into the solution, immediately after which a stop-watch was started and the flask containing the reaction solution was shaken while not removing it from the bath. This method of initiation relies on the very rapid solution of the ketone in a solution containing a large proportion of dioxan, and follows the practice of previous workers (6,21). After thorough mixing had been achieved, the flask was taken out of the bath, the water quickly wiped off the outside, and the solution poured into the sample cell without removing the latter completely from the cell-block. This entire process could be completed in less than a minute, allowing the first reliable optical density reading to be taken two minutes after the reaction had started. After taking readings for several minutes the final weight of the weighing bottle was measured, its top having been replaced immediately after addition of the ketone to prevent any remaining solid from picking up atmospheric moisture. For all but the fastest runs the cells were sealed with 'Parafilm', since it had been shown by weighing that as much as 1% of the solution could escape around the sides of the Teflon stopper in a three hour period. At least ten readings per half-life were taken over the first three or four half-lives, after which readings were taken spasmodically to monitor the approach to the infinity value, which was measured after 10-12 half-lives; this final optical density was stable over a further period of similar duration.

The variation in temperature during transfer of the reaction solution to the sample cell as described above was checked by means of thermocouples. A number of tests using dioxan showed that the temperature could change by up to 0.1 C°., either decreasing through the evaporation of water from the outside or increasing through over zealous wiping of the flask. The most satisfactory technique was found to be merely to surround the flask with a cloth while moving it to the spectrophotometer, which resulted in a temperature drop of no more than 0.05 C°. Once in the cell, the liquid approached the correct temperature with a half-time of about one minute.

The kinetic measurements were analysed by plotting $\log_{10}(D-D^{\infty})$ against t, from which the slope and intercept allowed the composite first order rate constant k_1 and (D^0-D^∞), respectively, to be obtained. These are related through the expression

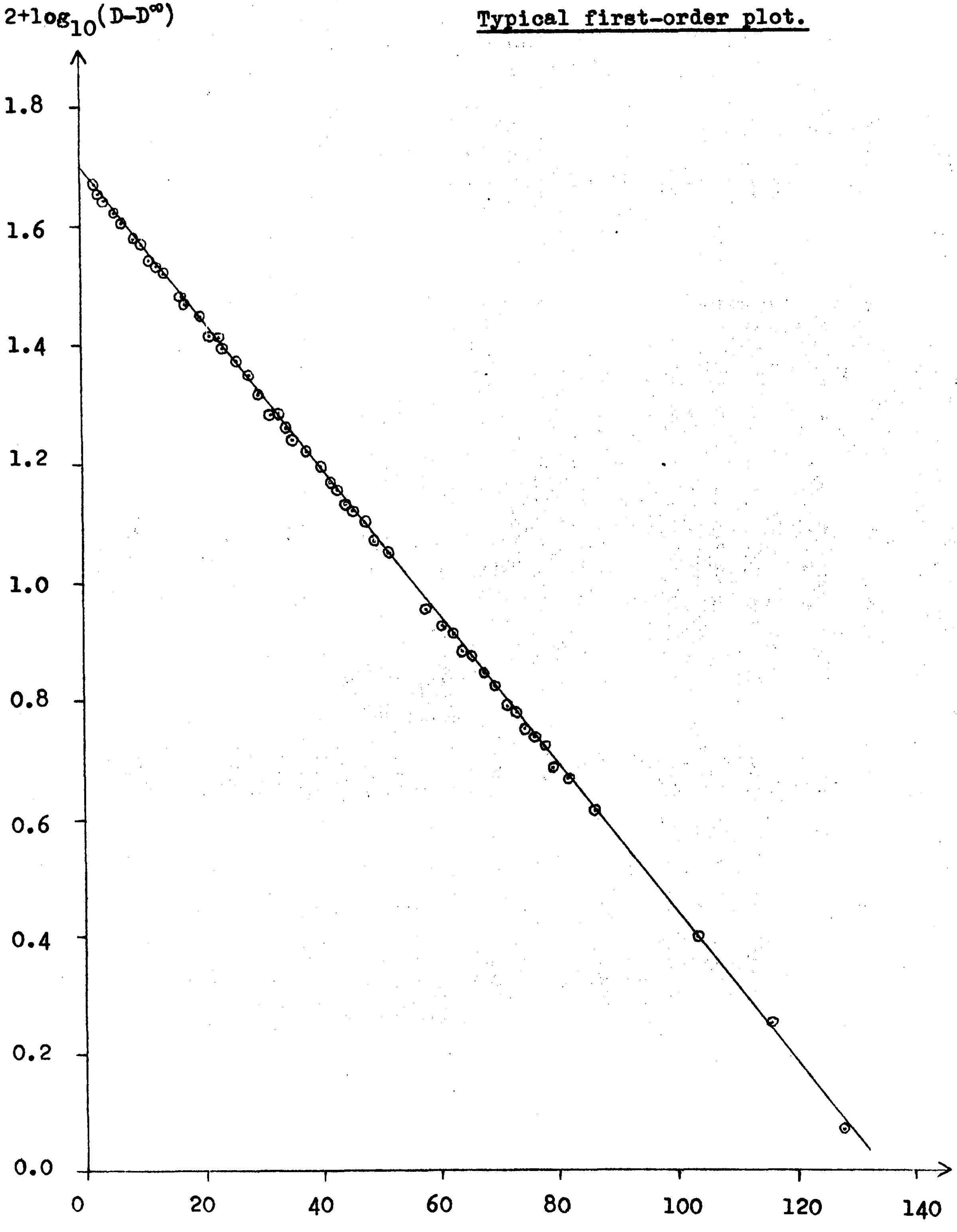
$$\log_{10}(D-D^\infty) = -\frac{kt}{2.303} + \log_{10}(D^0-D^\infty) \quad ,$$

which is obtained by integration of equation (20). Figure (1) shows the plot for the reaction catalysed by light water in a solution of water mole fraction $x_w = 0.320$, and is typical of the results for all catalysts. In this particular reaction the concentration of ketone was 0.0321 M. and the optical density decreased from 0.879 to 0.384 with a half-life of 24 minutes. The kinetics were observed to be strictly of the first order in ketone over 4-5 half-lives, and the slope could be defined to well within 1%.

The above description of the kinetic technique applies also with few modifications to the majority of the reactions conducted in the presence of added catalyst. In the present case with no added catalyst all the optical densities were recorded at 285 mμ, and reactions in the presence of light water were studied with half-lives ranging from 24 minutes to about 27 hours. Attempts to obtain accurate rate data for reactions catalysed by heavy water or by a 50% mixture of the two waters were restricted to the more highly aqueous half of this concentration range, since very low rates were considered to be most prone to error. For a given total water mole fraction the reactions catalysed by H_2O, D_2O, and H_2O-D_2O were conducted concurrently in the same cell-block, using a portion of the last solution as a common reference, and starting the runs in the order of increasing rate. Apart from achieving some economy of time, it was hoped that this would eliminate the effect of any thermostatting errors on the isotope effects. Three experiments using a lower concentration of heavy water were carried out as a kinetic test of the dryness of the dioxan, but were not designed to yield accurate rate data.

FIGURE 1

Typical first-order plot.



(2) Results for catalysis by light water

The results of the kinetic measurements in solutions composed of dioxan and light water are set out in Table 8. The equilibrium constants have already been discussed. The mean extinction coefficient for sym-dichloroacetone, obtained from the back-extrapolated optical densities, is 5% less than the mean value in dry dioxan reported in Chapter III, but the individual deviations in the present values are too large to allow any definite trend with x_w to be discerned.

The individual first order rate constants k_h and k_d have been calculated using the values of K_d measured in these experiments. Alternative analysis by means of the average equilibrium constants from Table 5 would change the kinetic orders by no more than 1%. The variation of these rate constants with x_w is shown in Figure (2), in which the present values of $\log_{10}k_h$ and $\log_{10}k_d$ (closed triangles and circles) and the values obtained over the same range of concentrations by Bell, Millington, and Pink using their equilibrium constants (open triangles and circles) are plotted against $\log_{10}x_w$. It can be seen that the two sets of values agree well in the more aqueous region of concentration, but that at low water mole fractions the present results fail to show the upwards curvature found by the previous workers; in fact the present dehydration values exhibit a slight downwards trend. The two sets differ by almost a factor of two in the composite rate constant at $x_w = 0.09$, a difference which is independent of the values chosen for K_d. The presence of water impurity in the dioxan in either the present or the previous work cannot explain the differences in both the rate and equilibrium constants at low x_w. The composite rate constant obtained by Bell and Jensen (21) at the single water mole fraction 0.199 lies 7% above the common interpolated value of the present work and that of Bell, Millington, and Pink.

FIGURE 2

Catalysis by light water-
Kinetic orders.

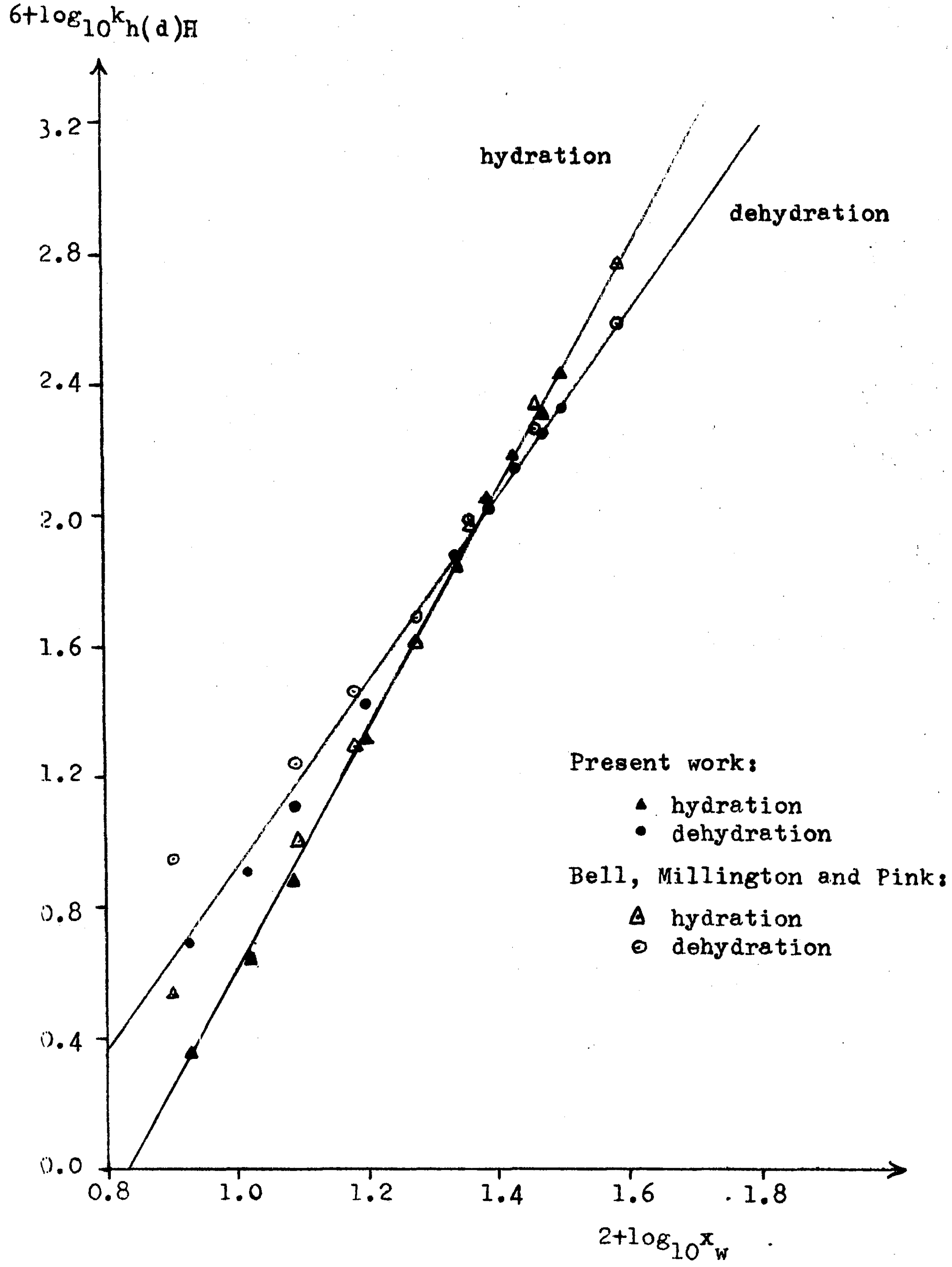


TABLE 8

Results for catalysis by light water

x_w	k_1(sec.$^{-1}$)	K_d	k_h(sec.$^{-1}$)	k_d(sec.$^{-1}$)	ϵ^o_{285}(M^{-1}cm.$^{-1}$)
0.320	4.80×10^{-4}	0.776	2.70×10^{-4}	2.10×10^{-4}	27.4
0.297	3.80×10^{-4}	0.816	2.09×10^{-4}	1.71×10^{-4}	27.1
0.273	2.93×10^{-4}	0.898	1.54×10^{-4}	1.39×10^{-4}	27.7
0.247	2.17×10^{-4}	0.936	1.12×10^{-4}	1.05×10^{-4}	27.7
0.220	1.45×10^{-4}	1.04	7.09×10^{-5}	7.40×10^{-5}	28.4
0.159	4.80×10^{-5}	1.29	2.09×10^{-5}	2.70×10^{-5}	27.2
0.123	2.09×10^{-5}	1.60	8.05×10^{-6}	1.29×10^{-5}	27.2
0.105	1.28×10^{-5}	1.81	4.56×10^{-6}	8.24×10^{-6}	27.9
0.0859	7.30×10^{-6}	2.17	2.30×10^{-6}	5.00×10^{-6}	not measured

kinetic orders with respect to x_w: hydration 3.65,
dehydration 2.79

The kinetic orders of reaction with respect to water have values which are necessarily closely similar to those which would be obtained from the data of the previous workers in the more aqueous region of concentration, but are higher than both their average and low concentration values. The lines in Figure (2) have been drawn by eye (as in the rest of this work), but it can be seen from the graph that the slope for hydration is defined to within 1%. The kinetic order for dehydration in the region of low water mole fraction would be about 6% greater than the value recorded here. The effect on the kinetic orders of expressing the water content of the solutions in terms of molarity rather than mole fraction is dealt with in the Discussion.

(3) Results: kinetic isotope effects

The results for catalysis by deuterium oxide are given in Table 9 in terms of their ratios with the corresponding quantities from Table 8. Small corrections have been applied to the measured rates to give the values relating to compositions identical with those of the H_2O-catalysed reactions, making use of the kinetic orders found for these reactions; the largest change made in any rate is 2½%, and the average change is 1%. No corrections have been made for the protium content of the heavy water. The isotope effects on the hydration rates have been calculated by equation (23), using the mean equilibrium isotope effect of 8.5% from the previous chapter. The required values of K_d have been taken from the kinetic experiments reported in Table 8, but use of the average values from the previous chapter would give indistinguishable results. The corresponding kinetic isotope effects on the dehydration rates are obtainable according to equation (24) by simply multiplying the hydration isotope effects by the constant ratio K_{dH}/K_{dD}, and for this reason they are not listed here.

TABLE 9

Catalysis by heavy water

x_w	k_{1H}/k_{1D}	k_{hH}/k_{hD}	$1-(K_{dD}/K_{dH})$ %	ϵ^{o}_{285} (M^{-1}cm.$^{-1}$)
0.320	4.05	3.90	8.1	not measured
0.297	4.15	3.99	7.0	26.6
0.273	4.12	3.95	11.9	27.7
0.247	4.20	4.03	5.8	26.9
0.220	4.22	4.02	10.5	26.6

k_{hH}/k_{hD} (mean) = 3.97 ± 0.06

These results show that the reaction proceeds about 4.0 times faster in the presence of light water than it does in solutions containing the same mole fraction of heavy water. This ratio differs by a factor of 1.5 from that reported by Bell, Millington, and Pink, but their experiments did not aim for high accuracy and may have been conducted with deuterium oxide containing a significant proportion of the lighter isotope. It was not considered feasible to obtain sufficiently accurate values outside the present range, since within it the rates already varied by a factor of 14.

Table 9 also shows the corrected results obtained from these experiments for the equilibrium isotope effect, and, although scattered, these average to 8.7 in support of the results of the previous chapter. The average extinction coefficient for sym-dichloroacetone is 2% less than in the presence of light water, but the fairly large deviations and the small number of values prevent the drawing of definite conclusions.

The results of the experiments using an equimolar mixture of the two waters are presented in a similar fashion in Table 10. The rates have been corrected to a standard total water content as before, and a small correction (never greater than 0.3%) has also been applied to give values corresponding to solutions made up from exactly equimolar amounts of the stock isotopic waters. Again no correction has been made for the protium present in the D_2O, and the subscript 'HD' therefore refers to solutions of deuterium atom fraction 0.496.

TABLE 10

Catalysis by equimolar H_2O-D_2O mixtures.

x_w	k_{1H}/k_{1HD}	k_{hH}/k_{hHD}	$1-(K_{dHD}/K_{dH})$ %	ϵ^{o}_{285} ($M^{-1}cm.^{-1}$)
0.320	1.90	1.85	6.1	30.2
0.297	1.92	1.87	-4.5	28.2
0.273	1.93	1.88	5.3	27.4
0.247	1.93	1.88	4.0	27.1
0.220	1.95	1.89	6.8	28.9

k_{hH}/k_{hHD} (mean) = 1.88 ± 0.02

The results in the last two columns of Table 10 are too scattered to allow detailed comparison with values for other isotopic compositions.

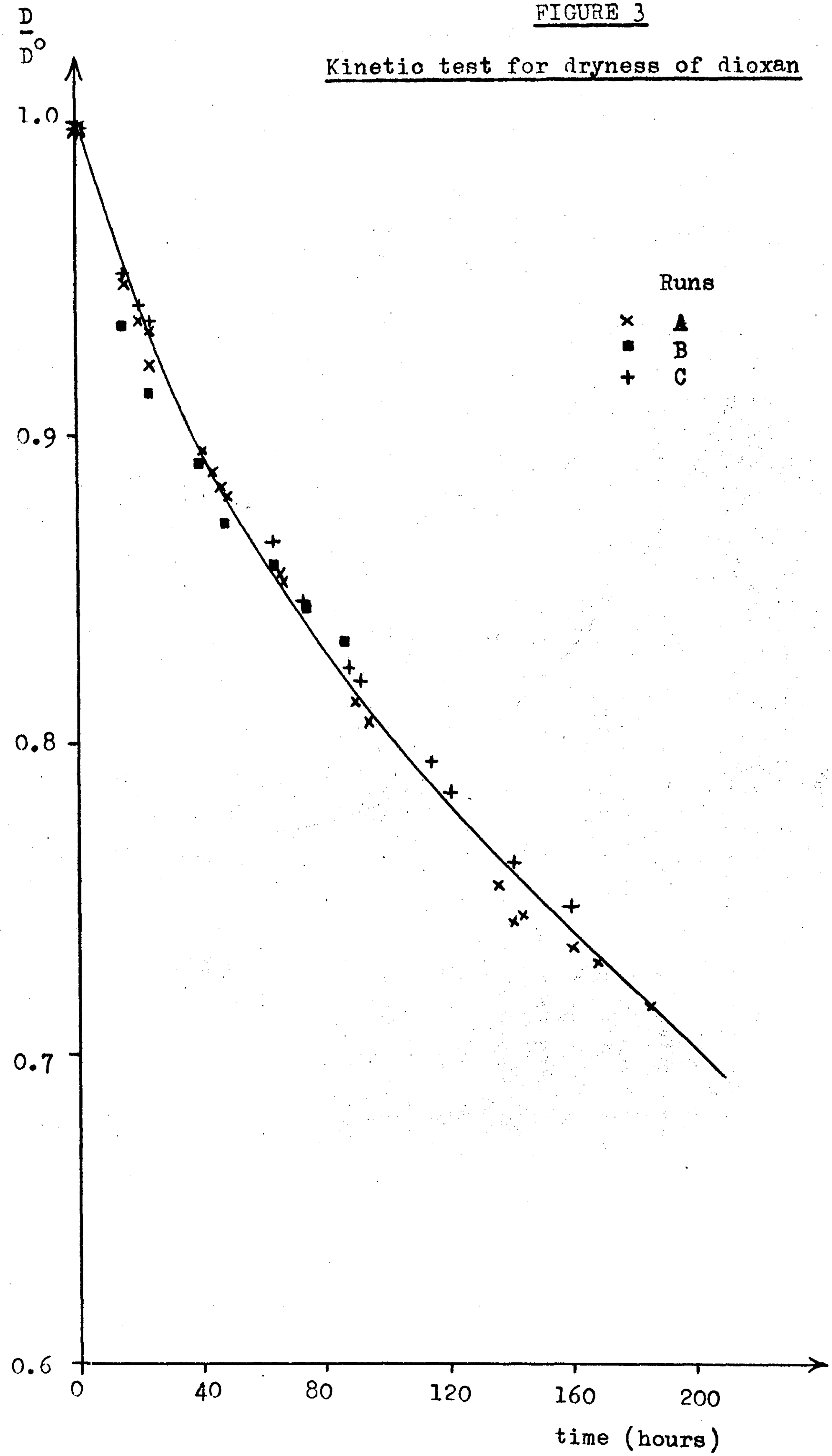
(4) A kinetic test for the dryness of the dioxan

The most likely source of error in the kinetic experiments was considered to arise from the possibility that the dioxan after drying might still contain a quantity of water which was not negligible compared with the amount added. A partial check against this is provided by the isotope effects in tables (9) and (10), which do not show the decrease with x_w which would occur if part of the rate were contributed by water impurity. Nevertheless it was considered desirable to devise a further test at low water concentrations, where the effect of water impurity would be most evident, especially in view of the divergence of the present results from those of the previous workers at these concentrations.

Three experiments were conducted in which the hydration of the ketone in a solution of deuterium oxide mole fraction 0.0859 was followed over the first two half-lives. Since the half-life under these conditions is about three days, the reaction was not followed for long enough to obtain an accurate rate constant, but readings taken over the space of a week should be sufficient to check the reproducibility. The results are given in Figure (3), in which the optical densities are expressed as a fraction of the initial value in each run. Run A was carried out using dioxan which had been kept for one week, run B made use of dioxan to which a quantity of deuterium oxide had been added before drying, and run C employed the same dioxan after re-subjecting it to the drying procedure. Since the three rates do not appear to differ by more than about 5%, it can be concluded that a second drying process is unnecessary and that distillation over sodium removes all the kinetically active water. It also follows that, since the samples of dioxan were kept

FIGURE 3

Kinetic test for dryness of dioxan



for different lengths of time, no kinetically significant quantity of water can be picked up from the atmosphere.

A Guggenheim plot of the data for run A gives a first order rate constant within a few percent of 1.8×10^{-6} sec^{-1}., which on combination with the appropriate value in Table 8 gives an approximate isotope effect of $k_{1H}/k_{1D} \simeq 4.0$, in reasonable agreement with the results at higher water concentrations.

(B) CATALYSIS BY PERCHLORIC ACID

For perchloric acid, as for all other catalysts, two sets of runs were performed. In one the variation of rate with catalyst concentration at a given mole fraction of water was studied in solutions containing light or heavy water; this established the linearity or otherwise of the catalytic plot and provided the most accurate value for the kinetic isotope effect. The second series consisted of a run for each water mole fraction in each of the two isotopic waters, and provided data on the order of the catalysed reaction with respect to water, as well as additional measurements of the isotope effect.

(1) Preparation of solutions

Stock solutions of the catalyst were prepared by adding about 0.04 ml. of 72% B.D.H. 'Analar' perchloric acid to 20 ml. of light and heavy water. The amount of protium thus introduced into the deutero solution was less than 0.2%, and was therefore neglected. The two solutions were titrated against the same approximately 0.02 M. sodium hydroxide solution using phenolphthalein as indicator, and this was standardised against two separately prepared potassium hydrogen phthalate solutions of similar concentration by means of the same indicator. The solid potassium hydrogen phthalate had previously been dried at 120°C. for two hours in an oven containing silica gel. The concentrations of the solutions were found to be:

$HClO_4$ in H_2O : 0.0266 M., $DClO_4$ in D_2O : 0.0339 M. ,

and the reaction media were made up by adding varying volumes of these stock solutions together with pure light or heavy water by means of the syringe to 10 ml. of dioxan.

(2) Catalytic plots

The results for the variation of the composite rate constant with perchloric acid concentration in solutions of water mole fraction 0.220 are set out in Tables 11 and 12. The two second order composite catalytic constants, k_H^c and k_D^c, for perchloric acid are obtained from the catalytic plots depicted in Figure (4), in which the points at zero catalyst concentration refer to the water-catalysed rates reported in the previous section. The rate is a linear function of the acid concentration within experimental error, which justifies the use of unbuffered solutions. Use of the SP700 recording instrument led to a rather large scatter in the dissociation equilibrium constant for the ketone hydrate, but within these limitations no systematic trend in either K_d or ϵ^o is discernible; this parallels the findings of Chapter IV.

TABLE 11

$HClO_4$: catalytic plot for $x_w = 0.220$

$10^4[HClO_4](M)$	$10^4k_1(sec.^{-1})$	K_{dH}	$\epsilon^o_{285}(M.^{-1}cm.^{-1})$
2.51	3.59	0.99	28.8
5.01	6.70	1.04	27.3
7.52	8.31	1.02	27.3
10.0	11.1	1.02	28.9
15.1	16.8	1.07	27.0

$k_H^c = 0.98_2\ M^{-1}sec.^{-1}$

TABLE 12

$DClO_4$: catalytic plot for $x_w = 0.220$

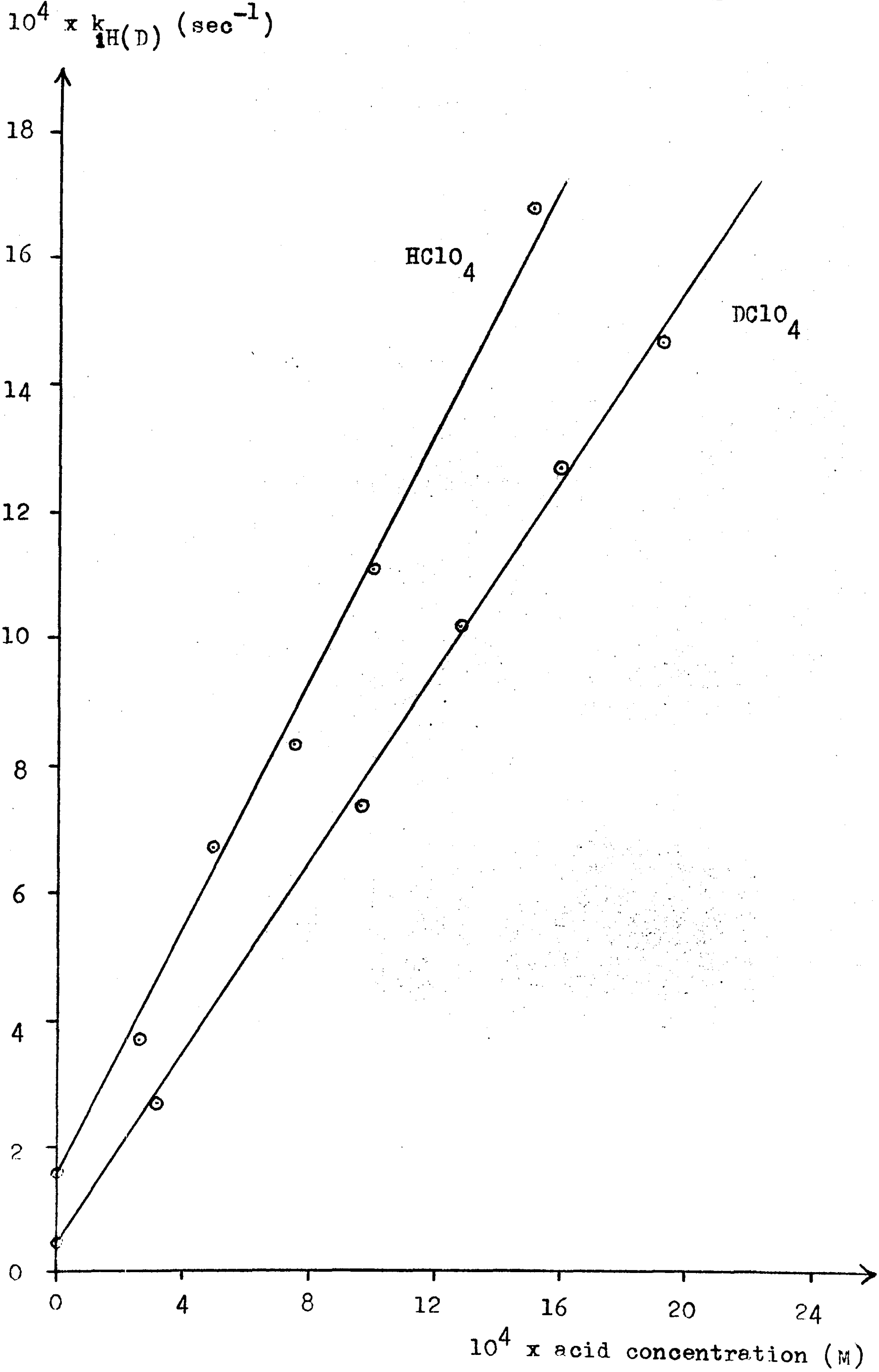
$10^4[DClO_4](M)$	$10^4k_1(sec.^{-1})$	K_{dD}	$\epsilon^o_{285}(M.^{-1}cm.^{-1})$
3.20	2.67	0.94	28.2
9.60	7.37	0.87	28.7
12.8	10.2	0.89	27.3
16.0	12.6	0.93	27.8
19.2	14.7	0.96	28.5

$k_D^c = 0.75_1\ M^{-1}sec.^{-1}$, therefore $k_H^c/k_D^c = 1.31$

Average equilibrium isotope effect = 11%.

FIGURE 4

Perchloric acid catalytic plots in light and heavy water.



The final optical densities were found to be stable over a period several times longer than the total reaction times, and the optical density of the reference did not change during the reaction. The latter readings showed that the addition of dilute perchloric acid to the dioxan raised its optical density by amounts of up to 0.015 absorbance units according to the concentration of the acid; this dependence on catalyst concentration but not on time ruled out the formation of acetaldehyde from small amounts of acetal impurity as the cause of these observations.

(3) Variation of rate constants with x_w

In Table 13 are set out the results obtained in solutions containing different mole fractions of light water. The composite catalytic constants k^c_H have been calculated using the results of the previous section for the contribution of the water-catalysed reaction, and in no case does this amount to more than 20% of the observed value. Division of the composite catalytic constants into the separate second order rate constants for hydration and dehydration, k^c_{hH} and k^c_{dH} respectively, has been achieved through the use of the average K_d values first presented in Table 5.

TABLE 13

$HClO_4$: variation of catalytic constants with x_w

x_w	$10^4[HClO_4]$(M)	$k^c_H(M^{-1}sec.^{-1})$	$k^c_{hH}(M^{-1}sec.^{-1})$	$k^c_{dH}(M^{-1}sec.^{-1})$
0.320	24.2	0.860	0.485	0.375
0.273	19.7	0.878	0.466	0.412
0.220	2.51-15.1	0.982	0.484	0.498
0.159	10.2	1.39	0.602	0.788
0.0859	5.21	2.35	0.721	1.63

TABLE 14

$HClO_4$/$DClO_4$: kinetic isotope effects

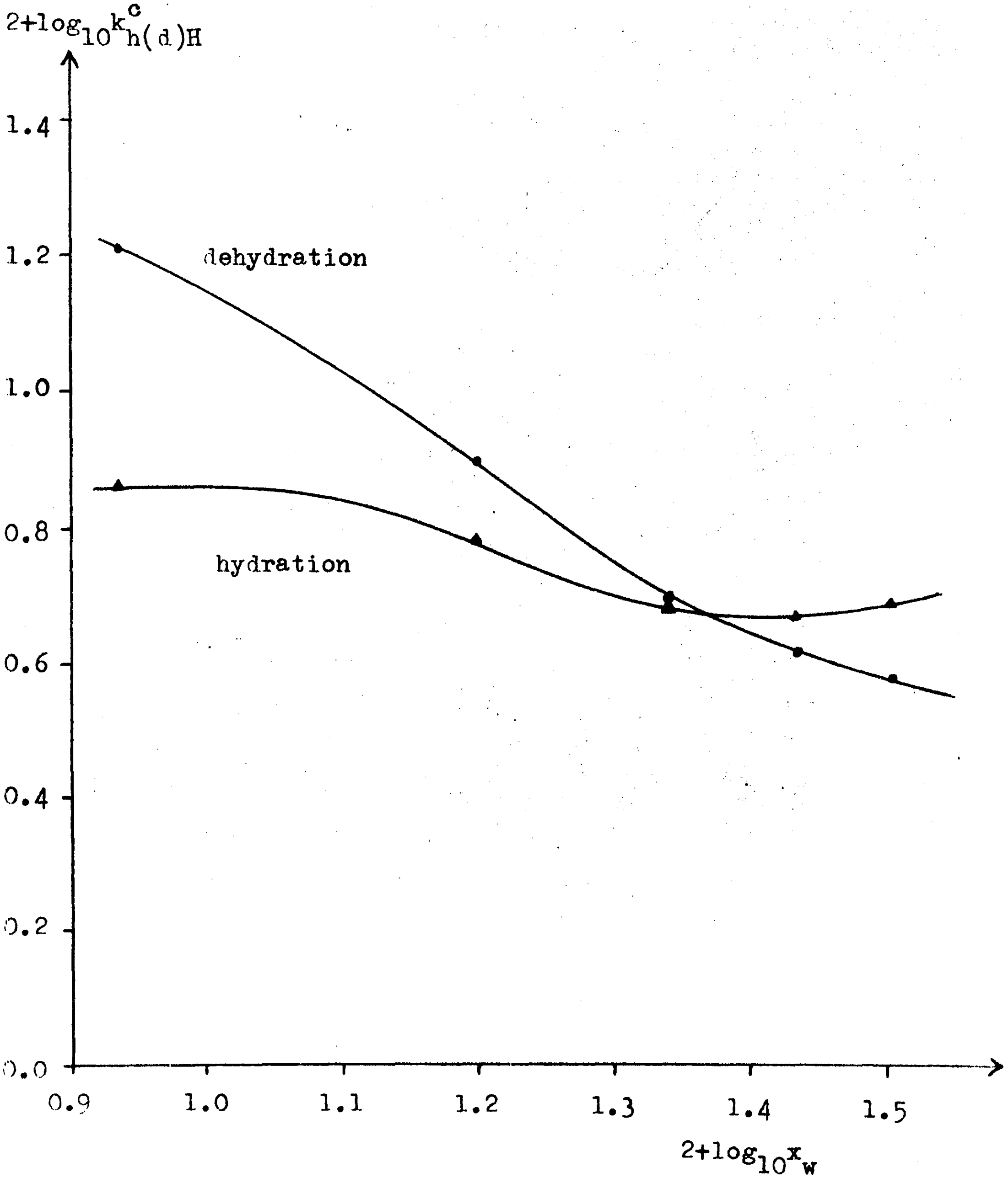
x_w	$10^4[DClO_4]$(M)	k_D^c(M^{-1}sec.$^{-1}$)	k_H^c/k_D^c	k_{hH}^c/k_{hD}^c
0.320	30.8	0.609	1.41	1.36
0.273	25.1	0.624	1.41	1.35
0.220	2.67-14.7	0.751	1.31	1.25
0.159	13.0	1.03	1.35	1.28
0.0859	6.65	1.78	1.32	1.24
			k_{hH}^c/k_{hD}^c (mean)=	1.29

The logarithms of the hydration and dehydration catalytic constants are plotted against the logarithms of the water mole fractions in Figure (5). The kinetic orders of reaction with respect to water can be seen to be negative and to vary with x_w, and in particular the rate of hydration appears to pass through a minimum in the region around $x_w = 0.27$. The curves in Figure (5) have a rather strange appearance, which may be partly spurious, but the near constancy of the isotope effects listed in Table 14 shows that the results in the heavy water solutions support their general form. The isotope effects on the individual catalytic coefficients for hydration have been calculated in the usual way, using the equilibrium isotope effect of 8.5% and the average K_d values from Chapter IV. The contribution by deuterium oxide to the observed rates for the two lowest mole fractions has been taken as equal to one quarter of the corresponding rates of catalysis by light water, but this correction is in each case less than 1% of the observed rate. The mean isotope effect has been calculated by giving equal weight to the value derived from the catalytic plots and the average of the other four values, a practice which has been followed for all the catalysts studied.

No corrections have been made at this stage either for the protium content of the deuterium oxide or the effect on the deuterium oxide mole fraction of its 0.444% larger molar volume. Wherever the solutions were made up by volume (i.e. for all catalysts except water), the heavy water solution has been given the same x_w value as the corresponding light water solution of the same v/v composition.

FIGURE 5

Perchloric acid: kinetic orders with respect to water mole fraction.



(C) CATALYSIS BY HYDROCHLORIC ACID

(1) Preparation of solutions

The experiments were conducted in a very similar manner to those of the previous section. Stock solutions of the acid in light and heavy water were made up by dilution of B.D.H. 'Analar' 35% hydrochloric acid, and added together with varying amounts of the pure waters to dioxan to give the reaction media. Standardisation of the stock solutions was carried out as before, and three proto and one deutero solution were used, having the concentrations:

[HCl] = 0.01145, 0.02291, 0.02564 M., [DCl] = 0.01645 M.

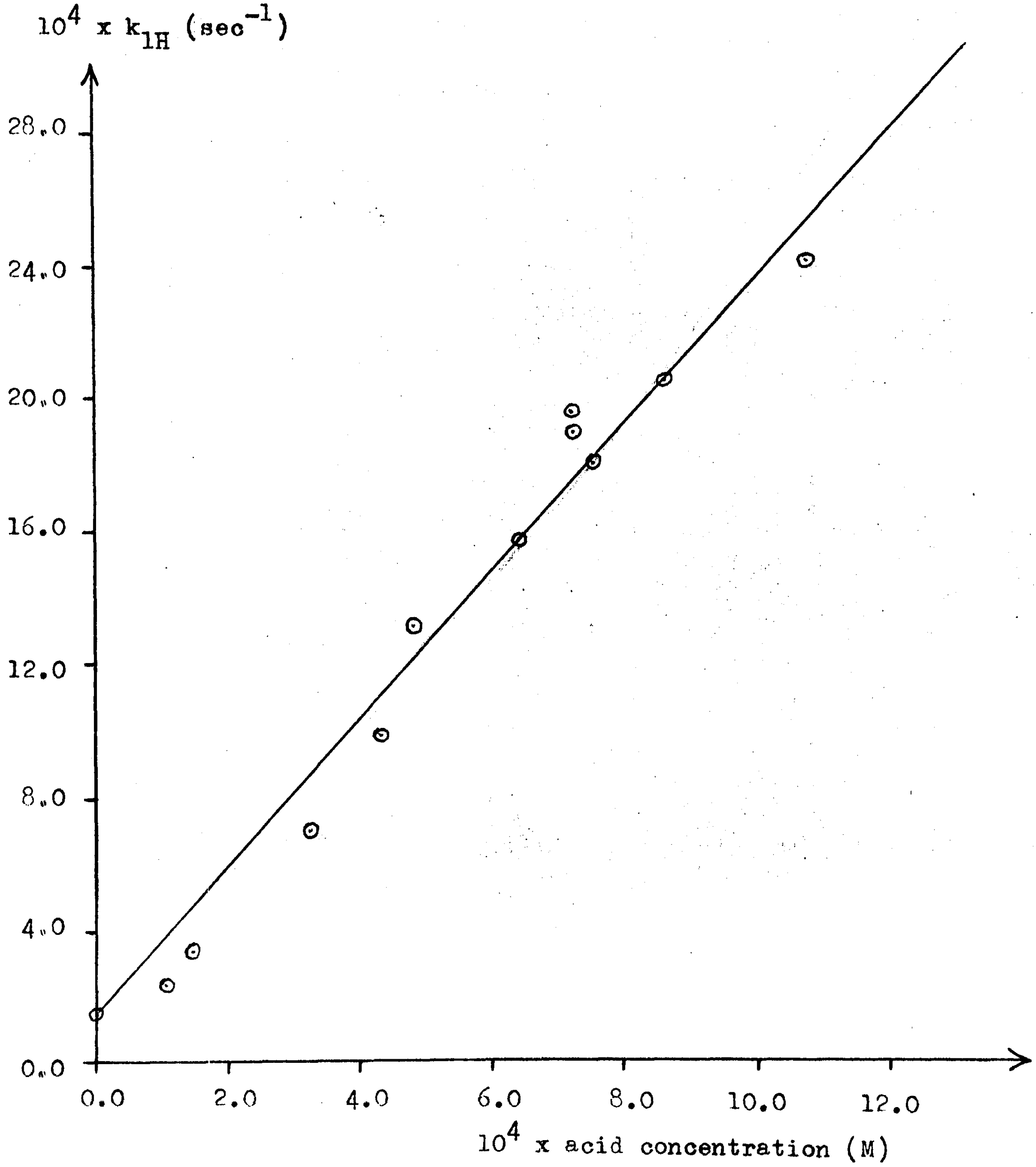
(2) Catalytic plot

The results obtained for the variation of the total composite first order rate constant with acid concentration at a constant water mole fraction of 0.220 are collected in Table 15. The corresponding catalytic plot, reproduced in Figure (6), shows a considerable degree of scatter, but it was found impossible to correlate the deviations with the sample or age of either the dioxan or the acid solution used. In fact, to make quite certain of this, some of these runs and some of those appearing in the catalytic plot for perchloric acid were carried out alternately using aliquots of the same sample of dioxan, thus showing that the degree of scatter depends on the nature of the acid.

Within the limitations imposed by these deviations it is possible to see a tendency towards low apparent catalytic constants at low acid concentrations, and this was confirmed by six additional runs not reproduced in the table in the concentration range 10^4[HCl] = 0.4-1.3 M., all of which corresponded to catalytic constants between 30% and 70% lower than that indicated by the straight line in Figure (6). Such behaviour could be caused by dissociation of the ion-pairs (in which form most of the hydrogen

FIGURE 6

Hydrochloric acid catalytic plot in light water.



chloride in the solution might reasonably be expected to exist) into catalytically less active species, but this explanation still leaves the absence of this effect for perchloric acid and the high degree of scatter in the present case unaccounted for. Accordingly an explanation in terms of adsorption of the catalyst onto the glass walls of the containing vessels was preferred. In any one experiment the extent of adsorption depends on the particular state of the surface and on the chemical nature of the catalyst, while the general shape of the plot can be reproduced if a Langmuir isotherm is assumed. This explanation would suggest that the true catalytic constant is probably higher than that given by the straight line in Figure (6), but the latter was considered more appropriate for comparison with results at other water mole fractions subject to the same effect.

TABLE 15

HCl : catalytic plot for $x_w = 0.220$

10^4[HCl] (M)	$10^4 k_1$ (sec.$^{-1}$)	K_d	ϵ^o_{285}(M^{-1}cm.$^{-1}$)
1.08	2.34	1.06	29.3
1.45	3.11	1.06	29.1
3.24	6.98	not measured	
4.32	9.83	not measured	
4.84	13.1	1.06	28.3
6.48	15.6	not measured	
7.26	19.5	1.05	27.7
7.26	18.9	not measured	
7.56	18.0	1.05	27.7
8.64	20.4	1.01	28.4
10.8	24.1	1.04	27.9
		mean = 1.05	mean = 28.3

$k^c_H = 2.2$ M^{-1}sec.$^{-1}$

Gold and Lowe (77) similarly attributed the unreliability of their pH readings in solutions containing less than 5×10^{-3} M. hydrochloric acid to surface effects. The fastest reaction studied had a half-life of 5 minutes, and all the reactions were found to give good first order kinetics over at least three half-lives.

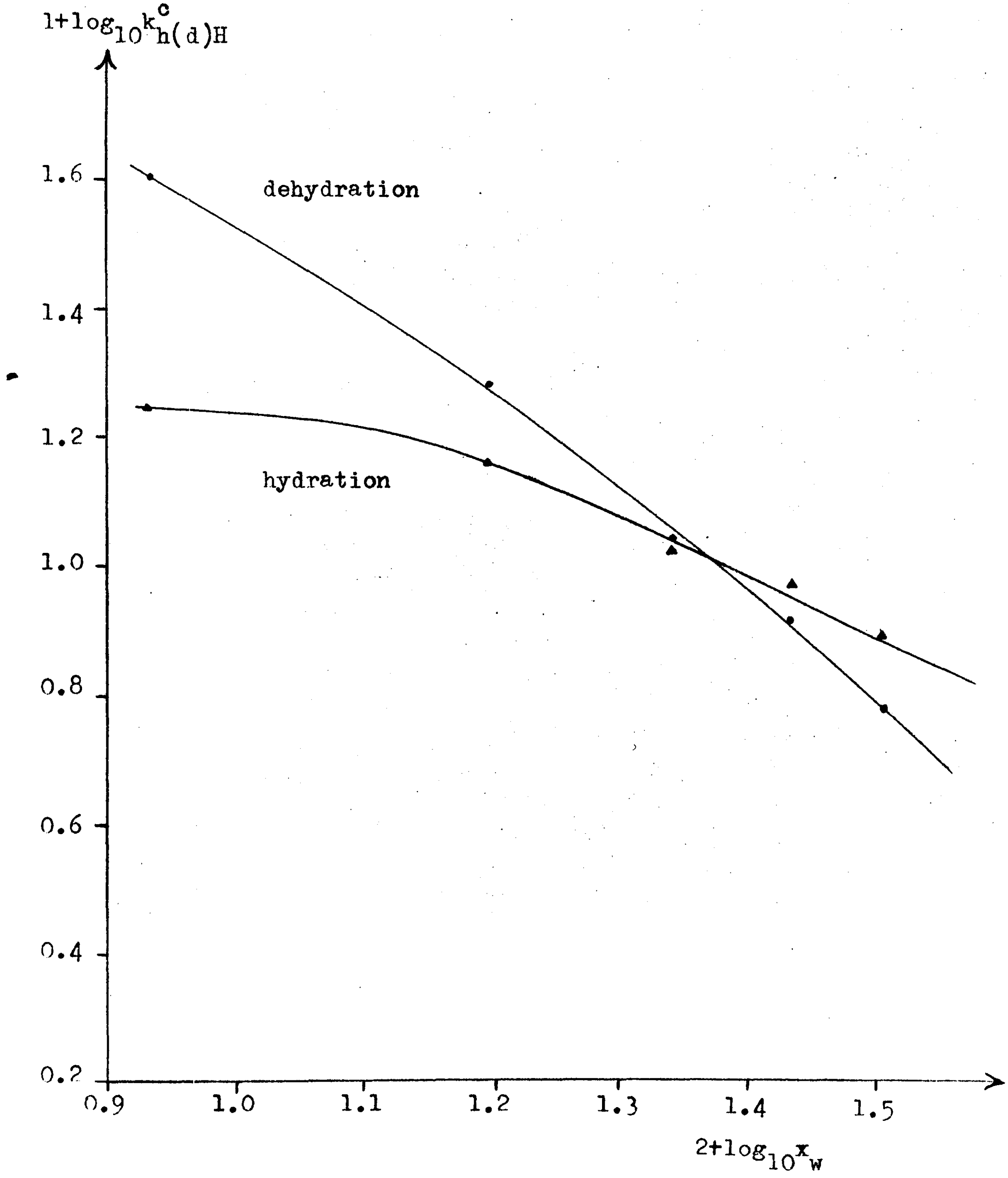
(3) Variation of rate constants with x_w

In view of the above uncertainties no attempt was made to establish a deutero catalytic plot, but reactions in the presence of each of the two waters were carried out over a range of water mole fractions in order to obtain approximate kinetic orders and isotope effects. The results are set out in the usual way in Tables 16 and 17. K_d values were not measured in these experiments as water was used in the reference cell, and accordingly use has again been made of the average values from Chapter IV. The largest correction for catalysis by water is 25% of the observed rate.

The kinetic order plot based on the data in Table 16 is shown in Figure (7). In contrast to the results for perchloric acid, the curves here are concave towards the composition axis, with slopes approaching zero at lower water concentrations, and the rates at any given composition are greater than in the former case. Interpolation from the present values by means of these curves gives composite second order rate constants for perchloric and hydrochloric acids which are respectively 18% and 25% lower at $x_w = 0.199$ than the corresponding results of Bell and Jensen (21), but the present work still bears out the findings of these workers that the catalytic effects of the two acids under these conditions are in the reverse order of their expected acid strengths. The results of Bell, Millington, and Pink (6) for hydrochloric acid catalysis are between 10% and 25% higher than the present measurements, but the general shape of the kinetic order plots is not affected. The kinetic isotope effects listed in Table 17 exhibit the degree of scatter expected from the attempts to construct the catalytic plot, but are sufficiently

FIGURE 7

Hydrochloric acid: kinetic orders with respect to water mole fraction.



constant to support the general form of the curves in Figure (7). The mean value of the isotope effect on the rate of hydration is 6% less than that for perchloric acid catalysis.

As in the case of perchloric acid, the presence of hydrogen chloride in the reference blanks raised their optical densities by a few hundredths of an absorbance unit. The effect here was roughly double that found in the previous case, but was again constant for the duration of each run. The concentrations of hydrochloric acid used in the above experiments were less than those known to cause phase separation (108).

TABLE 16

HCl : variation of catalytic constants with x_w

x_w	10^4[HCl](M)	k^c_H(M^{-1}sec.$^{-1}$)	k^c_{hH}(M^{-1}sec.$^{-1}$)	k^c_{dH}(M^{-1}sec.$^{-1}$)
0.320	10.4	1.39	0.783	0.607
0.273	8.48	1.78	0.945	0.835
0.220	1.08-13.0	2.20	1.08	1.12
0.159	4.40	3.43	1.48	1.95
0.0859	2.24	5.85	1.79	4.06

TABLE 17

HCl : kinetic isotope effects

x_w	10^4[DCl](M)	k^c_D(M^{-1}sec.$^{-1}$)	k^c_H/k^c_D	k^c_{hH}/k^c_{hD}
0.320	15.0	1.03	1.36	1.31
0.273	12.2	1.38	1.29	1.24
0.220	9.31	1.79	1.22	1.17
0.159	6.33	2.85	1.20	1.14
0.0859	3.22	4.23	1.38	1.30

k^c_{hH}/k^c_{hD} (mean) = 1.23

(D) CATALYSIS BY ACETIC ACID

(1) Preparation of solutions

The reaction media were made up as for the previous catalysts by mixing dioxan with small volumes of aqueous acetic acid and water in various proportions. Five stock solutions of aqueous acetic acid were used in all, of which two (labelled (a) and (c)) were prepared from B.D.H. concentrated volumetric solutions. The others were prepared by hydrolysis of acetic anhydride, and their concentrations related to either (a) or (c) by titration against 1 M. sodium hydroxide solution, using phenolphthalein as indicator. Since the sodium hydroxide solutions were also made up from B.D.H. standard solutions, these titrations served also to check the concentrations of the standard solutions of acetic acid. The various concentrations were found to be:

AcOH in H_2O: (a) 5.00 M., (b) 4.31 M., (c) 5.00 M.

AcOD in D_2O: (d) 4.29 M., (e) 4.29 M.

Acetic anhydride ('Analar' grade obtained from B.D.H.) was freed from traces of acetic acid by the method of Calcott, English, and Wilbur (as described by Weissberger (101) p.395), heating gently over 15% of its weight of coarse magnesium turnings for 20 hours, followed by refluxing for two hours. After decantation, the liquid was fractionally distilled (b.p. 137°C., lit. 136.4°C. (102), 139.5°C. (103)). 5.00 ml. of the distillate were hydrolysed with 20.00 ml. of light or heavy water for 8 hours, using a calcium chloride drying tube to prevent the entry of atmospheric water vapour, and the solution was finally filtered. The data of Batts and Gold (97) would indicate that hydrolysis must have been complete in a fraction of the time allowed, and this was confirmed by comparing the kinetic effects of solutions (a) and (b) in constructing the catalytic plot.

(2) Catalytic plots

Since a fairly high ratio of [AcOH] to [H_2O] is required to cause appreciable catalysis, reaction solutions which were made up by

TABLE 18

AcOH : formal catalytic plot for $x_w^\circ = 0.273$

[AcOH](M)	K_{dH}	10^4k_{hH}(sec.$^{-1}$)	10^4k_{dH}(sec.$^{-1}$)	ϵ^{o}_{285}(M^{-1}cm.$^{-1}$)	stock solution
0.0463	0.928	4.61	4.28	27.2	(a)
0.0926	0.961	6.94	6.66	28.6	(a)
0.116	0.959	8.73	8.37	28.0	(a)
0.159	1.01	9.50	9.60	28.6	(a)
0.160	1.00	10.9	10.9	27.4	(b)
0.185	1.02	12.3	12.5	28.1	(a)

Apparent $k^{c}_{dH} = 5.90 \times 10^{-3}$ M^{-1}sec.$^{-1}$

TABLE 19

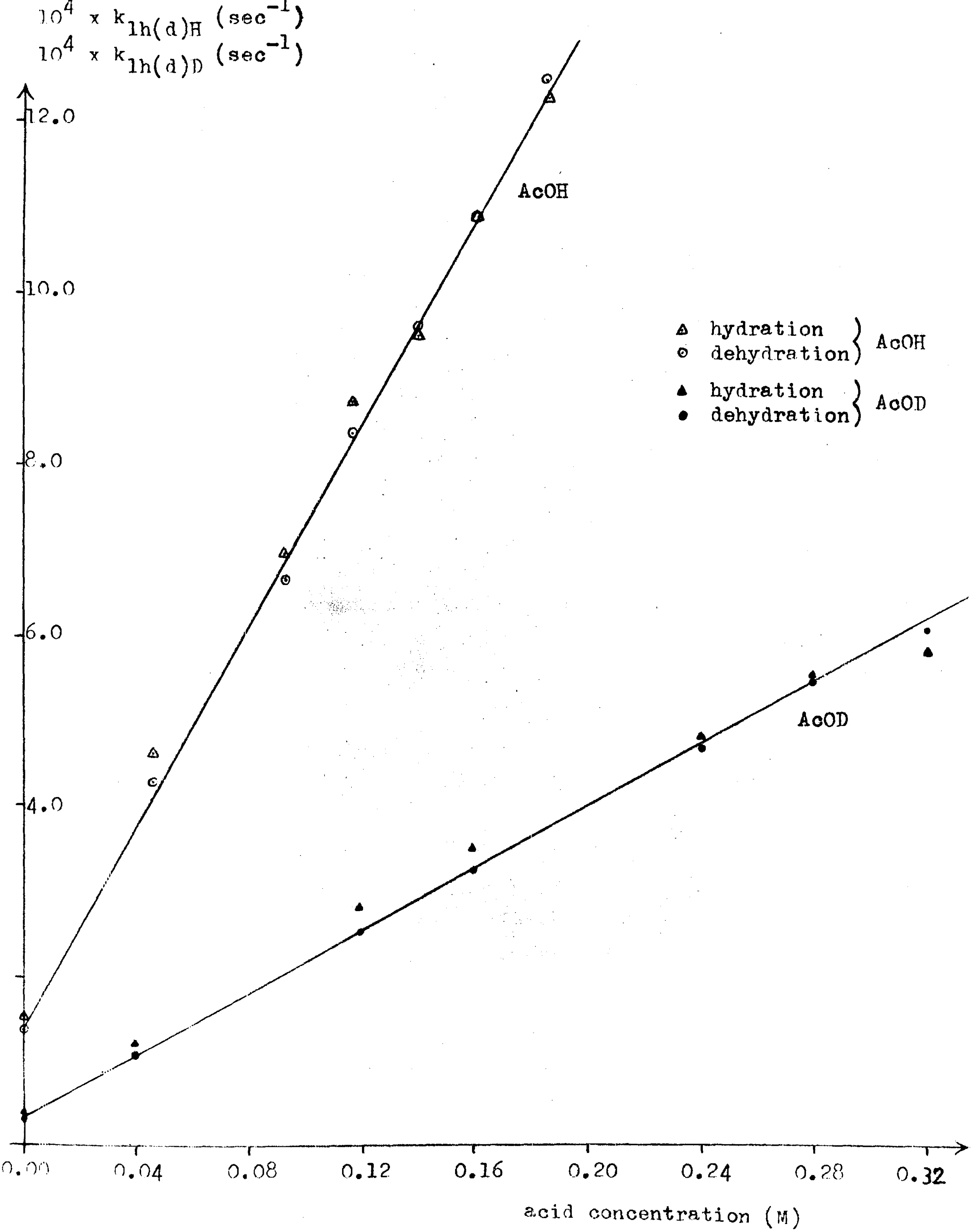
AcOD : formal catalytic plot for $x_w^\circ = 0.273$

[AcOD](M)	K_{dD}	10^4k_{hD}(sec.$^{-1}$)	10^4k_{dD}(sec.$^{-1}$)	ϵ^{o}_{285}(M^{-1}cm.$^{-1}$)	stock solution
0.0398	0.882	1.22	1.08	29.4	(d)
0.119	0.899	2.83	2.55	27.0	(d)
0.159	0.919	3.52	3.23	28.7	(d)
0.159	0.900	3.56	3.20	28.0	(e)
0.239	0.976	4.80	4.68	28.6	(d)
0.278	0.981	5.55	5.45	28.5	(d)
0.318	1.04	5.83	6.07	27.1	(d)
0.318	1.04	5.83	6.07	28.0	(e)

Apparent $k^{c}_{dD} = 1.85 \times 10^{-3}$ M^{-1}sec.$^{-1}$

FIGURE 8

Acetic acid: formal catalytic plots in light and heavy water.



adding a constant total aqueous volume (0.8 ml.) to aliquots of dioxan (10.0 ml.) contained mole fractions of water which decreased as the acid concentration increased. This approach was nevertheless adopted, and the catalytic constants at $x_w = 0.273$ obtained by back-extrapolation of the resulting formal catalytic plots to very small catalyst concentrations. The results obtained in the presence of light and heavy water are set out in Tables 18 and 19 respectively.

It is clear from the tables that the equilibrium constants in both series increase with the concentration of the catalyst. Since this necessarily implies a variation in the catalytic constants for either hydration or dehydration, or for both, the total composite first order rate constants have been divided into their forward and reverse contributions by the use of the experimental value for K_d measured in each run. The resulting quantities are plotted in Figure (8), in which best straight lines have been drawn through the dehydration points. For the deutero series it can be seen that the dehydration rates fall on a good straight line, while the hydration rates describe a curve concave to the concentration axis. The greater scatter of the proto plot, which can be attributed to its inclusion of reaction with half-times as low as five minutes, together with the smaller range of concentrations covered makes it more difficult to pick out such behaviour, but the results are not incompatible with it.

(3) Origin of non-linear behaviour

In order to be able to derive meaningful catalytic coefficients from the above results it is necessary to understand the cause of the variations in the equilibrium constant and the non-linear dependence of the hydration rate on the concentration of catalyst. That the change in the equilibrium constant was due merely to a variation in the activity of one of the participating species rather than to the formation of a new absorbing complex was established by two experiments.

The first test consisted in comparing the spectrum of an equilibrated solution in the presence of acetic acid with that in its absence. The former was provided by the solution 0.278 M. in acetic acid, whose kinetics are recorded in Table 19, and the latter by an analogous solution containing no acid; both were measured relative to solvent blanks and had final optical densities close to 0.5 absorbance units. The resulting optical densities, recorded on the SP500 instrument, are listed in Table 20 as fractions of their respective values at 285 mμ. The largest difference between the two columns is 2%, which shows that a new absorbing species can only be present in the unlikely event that its spectrum over this range is identical with that of the ketone.

TABLE 20

Effect of acetic acid on spectrum of ketone

λ(mμ)	relative optical densities	
	0.278M. AcOD	no acid present
320	0.323	0.323
310	0.562	0.559
300	0.810	0.803
290	0.972	0.967
285	1.00	1.00
280	0.986	0.992
270	0.858	0.866
260	0.656	0.667
250	0.491	0.482

For the second test the effect on the optical density of introducing catalyst into a solution which had been allowed to equilibrate without it was investigated. Three solutions were prepared:

(A) 20 ml. dioxan + 1.2 ml. H_2O + 0.18 g. sym-dichloroacetone,

(B) 20 ml. dioxan + 1.2 ml. H_2O,

(C) 20 ml. dioxan + 1.2 ml. 10 M. AcOH solution,

and were left for two days at 25°C. Mixing of equal volumes of (A) and (B) gave a solution of optical density 0.508, which remained constant over several hours, but when the process was repeated with (A) and (C), a solution was produced whose optical density rose over a period of about 20 minutes, giving in two experiments final optical densities of 0.567 and 0.563. In each case first order kinetic plots could be constructed, which allowed both back-extrapolation to initial optical densities of 0.497 and 0.494 and calculation of catalytic coefficients only 6% and 10% lower than that recorded in Table 22 for a solution of the same formal mole fraction of water and a somewhat lower catalyst concentration. In all cases appropriate solvent blanks were used in the reference cell. Although the smallness of the optical density change and the rapidity of the reaction ($t_{\frac{1}{2}} \simeq 4$ minutes) prevent undue significance from being attached to these measurements, it is clear that no absorbing complex can be rapidly formed between the catalyst and either the ketone or its hydrate. This conclusion is supported for the ketone by the ϵ^0 values recorded in Tables 18, 19, 22 and 23, while the slow formation of an absorbing complex is precluded by the observation of good first order kinetics for the runs recorded in these tables.

It can therefore be concluded that the changes in the equilibrium constant reflect changes in the activities of the components, most reasonably a decrease in the water activity. At least some of this decrease obviously arises from the way in which the solutions were made up, since the molarity of water in fairly concentrated aqueous acetic acid solutions can no longer be approximated to that in pure water. The possibility that some of the effect is also due to the removal of water in the reaction solutions by hydration of the acid is investigated in Chapter VI by means of experiments designed to produce more accurate equilibrium constants than those obtained here.

The above conclusions allow true catalytic constants at infinite dilution of the catalyst to be obtained from the plots in Figure (8), if the rate of change of the water catalysed rate with the catalyst concentration can be estimated in this region. In principle the latter can be obtained from the limiting variation of the equilibrium constant, equation (26), and the previously measured kinetic order of the water-catalysed dehydration rate with respect to water. The results of Chapter VI thus indicate the need for upward corrections of 5% and 7% to the slopes of the dehydration plots for deutero and proto catalysis, respectively, and such corrections are made before entering these rate constants in Tables 22 and 23.

(4) Kinetic orders and isotope effects

The usual set of experiments was carried out, measuring the rate of reaction in solutions made up by adding different volumes of the stock solutions (b) or (d) to a fixed volume of dioxan. These reactions had half-lives ranging from 4 to 70 minutes. Since the equilibrium constants are only known for the solutions investigated, the composite first order rate constant in each case was divided into its hydration and dehydration components, and from the latter of these was subtracted a value for the contribution of water catalysis, as calculated from the observed equilibrium constant, equation (26), and the measured kinetic order for water-catalysed dehydration. The largest correction for water catalysis was 12% of the total (for $x_w^\circ = 0.320$), made after a correction to the water-catalysed rate in the absence of catalyst of 21% of its value.

Since the ratio of the heavy to the light water equilibrium constants has a much greater influence on the isotope effect than their absolute magnitudes, values were chosen for these quantities which had the same geometric mean as the experimental values but which lay in the

TABLE 21

Smoothing of equilibrium constants

x_w^o	[catalyst] (M)	K_{dH} expl.	K_{dH} calc.	K_{dD} expl.	K_{dD} calc.
0.320	0.195	0.859	0.870	0.806	0.796
0.220	0.243	1.32	1.31	1.19	1.20
0.159	0.165	1.77	1.78	1.64	1.63
0.0859	0.0842	3.22	3.38	3.15	3.09

(x_w^o is a formal water mole fraction, referring to the analogous solution made up by volume in the absence of catalyst.)

TABLE 22

AcOH : variation of catalytic constants with x_w

x_w	$10^4 k_1$ (sec.$^{-1}$)	$10^3 k^c_{dH}$ (M^{-1}sec.$^{-1}$)	$10^3 k^c_{hH}$ (M^{-1}sec.$^{-1}$)	ϵ^c_{285} (M^{-1}cm.$^{-1}$)
0.320	29.3	6.13	7.91	29.5
0.273	-	6.31	7.14	28.0
0.220	25.3	5.73	5.56	29.2
0.159	14.2	5.40	4.12	29.0
0.0859	5.71	5.18	2.29	29.8

TABLE 23

AcOD : variation of catalytic constants with x_w

x_w	$10^4 k_1$	$10^3 k^c_{dD}$	$10^3 k^c_{hD}$	k^c_{hH}/k^c_{hD}	ϵ^c_{285}
0.320	9.64	1.99	2.81	2.81	29.7
0.273	-	1.94	2.40	2.97	28.5
0.220	8.14	1.79	1.90	2.93	27.6
0.159	4.64	1.72	1.43	2.88	28.7
0.0859	1.75	1.56	0.754	3.04	28.3

k^c_{hH}/k^c_{hD} (mean) = 2.94 ± 0.10

kinetic orders with respect to x_w: hydration 0.98, dehydration 0.19.
(units in table (23) are as in Table 22).

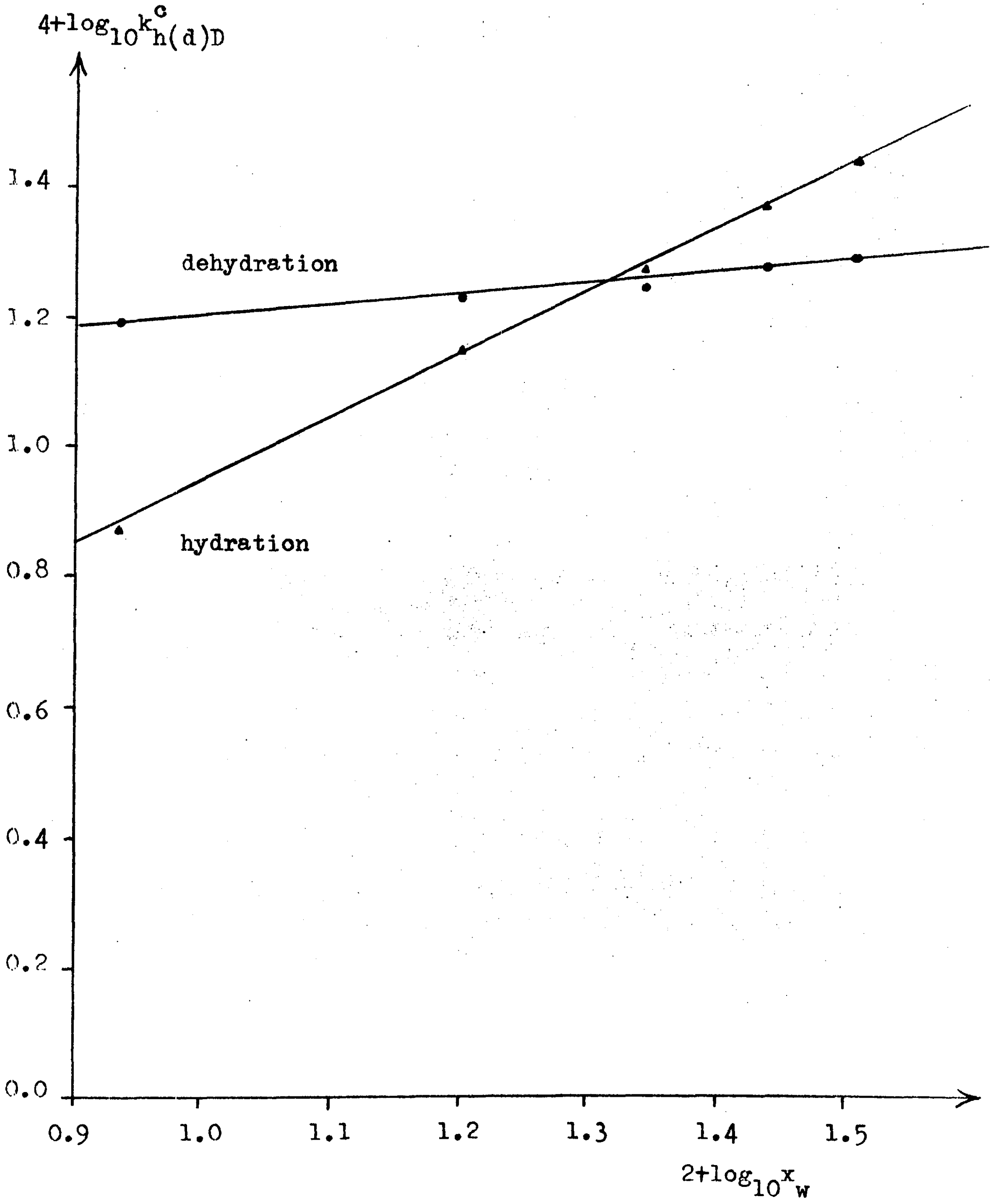
ratio 0.915 as found in Chapter IV. This approach was made possible by the virtual identity of the concentrations of the proto and deutero stock solutions. The experimental and smoothed equilibrium constants are recorded in Table 21, where it can be seen that the changes effected are rather small. The dehydration catalytic constants thus obtained were regarded as applying also to infinite dilution of the catalyst on the basis of the linear catalytic plot established above, and the corresponding hydration rate constants were then obtained by the use of the average equilibrium constants from Chapter IV.

The kinetic results are set out in Tables 22 and 23, in which the 0.5% difference in the concentrations of the proto and deutero solutions has been ignored. Corrections for water catalysis only amount to more than a few percent for the water mole fractions 0.320 and 0.273, so that the essential features of the results are not affected by the more tenuous aspects of the analysis. The application of this correction was checked for the results making up the first line of Table 23 by carrying out a run at the same formal deuterium oxide mole fraction and double the catalyst concentration; in the latter case the water-catalysed rate only amounted to 2-3% of the total, and the above analysis gave $k^c_{dD} = 1.98 \times 10^{-3}$ M^{-1}sec.$^{-1}$, in good agreement with the value quoted.

The kinetic orders of the infinite dilution acetic acid catalytic constants with respect to deuterium oxide mole fraction can be obtained from Figure (9). The results in heavy water have been used because these rates were considered to be better defined at the two highest mole fractions, but the approximate constancy of the experimental isotope effects demonstrates that essentially similar behaviour would be observed for the results in light water. Interpolation yields the composite catalytic constant 1.10×10^{-2} M^{-1}sec.$^{-1}$ in the presence of light water of mole fraction 0.199, which may be compared with the uncorrected value

FIGURE 9

Acetic acid: kinetic orders with respect to water mole fraction.



of 1.06 x 10^{-2} $M^{-1}sec.^{-1}$ obtained by Bell and Jensen (21). As for water-catalysis, but in contrast to catalysis by perchloric and hydrochloric acids, the present kinetic order plots are linear and of positive slope. The smallness of the dependence of the dehydration rate on the water mole fraction explains the linearity of the catalytic plots for dehydration (provided that water-catalysis is relatively unimportant), while the decrease of the hydration rate constants with x_w offers a similar explanation for the form of the hydration catalytic plots in Figure (8). Such considerations also serve to justify the analysis of the results presented in this section.

(5) Kinetic isotope effect in H_2O-D_2O mixture

Two runs were carried out at a formal water mole fraction of 0.273 in the presence of a mixture of the two waters. The reaction media were made up by adding 0.4 ml. each of light water and the stock solution of acetic acid in D_2O (e) to 10 ml. of dioxan. The results were as follows:

$$10^3k_1 = 1.36,\ 1.37\ sec.^{-1} \qquad mean = 1.36_5\ sec.^{-1}$$

The deuterium atom fraction n in these solutions was calculated to be 44.6% from the molarity of solution (e) and the relative quantities of acetic anhydride and heavy water used in making it, or 45.0% from the density measurements described in Chapter VI; the average value n = 44.8% is used here.

The above experimental first order rate constant must be divided into its hydration and dehydration components, and these then corrected for the contribution due to water-catalysis. The equilibrium constant was taken as 0.96 by linear interpolation between the appropriate value in the proto series and the average of the two corresponding values in the deutero series, all having the same acid concentration; these are both 12% larger than the corresponding values at zero acid concentration. This interpolated value was preferred to the average experimental one of 0.98 on the grounds that the ratio of the equilibrium constants has a much larger influence on the isotope effect than their absolute values, but the use of the latter would only change the individual rates by 1%. The component first order rate constants may now be written as:

$$k_{hHD} = 6.96 \times 10^{-4} \text{ sec.}^{-1}, \quad k_{dHD} = 6.69 \times 10^{-4} \text{ sec.}^{-1}$$

For the sake of consistency the dehydration rate was corrected for the water-catalysed contribution by the same procedure as was used to obtain the catalytic coefficients from the catalytic plots, i.e. the water-catalysed rate in the absence of catalyst was subtracted, and the difference corrected upwards by 6% and divided by the catalyst concentration. The required rate of water catalysis at n = 44.8% was obtained from a smooth curve of rate against n, using the data appropriate to $x_w = 0.273$ from Tables 8 - 10. The resulting value, $k_{dHD} = 5.84 \times 10^{-5}$ sec.$^{-1}$, should be accurate enough for the purpose of this correction. By this process k^c_{dHD} was found to be 3.84×10^{-3} M^{-1}sec.$^{-1}$, from which was calculated the value $k^c_{hHD} = 4.57 \times 10^{-3}$ M^{-1}sec.$^{-1}$ through the assumption of an equilibrium isotope effect of 5.0% for n = 44.8%. The required kinetic isotope effect therefore becomes

$$k^c_{hH}/k^c_{hHD} = 1.56,$$

where the subscript HD here refers to n = 44.8%. The calculation of this quantity has involved a fairly large number of corrections, but these were mainly small and related to the corrections applied to obtain k^c_{hH}/k^c_{hD}.

(6) Test for C-H isotopic substitution

It is convenient at this stage to report a test by p.m.r. for deuterium substitution in the alkyl portion of the ketone, since this was carried out in the presence of acetic acid catalyst. A solution containing 0.2894 g. of sym-dichloroacetone and 0.1290 g. of 'Analar' grade glacial acetic acid together with 5 ml. of dioxan and

0.4 ml. of deuterium oxide was made up by weight. Its p.m.r. spectrum was run after 12 hours and again after 10 days, and in both cases the ketone CH_2 peak and the acid CH_3 peak had heights in the approximate ratio 4:5. This result allows the relative amounts of ketone and hydrate to be estimated from the stoichiometric composition of the solution, the hydrate peak being presumably hidden by that of dioxan 0.8 p.p.m. upfield from the ketone; the approximate K_d value is 1.30, which is not far from the expected figure. It may therefore be concluded that the alkyl hydrogens of the ketone suffer negligible isotopic exchange in a period 1000 times longer than the half-life for hydration, and that such exchange may reasonably be neglected in interpreting the experimental results in general.

(E) CATALYSIS BY MONOCHLOROACETIC ACID

(1) Preparation of solutions

'Analar' monochloroacetic acid was obtained from B.D.H., and used without further purification. As in the previous case the relatively high ratio of catalyst to water concentrations required to give reasonably fast rates made it necessary to deuterate the catalyst before making up the solution in heavy water. This was achieved in the present case by repeated solution of the solid in deuterium oxide and evaporation of the solvent. 6 g. of the acid were dissolved in 10 ml. of D_2O in a 100 ml. round-bottomed flask and rotated in a flash evaporator under vacuum at 60-80°C. for one hour. The residue, which crystallised on cooling, was dissolved in a further batch of solvent, and the process repeated two times in all. The 5 g. of solid eventually recovered were dissolved in 25 ml. of heavy water to give solution (a). This was titrated in 2 ml. aliquots against standard 1 M. sodium hydroxide solution from a microburette using phenolphthalein as indicator, the sodium hydroxide solution having been made up from B.D.H. concentrated volumetric solution.

Another sample of solid was subjected to the above procedure with the use of light water as solvent, as a check against any unforeseen complications. This was dissolved in water to give a rather more concentrated solution than (a), titrated against the same sodium hydroxide solution, and then diluted to give as closely similar a concentration to that of (a) as possible. It was finally re-titrated and labelled (b). Solution (c) was made up by simply dissolving the acid in water, and was standardised by titration against the same sodium hydroxide solution. The concentrations of the above stock solutions were found to be:

$CH_2ClCOOD$ in D_2O: (a) 1.82 M.

$CH_2ClCOOH$ in H_2O: (b) 1.83 M., (c) 2.76 M.

After two weeks a p.m.r. spectrum of (a) was run. Two singlets were observed, one due to the CH_2 protons, and the other 0.5 p.p.m. downfield attributable to the exchangeable protons. The ratio of the peak intensities was 4:1, from which the protium atom fraction was calculated to be 0.8%, i.e. the same figure as for the deuterium oxide itself as recorded in Chapter III. This showed that the deuterating procedure was effective, that no exchange of the CH_2 protons had occurred, and that the precautions taken against the intrusion of atmospheric moisture during two weeks of kinetic experiments were satisfactory.

(2) <u>Catalytic plots</u>

The reaction solutions were made up in the usual way, and catalytic plots were constructed for both proto and deutero solutions at a formal water mole fraction of 0.273. The results are set out in Tables 24 and 25, and plotted in Figure (10). The equilibrium constants again show an upward trend with catalyst concentration, but this is less marked than in the previous case since the stronger catalytic effect of monochloroacetic acid made the use of such high concentrations neither necessary nor possible. The dehydration rates for both isotopes are linear in catalyst concentration, while curvature of the hydration plots is apparent. Rate constants at infinite dilution can be obtained from the dehydration plots as before, and in this case the corrections to the deutero and proto slopes amount to 3% and 4% respectively. The corrected rates are entered in Tables 27 and 28.

(3) <u>Kinetic orders and isotope effects</u>

Kinetic runs over a range of water concentrations were carried out as in the case of acetic acid, using the stock solutions (a) and (b) of nearly identical concentrations. The results were similarly analysed, and the largest correction for water catalysis amounted to 12% of the total dehydration rate, made as usual for the

TABLE 24

$CH_2ClCOOH$: formal catalytic plot for x_w^o = 0.273

$[CH_2ClCOOH]$(M)	K_{dH}	10^4k_{hH}(sec.$^{-1}$)	10^4k_{dH}(sec.$^{-1}$)	ϵ^o_{285}(M^{-1}cm.$^{-1}$)	stock solution
0.0169	0.887	3.83	3.39	28.2	(b)
0.0339	0.916	5.95	5.45	29.0	(b)
0.0508	0.933	7.92	7.38	28.8	(b)
0.0512	0.918	7.98	7.32	27.9	(c)
0.0677	0.957	9.81	9.39	29.7	(b)

Apparent k^c_{dH} = 1.18 x 10^{-2} M^{-1}sec.$^{-1}$

TABLE 25

CH_2ClOOD : formal catalytic plot for x_w^o = 0.273

$[CH_2ClCOOD]$(M)	K_{dD}	10^4k_{hD}(sec.$^{-1}$)	10^4k_{dD} (sec.$^{-1}$)	ϵ^o_{285}(M^{-1}sec.$^{-1}$)
0.0169	0.827	1.18	0.973	29.6
0.0337	0.832	1.87	1.56	29.1
0.0506	0.833	2.65	2.20	27.9
0.0674	0.863	3.26	2.82	27.7
0.101	0.884	4.64	4.11	28.8
0.135	0.929	5.75	5.35	27.5

Apparent k^c_{dD} = 3.76 x 10^{-3} M^{-1}sec.$^{-1}$

TABLE 26

Smoothing of equilibrium constants

x_w^o	[catalyst](M)	K_{dH}		K_{dD}	
		expl.	calc.	expl.	calc.
0.320	0.0831	0.872	0.863	0.783	0.790
0.220	0.0517	1.09	1.09	0.989	0.993
0.159	0.0352	1.38	1.39	1.28	1.27
0.0859	0.0179	2.25	2.25	2.06	2.06

TABLE 27

$CH_2ClCOOH$: variation of catalytic constants with x_w

x_w	$10^4 k_1$ (sec.$^{-1}$)	$10^3 k^c_{dH}$ (M^{-1}sec.$^{-1}$)	$10^3 k^c_{hH}$ (M^{-1}sec.$^{-1}$)	ϵ^c_{285} (M^{-1}cm.$^{-1}$)
0.320	26.5	13.0	16.8	27.8
0.273	-	12.3	13.9	28.7
0.220	12.8	12.6	12.2	29.9
0.159	7.04	10.8	8.24	28.0
0.0859	2.61	9.82	4.35	25.4

TABLE 28

$CH_2ClCOOD$: variation of catalytic constants with x_w

x_w	$10^4 k_1$	$10^3 k^c_{dD}$	$10^3 k^c_{hD}$	k^c_{hH}/k^c_{hD}	ϵ^c_{285}
0.320	8.39	4.06	5.73	2.93	29.2
0.273	-	3.87	4.78	2.91	28.4
0.220	3.98	3.78	4.01	3.04	30.9
0.159	2.20	3.33	2.78	2.96	30.0
0.0859	0.884	3.29	1.59	2.74	28.7

k^c_{hH}/k^c_{hD} (mean) = 2.92 ± 0.13

kinetic orders with respect to x_w: hydration 0.98, dehydration 0.19 (units in Table 28 are as in Table 27).

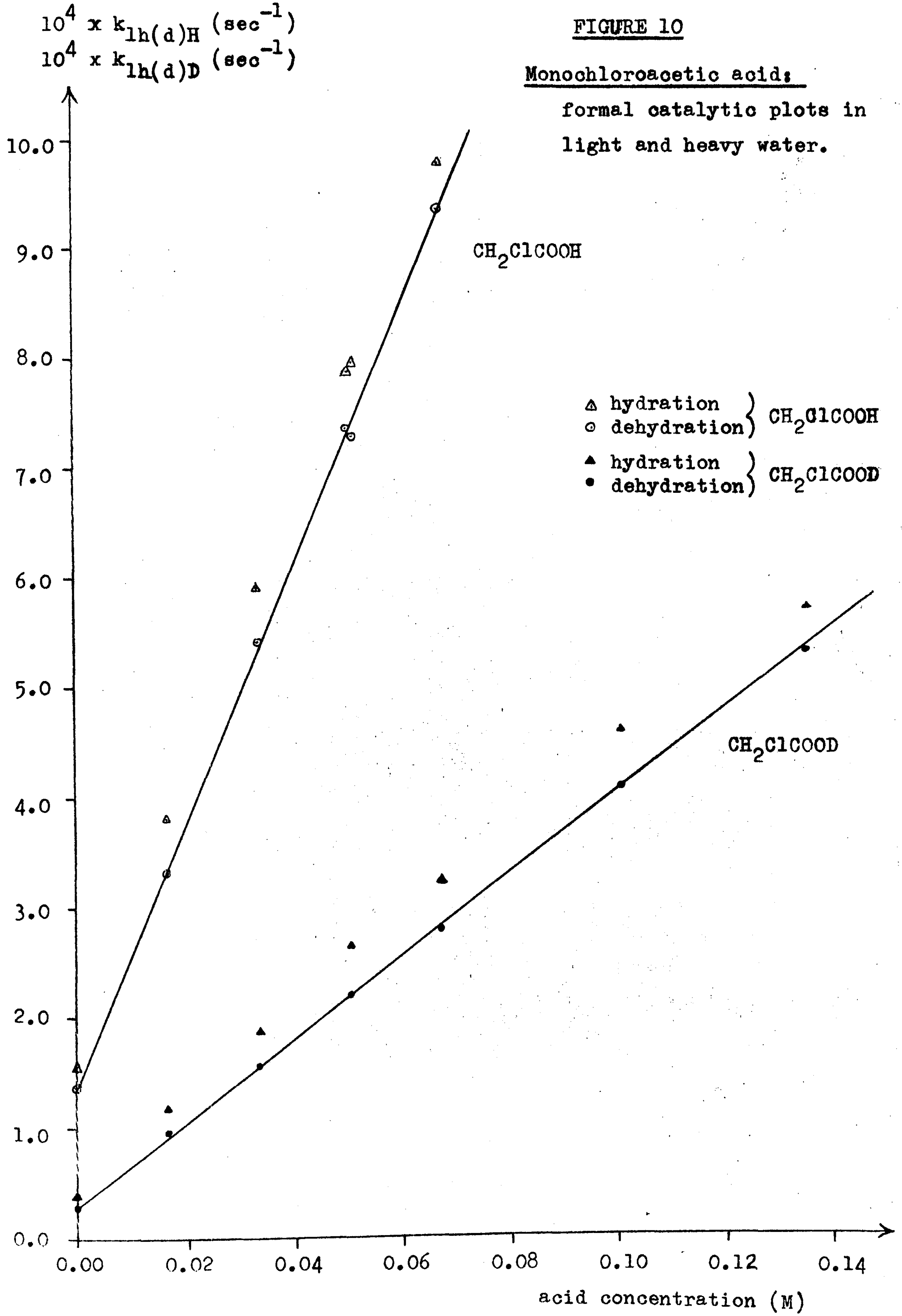


FIGURE 10

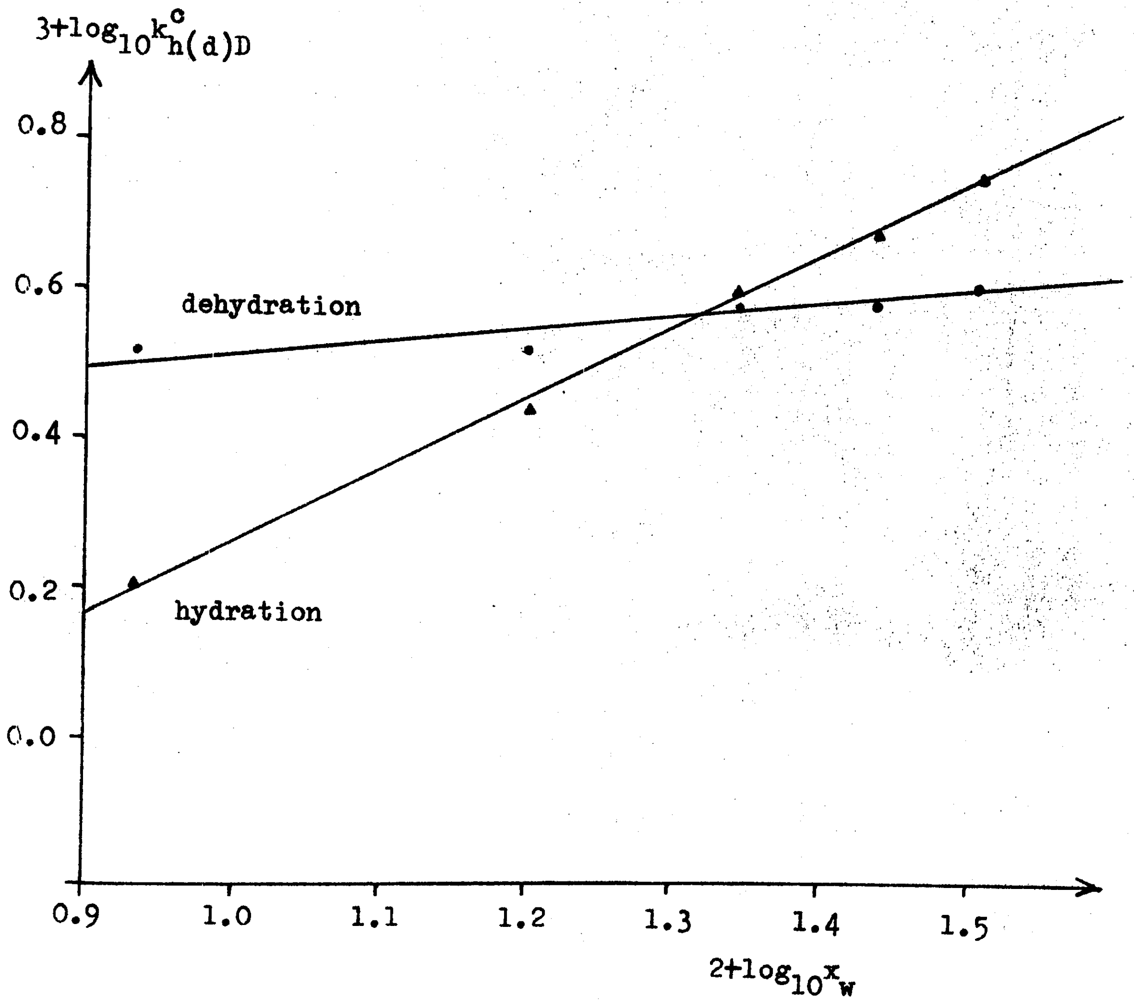
Monochloroacetic acid: formal catalytic plots in light and heavy water.

solution having a formal mole fraction of light water of 0.320. The latter was the fastest run of the series, having a half-life of 4½ minutes, while the slowest had a half-time of 130 minutes. The kinetic order plots for the deutero reactions are reproduced in Figure (11), and the fifth column of Table 28 shows that very similar plots would be obtained from the results obtained in the presence of light water.

The kinetic orders with respect to water and the average kinetic isotope effects are identical within experimental error with those found for acetic acid. Similarly the difference of 2% between the most closely defined values of the kinetic isotope effect for the two catalysts, i.e. those at $x_w = 0.273$, is possibly not experimentally significant. The rate constants in the present case are about twice those found for acetic acid, and in particular interpolation from Figure (11) and combination with the average isotope effect from Table 28 yields a composite catalytic constant at the light water mole fraction 0.199 of 2.23×10^{-2} $M^{-1}sec.^{-1}$, which may be compared with the uncorrected value of 2.12×10^{-2} $M^{-1}sec.^{-1}$ found by Bell and Jensen (21).

FIGURE 11

Monochloroacetic acid: kinetic orders with respect to water mole fraction.



(F) CATALYSIS BY TRICHLOROACETIC ACID

(1) Preparation of solutions

'Analar' trichloroacetic acid was obtained from B.D.H., and a sample was purified and dried by sublimation at 40-60°C. under $1\frac{1}{2}$ mm. pressure. After four hours about 1 g. had collected on the cold finger as a solid glassy shell, which picked up water from the air much more slowly than the original finely divided crystals. Two 25 ml. solutions in heavy and light water were made up accurately from this material, and their concentrations checked by titrating 2 ml. portions against 0.1 M. sodium hydroxide solution, which had been standardised against 0.2 M. hydrochloric acid made up from B.D.H. concentrated volumetric solution. The light water solution was then diluted to bring it to the same concentration as that in D_2O, and was finally titrated against the same solution of sodium hydroxide. These stock solutions had the following concentrations:

CCl_3COOH in H_2O: 0.159 M., CCl_3COOD in D_2O: 0.159 M.

The additional 0.15 atom % of protium thus introduced into the deutero solution was neglected.

(2) Catalytic plots

A series of runs was performed as before at a formal water mole fraction of 0.273. The results are presented in Tables 29 and 30, and plotted in Figure (12). The equilibrium constants in Table 29 provide no evidence for a trend with catalyst concentration, and this is supported by the measurements of Chapter VI. For the deutero solutions a monotonic variation is observable, but this is almost certainly spurious and is in any case small. It was therefore considered preferable to return to the procedure of plotting the composite rate constants against catalyst concentration, since division into the separate hydration and dehydration contributions by the use of the experimental equilibrium constants inevitably introduces additional experimental errors.

TABLE 29

CCl_3COOH : catalytic plot for x_w = 0.273

$[CCl_3COOH]$(M)	10^4k_1(sec.$^{-1}$)	K_{dH}	ϵ^o_{285}(M^{-1}cm.$^{-1}$)
0.00295	6.93	0.872	28.0
0.00590	10.5	0.932	27.1
0.00590	10.4	0.900	28.6
0.00885	13.7	0.916	26.9
0.0103	16.1	0.878	not measured
0.0118	17.6	0.896	26.6

K_{dH} (mean) = 0.899 (K^o_{dH} = 0.884)

k^c_H = 0.126 M^{-1}sec.$^{-1}$

TABLE 30

CCl_3COOD : catalytic plot for x_w = 0.273

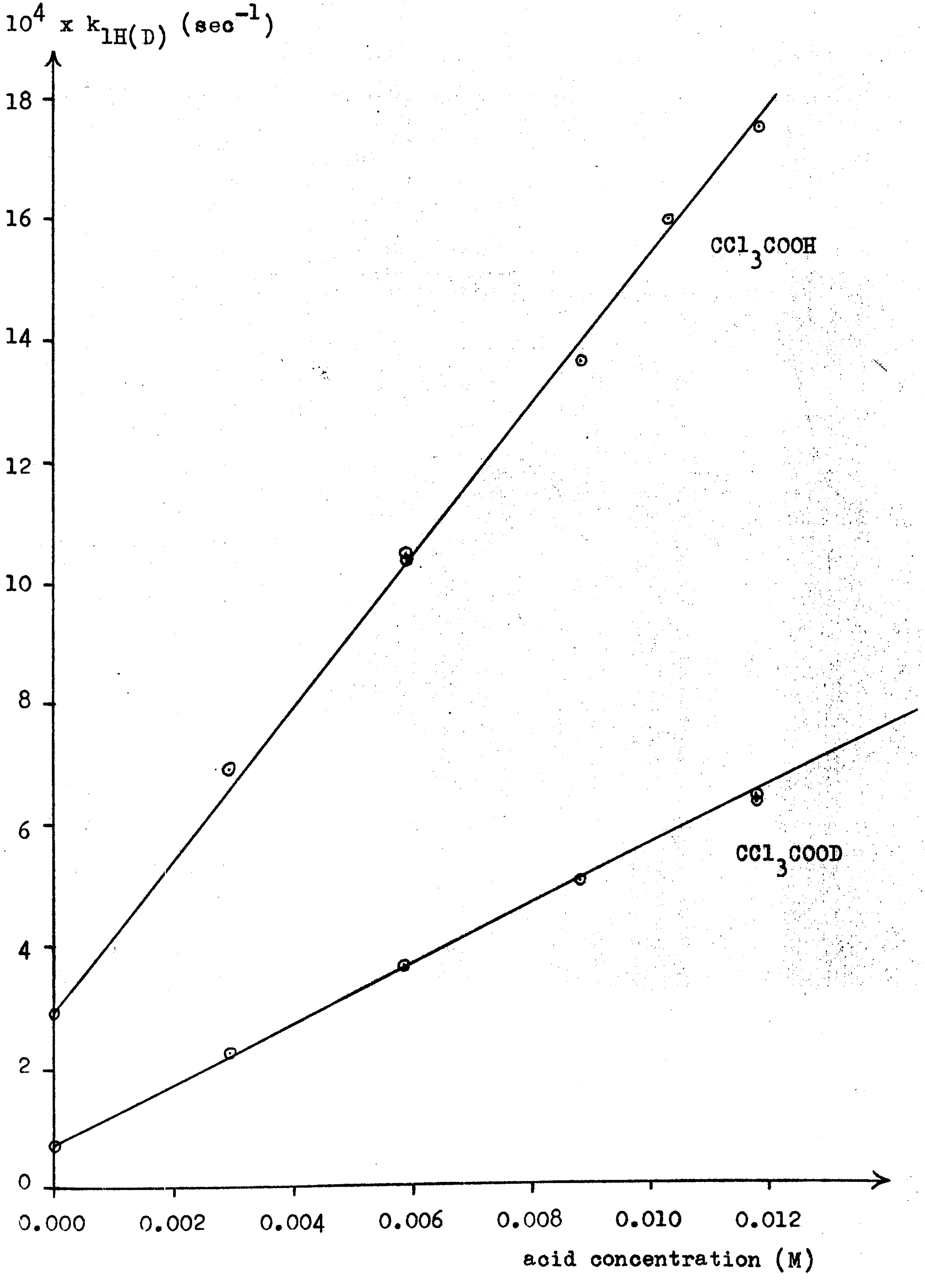
$[CCl_3COOD]$(M)	10^4k_1(sec.$^{-1}$)	K_{dD}	ϵ^o_{285}(M^{-1}cm.$^{-1}$)
0.00294	2.25	0.781	not measured
0.00588	3.66	0.795	28.8
0.00883	5.09	0.803	26.3
0.0118	6.41	0.845	29.0
0.0118	6.46	0.822	28.3

K_{dD} (mean) = 0.809 (K^o_{dD} = 0.809)

k^c_D = 0.0495 M^{-1}sec.$^{-1}$, therefore k^c_H/k^c_D = 2.54

FIGURE 12

Trichloroacetic acid: catalytic plots in light and heavy water.



(3) Kinetic orders and isotope effects

A series of runs was carried out over a range of light water mole fractions, and the results are set out in Table 31. Division of the composite catalytic constant has been effected by the use of the average equilibrium constants of equation (26), but the standard deviation relative to these of the experimental values listed in the table is only 2%. The contribution of the water-catalysed reaction at $x_w = 0.190$ was assessed by interpolation from Figure (2), and the largest correction made for water catalysis was of 13%.

TABLE 31

CCl_3COOH : variation of catalytic constants with x_w

x_w	$10^3[CCl_3COOH]$ (M)	$10^2k^c_{hH}$ ($M^{-1}sec.^{-1}$)	$10^2k^c_{dH}$ ($M^{-1}sec.^{-1}$)	K_{dH}	ϵ^o_{285} ($M^{-1}cm.^{-1}$)
0.273	2.95-11.8	6.66	5.89	0.899	27.4
0.220	9.02	5.50	5.66	1.04	27.6
0.190	7.59	4.89	5.59	1.20	29.0
0.159	6.13	4.25	5.56	1.34	29.5
0.0859	3.12	2.31	5.21	2.26	28.7

The series of runs with the heavy water solutions was mostly carried out by a different technique from that described in section (A) and used hitherto. This consisted in initiating the reactions by injecting an aqueous solution of the catalyst into a solution of the ketone in dioxan contained in the spectrophotometric cell, by which method, apart from the general desirability of using more than one technique, it was hoped that more accurate measurements of ϵ^o_{285} in aqueous dioxan would be obtained. The injection was carried out by means of a Hamilton syringe (CR 700-200), in which release of a spring drove a teflon-tipped plunger down a glass barrel from a pre-set position, thus rapidly expelling a fixed volume of liquid through the stainless steel needle.

A number of preliminary tests were carried out to check certain features of the operation. The reproducibility of the volume delivered by the syringe decreased from ± 0.1% for its maximum volume of 0.2 ml. to ± 0.5% for 0.04 ml., so that in the present experiments the volume added was kept above 0.1 ml. The accuracy was found to fall off much more sharply, and the syringe was therefore graduated before each experiment using a volume of the stock solution close to that required. Experiments with potassium permanganate solution established firstly that, if the end of the needle was held close to the bottom of the liquid already in the cell, the force of ejection was sufficient to cause instant mixing of the solutions, and secondly that the optical density of a solution in a 1 cm. cell in the SP500 instrument was only independent of its volume provided that this exceeded 2.3 ml. Finally tests with thermocouples showed that, if the syringe was first filled several times with the thermostatted solution to be added, addition of 0.2 ml. to ten times its volume in the thermostatted cell compartment changed the temperature by less than 0.02°C.

For the purpose of these runs a stock solution of sym-dichloroacetone in dioxan was prepared, and its optical density at 25°C. measured relative to the pure solvent. About 2½ ml. each of this solution and pure dioxan were put in the sample and reference cells respectively, the exact amounts determined by weight, and both the two cells and the stock solution of acid in D_2O left to attain temperature equilibrium. The calculated volumes of the latter were then added by means of the syringe to the reference and sample cells, and a stop-watch started at the appropriate moment. The first reading could be taken after one minute, after which time the optical density in the fastest run had dropped by 2-3%. All these experiments were performed on the SP500 instrument, used as usual in the null balance mode. The above technique was used by way of a test for the duplicate run recorded on the last line of table 30.

The kinetic results are reported in Table 32, and have been analysed as before by means of the equilibrium data from Chapter IV. The largest correction applied for the water-catalysed reaction amounted to 13% of the observed first order rate constant. The technique described above was used for the reactions in solutions of $x_w > 0.159$, while the remaining two were carried out by the more usual method of adding the solid ketone. The variation of the catalytic constants with deuterium oxide mole fraction is shown in Figure 13, from which it is apparent that the kinetic orders are very similar to or just a little less than those found for acetic and monochloroacetic acids. Interpolation yields a composite catalytic constant of 0.106 M^{-1} sec.$^{-1}$ at x_w = 0.199 in the presence of light water, which may be compared with the value of 0.110 M^{-1}sec.$^{-1}$ found by Bell and Jensen (21).

TABLE 32

CCl_3COOD : variation of catalytic constant with x_w

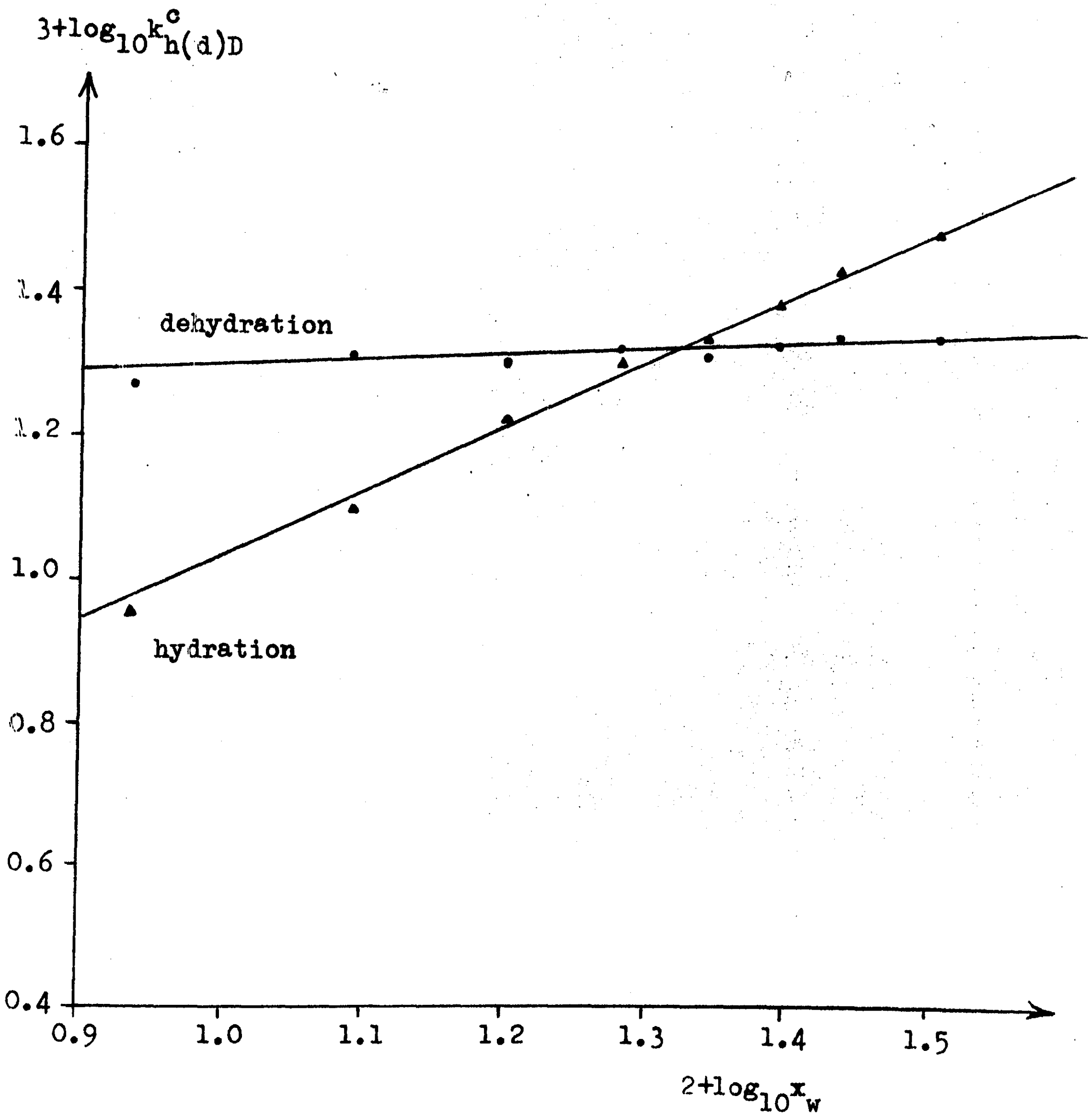
x_w	$10^3[CCl_3COOD](M)$	$10^2k^c_{hD}(M^{-1}sec.^{-1})$	$10^2k^c_{dD}(M^{-1}sec.^{-1})$
0.320	14.4	3.10	2.20
0.273	2.94-11.8	2.74	2.21
0.247	10.4	2.47	2.14
0.220	9.00	2.20	2.07
0.190	7.57	2.03	2.13
0.159	6.11	1.68	2.02
0.123	4.63	1.26	2.05
0.0859	3.12	0.903	1.87

kinetic orders with respect to x_w: hydration 0.91, dehydration 0.09

The other data obtained from these experiments are presented in Table 33. Comparison of the equilibrium constants with those expected on the basis of the results of Chapter IV, designated

FIGURE 13

Trichloroacetio acid: kinetic orders with respect to water mole fraction.



'(calc.)', suggests that the catalyst causes no significant increase, although experimental errors at low x_w are present as usual. The percentage decrease of the initial extinction coefficient at 285 mμ relative to its value in dry dioxan, although of the same order of magnitude as the amount by which the optical density readings have been back-extrapolated, is evidently real; these figures provide some basis for the comparison presented in Chapter IV between the equilibrium constants derived by those two different approaches. The calculation of $\Delta\epsilon^{\circ}/\epsilon^{\circ}$ has neglected the volume change of mixing of water and dioxan. From the density measurements of Hovorka, Schaefer, and Dreisbach (109) and of Griffiths (110) this effect should increase the extinction coefficient change by 0.2-0.3%. The smallness of the scatter in the results of the fourth column of Table 33 suggests that partial hydration of the solid ketone and/or errors in the weighings, but not in the back-extrapolation of the optical density readings, are responsible for the much larger variations in the extinction coefficients normally found.

TABLE 33

Equilibrium constants, extinction coefficients, and kinetic isotope effects

x_w	K_{dD}(expl.)	K_{dD}(calc.)	$-\Delta\epsilon^{\circ}/\epsilon^{\circ}$ (%)	k^c_{hH}/k^c_{hD}
0.320	0.740	0.709	1.7	-
0.273	0.809	0.809	2.0	2.43
0.247	0.850	0.864	1.1	-
0.220	0.938	0.943	1.1	2.50
0.190	1.08	1.05	1.3	2.41
0.159	1.27	1.20	2.0	2.53
0.123	1.44	1.63	-	-
0.0859	1.95	2.07	-	2.56

k^c_{hH}/k^c_{hD} (mean) = 2.46 ± 0.08

(4) Isotope effects in H_2O-D_2O mixtures

Three runs were carried out at a total water mole fraction of 0.273 by introducing solid ketone into a solution made up by adding equal volumes of light water and the deutero stock solution to dioxan. In all cases the acid concentration was 0.00588 M., and the individual results were:

$10^4 k_1$(sec.$^{-1}$) = 6.74, 6.78, 6.56, mean = 6.69

K_{dHD} = 0.840, 0.850, 0.834, mean = 0.841

ϵ^{o}_{285}(M^{-1}cm.$^{-1}$) = 29.9, 28.2, 29.6, mean = 29.2

In the absence of catalyst $k_1 = 1.52 \times 10^{-4}$ sec.$^{-1}$; therefore, $k^{c}_{HD} = 8.79 \times 10^{-2}$ M^{-1}sec.$^{-1}$, $k^{c}_{H}/k^{c}_{HD} = 1.43$, and $k^{c}_{hH}/k^{c}_{hHD} = 1.40$

Use has been made of the equilibrium isotope effect of 5.5% from Chapter IV, whereas combination of the above average experimental equilibrium constant with the smoothed K_{dH} value for $x_w = 0.273$ would correspond to an isotope effect of 4.9%. The rather complicated series of corrections which were necessary in the analogous work with acetic acid is not needed here, on account of the much lower catalyst concentration employed.

(G) CATALYSIS BY BENZOIC ACID

(1) Preparation of solutions

Benzoic acid (laboratory reagent grade) was obtained from B.D.H., and purified by twice recrystallising from hot water. After drying at 50°C. in a Gallenkamp vacuum drying apparatus (DK-720) containing silica gel for 12 hours, the melting point was found to be 122-122.5°C. (lit. 122.4°C. (102), 122°C. (103)). About 5 g. of this material was recrystallised from two 10 ml. portions of heavy water to produce deutero-benzoic acid of at least 99% isotopic purity, which on final solution in the reaction mixture should contain a negligible proportion of protium; the deuterated substance had m.p. 120.5-121°C.

Since stock aqueous solutions of benzoic acid could not be made up, a different technique was called for. Instead stock solutions of aqueous dioxan were made up by weight, and 10 ml. aliquots added to weighed amounts of catalyst; 5 ml. of this served in each case as the reaction medium, the remainder being used as the reference. The reactions were recorded on the SP700 recording instrument, the only spectrophotometer possessed at the time, and readings were taken at 300 mμ because of the high absorption of the acid at lower wavelengths.

(2) Results

Sets of proto and deutero runs were performed at two different water mole fractions, and the results are set out in Tables 34 - 37. Although rather less accurate on account of the use of the recording instrument, the equilibrium constants show a qualitatively similar trend with catalyst concentration to that observed for acetic and monochloroacetic acids. Accordingly the experimental equilibrium constants have been used to separate the composite first order rate constants into those for hydration and dehydration, and these quantities are plotted in Figures (14) and (15).

TABLE 34

PhCOOH : formal catalytic plot for $x_w^{o} = 0.292$

[PhCOOH](M)	K_{dH}	10^4k_{hH}(sec.$^{-1}$)	10^4k_{dH}(sec.$^{-1}$)	ϵ^{o}_{300}(M^{-1}cm.$^{-1}$)
0.0140	0.856	3.42	2.93	23.6
0.0567	0.901	7.68	6.92	23.2
0.0747	0.887	9.64	8.56	22.6
0.106	0.913	12.2	11.1	24.9
0.155	0.904	17.3	15.6	23.5

$K^{o}_{dH} = 0.839$ Apparent $k^{c}_{dH} = 9.17 \times 10^{-3}$ M^{-1}sec.$^{-1}$

TABLE 35

PhCOOD : formal catalytic plot for $x_w^{o} = 0.292$

[PhCOOD](M)	K_{dD}	10^4k_{hD}(sec.$^{-1}$)	10^4k_{dD}(sec.$^{-1}$)	ϵ^{o}_{300}(M^{-1}cm.$^{-1}$)
0.0387	0.788	1.96	1.54	24.1
0.0643	0.822	2.78	2.29	23.6
0.114	0.928	4.36	4.05	23.7
0.161	0.879	6.07	5.33	23.0

$K^{o}_{dD} = 0.768$ Apparent $k^{o}_{dD} = 3.14 \times 10^{-3}$ M^{-1}sec.$^{-1}$

TABLE 36

PhCOOH : formal catalytic plot for $x_w^{o} = 0.0875$

[PhCOOH](M)	K_{dH}	10^4k_{hH}(sec.$^{-1}$)	10^4k_{dH}(sec.$^{-1}$)	ϵ^{o}_{300}(M^{-1}cm.$^{-1}$)
0.0504	2.23	1.97	4.38	23.6
0.106	2.41	3.96	9.54	24.7
0.141	2.47	4.99	12.3	24.4
0.191	2.48	6.32	15.7	24.0

$K^{o}_{dH} = 2.19$ Apparent $k^{c}_{dH} = 8.70 \times 10^{-3}$ M^{-1}sec.$^{-1}$

FIGURE 14

Benzoic acid: formal catalytic plots in light and heavy water at $x_W^o = 0.292$

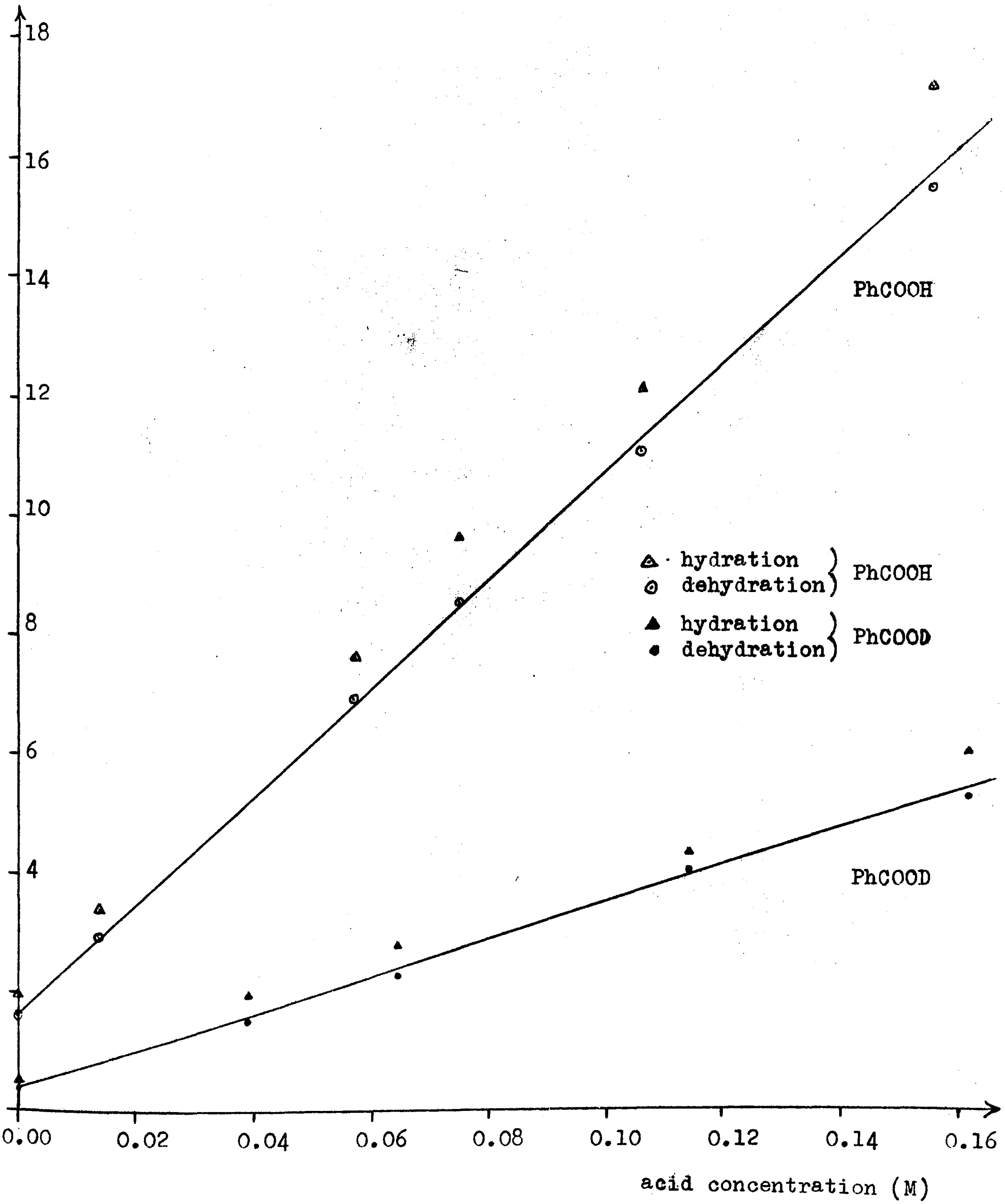
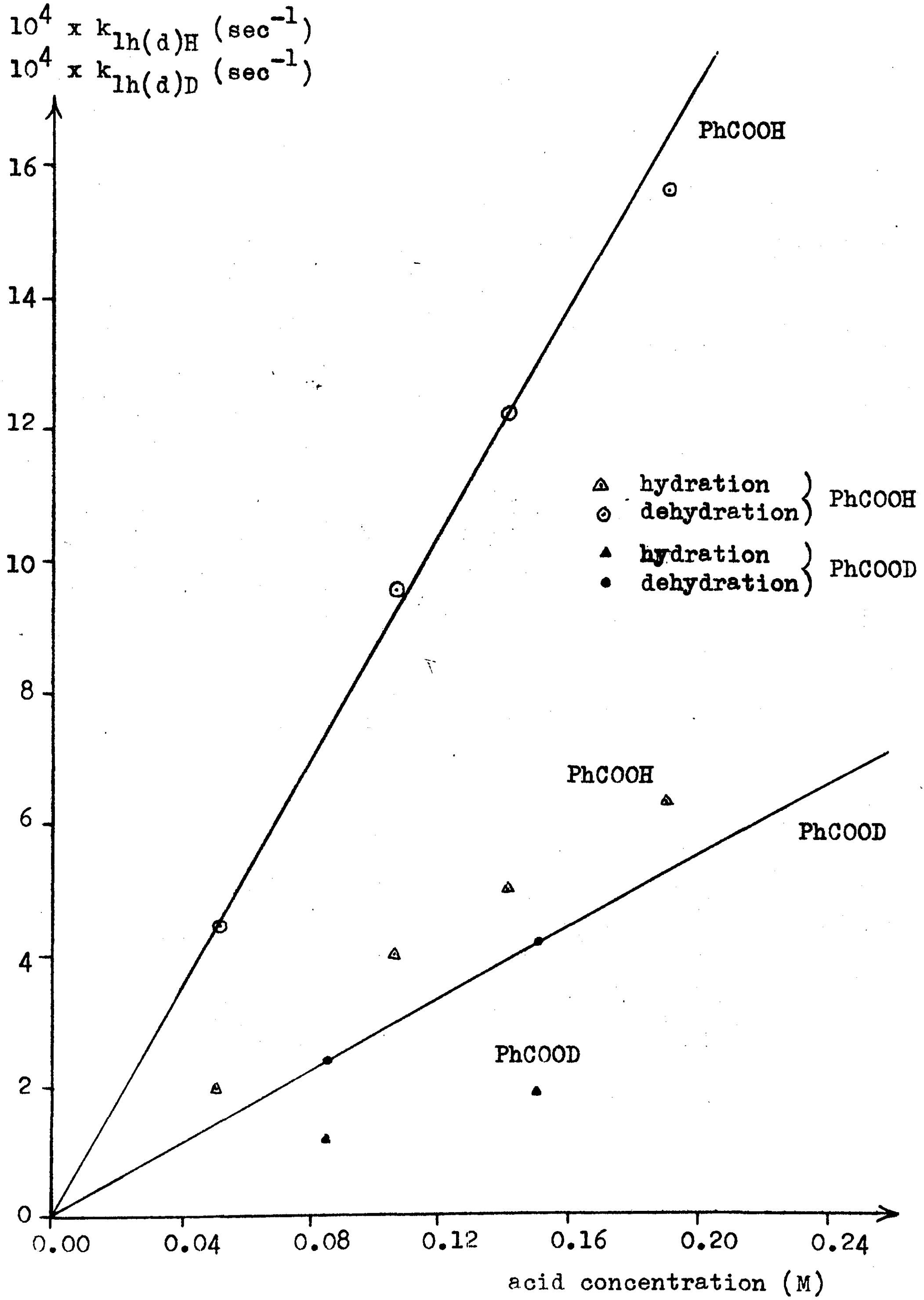


FIGURE 15

Benzoic acid: formal catalytic plots in light and heavy water at $x_w^o = 0.0875$



The average extinction coefficient of the ketone at 300 mμ is 23.9, which may be compared with the value 23.5 in dry dioxan.

The results for the lower water mole fraction, where the ratios of catalyst to water concentration are higher, show the characteristic curvature of the hydration plots and the at least more nearly linear shape of those for dehydration. Straight lines have been drawn through the latter for both water mole fractions by analogy with the other carboxylic acids. The correction for the rate of decrease of the water-catalysed rate with increasing catalyst concentration can be estimated from the equilibrium constants at $x_w^o = 0.292$ to be about 4% for the proto and 3% for the deutero series at this water mole fraction, giving the corrected catalytic constants for limitingly small catalyst concentrations presented in Table 38. The smallness of the water-catalysed rate at $x_w^o = 0.0875$ makes such a correction negligible in this case. The K_d^o values quoted at the foot of each table are calculated from equation (26) and the mean equilibrium isotope effect of 8.5%. It is interesting that the water activity appears to decrease with increasing catalyst concentration even when the stoichiometric mole fraction of the water decreases by less than 2%.

The kinetic orders of reaction have been calculated for the deutero solutions for the sake of consistency with the other carboxylic acids; those for the proto reactions would be 0.05 units less in each case. The 6% difference between the two measurements of the kinetic isotope effect is not much larger than the variations in the results for the other catalysts. The kinetic orders and the isotope effect are intermediate between those found for trichloroacetic acid on the one hand and acetic and monochloroacetic acids on the other.

Interpolation from the above results yields a composite

TABLE 37

PhCOOD : formal catalytic plot for $x_w^\circ = 0.0875$

[PhCOOD](M)	K_{dD}	$10^4 k_{hD}$(sec.$^{-1}$)	$10^4 k_{dD}$(sec.$^{-1}$)	ϵ°_{300}(M^{-1}cm.$^{-1}$)
0.0842	1.99	1.18	2.34	25.0
0.150	2.22	1.88	4.18	25.1

$K^\circ_{dD} = 2.00$ Apparent $k^c_{dD} = 2.77 \times 10^{-3}$ M^{-1}sec.$^{-1}$

TABLE 38

Kinetic orders and isotope effects

x_w	$10^3 k^c_{hH}$	$10^3 k^c_{dH}$	$10^3 k^c_{hD}$	$10^3 k^c_{dD}$
0.292	11.4	9.54	4.21	3.23
0.0875	3.97	8.70	1.38	2.77

(contents of last four columns have units M^{-1}sec.$^{-1}$)

Kinetic orders in D_2O with respect to x_w: hydration 0.92, dehydration 0.13

Isotope effects:

x_w	0.292	0.0875
k^c_{hH}/k^c_{hD}	2.70	2.87

……………………

catalytic constant of 1.74×10^{-2} M^{-1}sec.$^{-1}$ at $x_w = 0.199$, compared with the value 1.80×10^{-2} M^{-1}sec.$^{-1}$ found by Bell and Jensen (21). Comparison with the work of Bell, Millington, and Pink (6) is complicated by the scatter in their results, but it can nevertheless be seen that the lower kinetic orders found in their work (hydration 0.69, dehydration −0.2) are chiefly due to the observation of composite rate constants at low water mole fractions which are higher than found in the present study. Since similar remarks apply to water catalysis, it is perhaps tempting to suggest that their dioxan was not perfectly dry, but this would still leave unexplained the higher rates found by these workers for hydrochloric acid catalysis. The previous workers also did not observe any systematic variation of the equilibrium constants with benzoic acid concentration, but this has a minor effect on the kinetic orders.

(H) CATALYSIS BY O-DICHLOROPHENOL

It was considered desirable to investigate a catalyst intermediate in acidity between acetic acid and water, and of different structure; o-dichlorophenol was chosen as it has the lowest pK_a (6.79) of the dichlorophenols (111). Laboratory reagent grade material was obtained from B.D.H., recrystallised to constant melting point from petroleum spirit (b.p. 60-80°C.), and the white crystals dried under vacuum at room temperature. The final product had m.p. 65.9-66.2°C. (lit. 68-69°C. (102), 67°C. (103)). The reaction media were made up from weighed amounts of the catalyst, as in the case of benzoic acid, and the optical densities followed at 315 $m\mu$ on account of the strong absorption of the catalyst at lower wavelengths.

The kinetic experiments were only partially successful, largely because of the small catalytic effect. Catalyst concentrations of up to 1.5 M. were required to give rates two or three times those observed in its absence, and this resulted in increases in the equilibrium constants of up to 40%. Division of the first order rate constants into their hydration and dehydration components and correction of these for water catalysis both introduced errors resulting from inaccuracies in the experimental equilibrium constants, besides placing heavy reliance on the assumptions behind the size of the water rate contribution. The high concentrations of catalyst raised the question of the composition scale to be used, the volume molarity scale being arbitrarily adopted here, and established by means of density measurements on the reaction solutions; however, as shown in the following chapter, use of the mole fraction scale would make little difference to the results. Having obtained figures for the separate catalytic coefficients at a given catalyst concentration, there was no known way of extrapolating to limitingly small catalyst concentrations, since neither the hydration nor dehydration kinetic orders with respect to water were close to zero, and the corrected formal catalytic plots showed too many accumulated deviations. Formal catalytic plots of the uncorrected data indicated that errors of up to 5% were often present in the experimental first order rate constants, which ruled out any purely empirical method of obtaining the required infinite dilution catalytic coefficients.

A series of runs was carried out at each of the formal water mole fractions 0.159, 0.220, 0.273, and 0.320, and the results analysed by the two methods used for the carboxylic acids. The first consisted in drawing the best straight line through the first order dehydration points, and correcting its slope for the variation of the water-catalysed rate with catalyst concentration, while in the second method each first order dehydration rate was separately corrected for the contribution of water catalysis and the best straight line drawn through the corrected values. The hydration rate constants were then obtained via the infinite dilution equilibrium constants.

Both methods gave very similar kinetic orders. The catalytic constants in Table 39 were obtained by the second method, in which the individual points deviated by up to 10% from the rates quoted, and similar deviations were observed in plotting the logarithms of these quantities against the logarithms of the water mole fractions. A kinetic order plot based on the uncorrected dehydration slopes of the first method of analysis outlined above gave values 0.2 units lower, reflecting the greater importance of the water-catalysed rate at higher water mole fractions. Although the kinetic orders can be defined reasonably closely on account of the large range of rates covered, the rather low order of accuracy of the individual catalytic coefficients made it not worthwhile to attempt to measure any kinetic isotope effects.

TABLE 39

o-Dichlorophenol : kinetic orders

x_w	k^c_{dH} (M^{-1} sec.$^{-1}$)	k^c_{hH} (M^{-1} sec.$^{-1}$)	number of runs
0.320	3.1×10^{-4}	4.0×10^{-4}	5
0.273	2.3×10^{-4}	2.6×10^{-4}	5
0.220	1.7×10^{-4}	1.6×10^{-4}	3
0.159	8.5×10^{-5}	6.5×10^{-5}	3

kinetic orders with respect to x_w: hydration 2.5, dehydration 1.7

That the observed optical density changes during a run corresponded only to the process of ketone hydration was checked by the criteria used for the carboxylic acids. The infinity readings were stable over at least a further 12 half-lives, and good first order plots were obtained. On introducing catalyst into an equilibrated solution of the ketone by the same technique as was used for acetic acid, the bulk of the optical density increase occurred slowly with a first order rate constant similar to that expected on the basis of the above results. Scanning of the spectrum of the equilibrated solution in the presence of the catalyst was prevented by the high absorption of the latter, but the ratio of the optical densities at 320 and 310 mμ measured relative to a solvent blank in the presence of 1.7 M. o-dichlorophenol at x^o_w = 0.159 was found to be 0.572, which compares favourably with the value 0.578 from Table 20 in the absence of the catalyst.

CHAPTER VI

THE HYDRATION OF THE CATALYSTS IN SOLUTION

The kinetic measurements of the previous chapter are in principle interpretable in terms of the difference between the ground and transition states for each reaction. The measurements reported in the present chapter were designed primarily to make use of the variation of the equilibrium constant with catalyst concentration to yield information concerning the hydration of the various catalysts, in order that the kinetic orders of reaction might be understood in terms of the degrees of hydration of the transition states. It has been assumed that the changes in the equilibrium constant are due solely to changes in the water activity, and that this in turn is a function of the amount of water present and independent of the chemical composition of the solution. Accordingly any increase in K_d above the value predicted for the stoichiometric composition of the solution is attributed entirely to removal of water by hydration of the catalyst. The status of these assumptions and of the resulting hydration numbers is considered in the Discussion.

Since the observation of catalyst hydration through the decrease in the water activity requires that the catalyst concentration cannot be negligible relative to that of the water, it is necessary to consider the scale of composition to be used. The importance of this point arises from the need to apply a composition-K_d correlation obtained in water-dioxan mixtures to solutions containing relatively large quantities of catalyst. It is discussed for each catalyst individually.

(1) Acetic acid

In order to determine to what extent the value predicted for K_d in a solution made up by adding aqueous acetic acid to dioxan depends on the composition scale used, it was necessary to know the densities of the final solution and of the aqueous acetic acid used. The latter was determined to a sufficient degree of accuracy by making up different amounts of glacial acetic acid (B.D.H. laboratory reagent grade) to 25 ml. in a graduated flask at room temperature and determining the weight of each solution. The resulting relative densities fell on a smooth curve, which was used to determine the composition of the water-acetic acid-dioxan solutions. This curve showed a maximum relative density of 1.070 very close to the composition $AcOH.H_2O$, which agrees with the more accurate results of Drucker (112) at 25°C.

In order to investigate the densities of the reaction solutions, a solution was made up by adding 1 ml. of 10.5 M. acetic acid in water to 10 ml. of dioxan, and 5 ml. of this solution discharged from a pipette was found to have a weight within 0.1% of that calculated from the measured densities of the two components on the assumption of zero volume change on mixing. It would therefore appear that this volume change on mixing can be neglected for the present purposes, just as in the case of dioxan-water mixtures (109,110).

It is now possible to investigate the extent of divergence of the mole fraction and volume molarity scales. The solution of highest catalyst concentration used in the present study was obtained by adding a portion of 10 M. aqueous acetic acid to ten times its volume of dioxan, and in this the water mole fraction is calculated from the above results to be 0.168 and the concentration 2.33 M. Since it can be calculated that a solution of water of this molarity in dioxan has a water mole fraction of 0.172, it follows that the two scales do not diverge significantly in the concentration range of interest. This situation occurs because the difference in the molar volumes of dioxan and acetic acid has been reduced by a factor roughly equal to the mole fraction of acetic acid in the solution.

The mole fraction scale has been used in the present calculations of hydration number, since the K_d values in aqueous dioxan have already been correlated with this variable in equation (26), but a correlation with water molarity should give results which are only slightly lower.

Experiments were conducted with the object of measuring the variation of the equilibrium constant over a larger range in the ratio [catalyst] : [water] than was possible in the kinetic experiments. Since the most important results are for low catalyst concentrations, a differential method was used. A stock solution of sym-dichloroacetone in dioxan was prepared. To one portion of this was added one tenth of its volume of 10.0 M. aqueous acetic acid solution, while to another was added the same volume of water, and equilibrated solutions containing different concentrations of catalyst were obtained from these by mixing them in various proportions. The aqueous acetic acid was taken from an ampoule of B.D.H. concentrated volumetric solution, and its concentration established by titration against standard 1 M. sodium hydroxide solution, after ten-fold dilution of a sample of the acid. Its relative density was found to be 1.061 by interpolation from either the above results or from those of Drucker (112).

The optical densities were measured on the SP500 instrument at 285 $m\mu$, using the stock solution with catalyst absent as the reference. Analogous solutions in the absence of ketone showed that the maximum concentration of catalyst used increased the optical density by 0.011 units, and corrections have accordingly been made for this on a linear basis in the results recorded in the tables. Each reaction solution was left overnight at 25°C., and the readings were repeated after a further half hour in order to check that equilibrium had been reached. Measurements were taken at formal water mole fractions of 0.320 and 0.190, and the results are presented in Tables 40 and 41. The optical densities of the equilibrated solutions in the absence of catalyst were

0.350 and 0.448, respectively, and the ϵ°_{285} values calculated from these through equation (26) differed by no more than 2% from the expected values. The corresponding calculated values for the initial optical density before hydration have been used to compute K_d for each solution for the sake of consistency in the x_w-K_d correlation.

TABLE 40

HYDRATION OF ACETIC ACID AT $x_w^{\circ} = 0.320$

x_w^s	x_c	ΔD^{∞}	x_w^a	q	$\Delta x_w/x_w^s$
0.298	0.00983	0.034	0.250	4.88	0.162
0.274	0.0201	0.055	0.216	2.87	0.211
0.249	0.0307	0.072	0.193	1.82	0.224
0.223	0.0418	0.104	0.157	1.57	0.294
0.196	0.0534	0.122	0.140	1.05	0.286
0.167	0.0654	0.144	0.122	0.70	0.274

x_w^s and x_w^a are stoichiometric and apparent water mole fractions, respectively.

$\Delta x_w = x_w^s - x_w^a$, and x_c is the mole fraction of catalyst.

ΔD^{∞} is the change in the equilibrium optical density brought about by the catalyst in a 1 cm. cell, and q is the mean hydration number of the catalyst.

TABLE 41

HYDRATION OF ACETIC ACID AT $x_w^{\circ} = 0.190$

x_w^s	x_c	ΔD^{∞}	x_w^a	q	$\Delta x_w/x_w^s$
0.176	0.00581	0.038	0.151	4.34	0.143
0.173	0.00699	0.045	0.145	4.07	0.164
0.169	0.00876	0.047	0.143	2.99	0.155
0.161	0.0118	0.073	0.122	3.29	0.241
0.129	0.0241	0.118	0.0928	1.50	0.281
0.0948	0.0370	0.159	0.0714	0.63	0.247

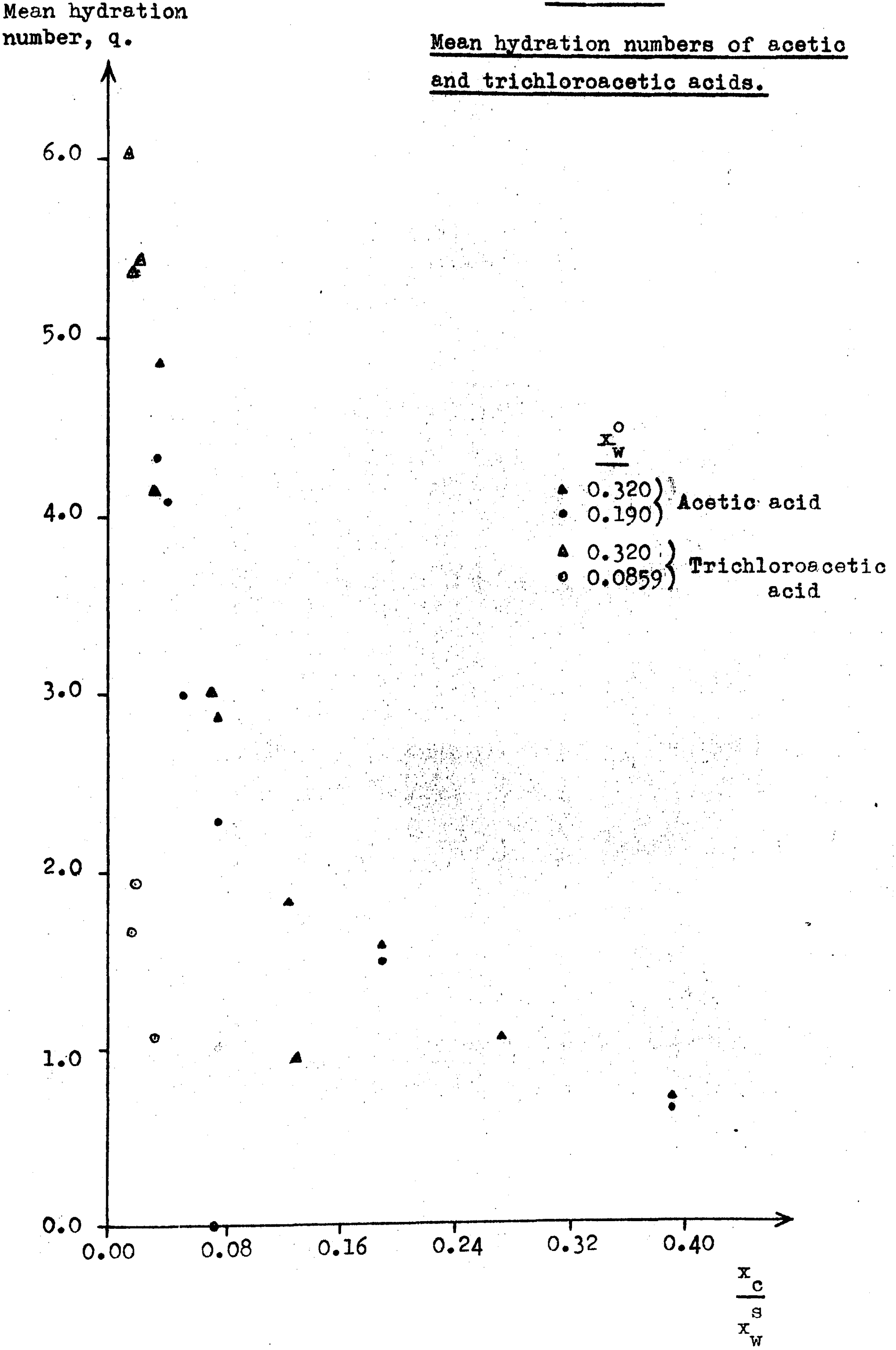
The first two columns in the tables refer to the stoichiometric mole fractions of water and catalyst, respectively, and the fourth column to the apparent water mole fraction calculated from K_d. The mean hydration numbers, q, appearing in the fifth column have been calculated by dividing the decrease in the water mole fraction, Δx_w, by x_c, this being possible because of the fairly small magnitude of Δx_w. In figure (16) are plotted the hydration numbers against the stoichiometric ratio x_c/x_w^s, from which it can be seen that the absolute mole fractions are not of great importance in the range of compositions studied. It is also apparent that as x_c/x_w^s increases the hydration numbers decrease asymptotically, a necessary feature of an interpretation in terms of catalyst hydration. Another basic thermodynamic requirement is that the fraction of bound water, $\Delta x_w/x_w^s$ should increase with x_c/x_w^s, and the last column in each of the tables shows that this is so except at the highest acetic acid concentrations. Since the sensitivity of the method necessarily becomes very low at low catalyst concentrations, it has not been possible to obtain values in the region where q should tend towards a limiting value; a minimum value of $q \simeq 4$ may be put on the mean hydration number at infinite dilution of the catalyst in solutions of these water mole fractions. In making corrections to obtain catalytic rate constants from the slopes of the formal catalytic plots for acetic and monochloroacetic acids in the previous chapter an effective hydration number of 6 was assumed in order to take into account also the decrease in the stoichiometric water mole fraction with increasing catalyst concentration.

(2) <u>Trichloroacetic acid</u>

An analogous set of experiments was performed with trichloroacetic acid at formal water mole fractions of 0.320 and 0.0859. The stock solution of aqueous trichloroacetic acid was found to be 4.30 M. by titration with standard 1 M. sodium hydroxide

FIGURE 16

Mean hydration numbers of acetic and trichloroacetic acids.



solution using phenolphthalein as indicator, and its relative density was accordingly taken as 1.315 by interpolation from the results of Drucker (112). Assuming by analogy with acetic acid that the volume change on adding the aqueous solution of acid to dioxan is negligible, it was concluded that the divergence of the mole fraction and volume molarity scales in the composition range of interest could similarly be neglected.

The solutions were prepared and the measurements taken in the same manner as for acetic acid, making a similarly small correction for the optical density increase brought about by the acid. The results are presented in Tables 42 and 43, and are plotted in Figure (16) along with those for acetic acid. The

TABLE 42

HYDRATION OF TRICHLOROACETIC ACID AT $x_w^o = 0.320$

x_w^s	x_e	ΔD^∞	x_w^a	q	$\Delta x_w/x_w^s$
0.306	0.00422	0.022	0.280	6.05	0.0834
0.303	0.00508	0.025	0.276	5.38	0.0903
0.298	0.00638	0.033	0.263	5.44	0.117
0.290	0.00858	0.039	0.254	4.14	0.123
0.255	0.0178	0.082	0.201	3.02	0.212
0.219	0.0277	0.090	0.193	0.94	0.119

TABLE 43

HYDRATION OF TRICHLOROACETIC ACID AT $x_w^o = 0.0859$

x_w^s	x_e	ΔD^∞	x_w^a	q	$\Delta x_w/x_w^s$
0.0813	0.00112	0.017	0.0794	1.67	0.0230
0.0802	0.00135	0.022	0.0776	1.94	0.0327
0.0760	0.00225	0.033	0.0736	1.06	0.0315
0.0653	0.00456	0.057	0.0654	0.00	0.00
0.0544	0.00688	0.069	0.0616	<0.00	-

hydration numbers at $x_w^o = 0.320$ show the same general behaviour as found for acetic acid; the values appear to continue to increase at the lower acid concentrations studied here, although in this region they are particularly sensitive to experimental error. The findings of these experiments are in agreement with the apparent absence of any variation in the equilibrium constants found at much lower catalyst concentrations in the kinetic studies.

The results in Table 43 for a low formal water mole fraction are considerably lower than those for the other three sets, presumably because a sufficiently large decrease has been made in the water mole fraction. They are also rather less reliable since a relatively large change in the water mole fraction is indicated by only a small change in the equilibrium optical density. Moreover the apparent water mole fractions are all outside the region for which equation (26) was obtained, while the appearance of a negative mean hydration number at the highest acid concentration shows that too much weight should not be placed on the quantitative aspect of these results.

Separate experiments were not carried out for benzoic and monochloroacetic acids, nor are the equilibrium constants found in the kinetic studies accurate enough for quantitative interpretation. Nevertheless it can be seen from those figures that these catalysts are hydrated to an extent which is qualitatively similar to that found for the above carboxylic acids.

(3) o-Dichlorophenol

Although the only data available for the variation of equilibrium constant in the presence of this catalyst are those collected in the kinetic experiments, the magnitude of the observed effect makes it possible to use these measurements for a semi-quantitative calculation of the hydration numbers. The usual question concerning the composition scale was resolved by measurements made of the 5 ml. of each solution used. These showed that the volume of the aqueous dioxan solution increased by 10.2%

on solution of one mole of the phenol in one litre, the relation being found to be both linear (at least up to 1.1 M.) with a standard deviation in the density of 0.2%, and independent of the water mole fraction. Since the addition of one mole of dioxan to one litre would increase the volume by 8.5%, the difference between the mole fraction and volume molarity scales may be neglected provided that the equilibrium constants are not regarded as significant to better than 2%.

The results are presented in Table 44 for four different formal water mole fractions. Although the mean hydration numbers exhibit a high degree of scatter, it can be seen that they fall mostly in the range 0.5-1.0 with a slight tendency towards lower values at lower water mole fractions. Comparison of the first five values in Table 44 with those in Table 40 falling in a similar range of catalyst concentration shows that the degree of hydration of the phenol is lower than that of acetic acid, but that the bound water is more tenaciously held; these remarks might reasonably be expected to apply also in the limit of zero catalyst concentration.

[illegible]	0	1.31			
[illegible]	0.0271	1.49	0.137	0.69	0.124
[illegible]	0.0485	1.53	0.134	0.35	0.112
[illegible]	0.0767	1.54	0.107	0.52	0.272

TABLE 44

HYDRATION OF O-DICHLOROPHENOL

x_w^s	x_e	K_d(expl.)	x_w^a	q	$\Delta x_w/x_w^s$
0.320	0	0.775			
0.314	0.0203	0.823	0.300	0.68	0.0440
0.312	0.0294	0.853	0.285	0.92	0.0866
0.302	0.0578	0.896	0.266	0.63	0.120
0.302	0.0578	0.906	0.262	0.70	0.134
0.291	0.0929	1.160	0.188	1.11	0.355
0.273	0	0.884			
0.268	0.0229	0.981	0.234	1.47	0.125
0.263	0.0406	0.989	0.232	0.77	0.119
0.255	0.0714	1.071	0.208	0.65	0.183
0.245	0.107	1.212	0.178	0.63	0.275
0.241	0.121	1.286	0.165	0.63	0.315
0.220	0	1.03			
0.212	0.0389	1.17	0.186	0.68	0.124
0.205	0.0737	1.36	0.154	0.70	0.251
0.197	0.108	1.58	0.128	0.64	0.350
0.159	0	1.31			
0.155	0.0271	1.49	0.137	0.65	0.114
0.151	0.0485	1.52	0.134	0.35	0.112
0.147	0.0767	1.84	0.107	0.52	0.272

DISCUSSION

CHAPTER VII

KINETIC ORDERS AND TRANSITION-STATE CONSTITUTIONS

(1) Molecularity with respect to ketone and catalyst

The question of the number of molecules of ketone incorporated into the transition-state may be dealt with very briefly, since the range of concentrations studied (< 0.05 M.) was low enough for the variation of its activity coefficient with concentration to be neglected. The good first order plots observed in the kinetic experiments are therefore indicative of a reaction unimolecular in ketone.

Turning to the role of catalysts other than water, the considerations of the previous chapter show that the choice of composition variable will not materially affect the shape of the catalytic plot for any of the systems studied. These plots were linear for the catalysts studied in dilute solution (perchloric, hydrochloric, and trichloroacetic acids), while the curvature found for the more concentrated cases (monochloroacetic, acetic, and benzoic acids) could be explained quantitatively, through the use of the experimental equilibrium constants, in terms of catalyst hydration. The cryoscopic measurements of Bell and Arnold (115) show that trichloroacetic acid exists entirely in the monomeric form in dry dioxan up to 0.5 M., and, if this is attributed to the availability of hydrogen-bond acceptor sites more basic than the carbonyl oxygen of the acid, it can be assumed that all the carboxylic acids are similarly monomeric in the aqueous dioxan solutions of interest. It may therefore be concluded that a single molecule of each of these six added catalysts is involved in the activation equilibrium, most reasonably by incorporation into the transition-state; for the two mineral acids both partners in the ion pair must be involved.

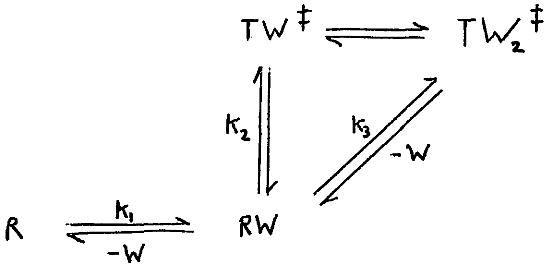
The situation in the case of o-dichlorophenol is less clear, since the scatter in the corrected experimental rate constants prevents observation of the linearity or otherwise of the catalytic plots. Cryoscopic measurements by Tonomura and co-workers (116) have shown that 1 M. phenol is about 20% dimerised in dry dioxan at 25°C., so that given the greater basicity of water and the steric hindrance by the ortho-substituents to dimerisation, the catalyst should be essentially monomeric in the solutions of interest. Since the catalytic plots were certainly not strongly curved, the rate constants obtained may therefore be regarded as approximating to those for a reaction unimolecular in o-dichlorophenol.

(2) Molecularity with respect to water: general approach

The problem of the molecularity of a reaction with respect to a substance present in appreciable concentration is a notoriously intractable one, since normally in this region the various alternative measures of composition diverge and the activity coefficients on any scale are composition-dependent. Nevertheless a considerable quantity of work has been undertaken to measure and interpret the variation of equilibrium and rate constants in the middle regions of solvent composition, particularly in regard to the mechanistically important kinetic effect of water. The theoretical basis is discussed first, and is then applied to the results obtained in the present work.

There are essentially three types of experiment capable of giving information concerning the hydration of any species: kinetic (i.e. the observation that some water molecules are not in rapid equilibrium with the bulk of the solvent), structural (i.e. the use of properties reflecting the environment of an atom or molecule), and thermodynamic (i.e. interpretation of the thermodynamic properties of the system in terms of hydration). Although structural methods might in principle be the most desirable, for the purpose of investigating a transition-state only the thermodynamic approach is possible. This involves the assumption that the interactions contributing to the measured activity coefficient ratio can be either accounted for explicitly in terms of hydration equilibria or can be cancelled in some way.

If the degrees of hydration on both sides of the reaction equilibrium do not vary with the solvent composition, the reaction can be represented very simply by a single equilibrium constant containing a measure of the amount of free water raised to the appropriate power. More generally the effect of changing degrees of hydration may be treated as in the following simple case, which deals with the equilibrium between an unhydrated and monohydrated reactant, R and RW, and a mono- and dihydrated transition-state



(or product), $TW^{\ddagger}$ and $TW_2^{\ddagger}$. Using the same composition variable throughout (represented by square brackets), but without specifying its nature,

$$C_R = [R] + [RW] \quad \text{and} \quad C_T = [TW^{\ddagger}] + [TW_2^{\ddagger}] \quad ,$$

where C represents the total amount of each species. Therefore,

$$K_1 = \frac{[RW]}{[R][W]} \; , \quad K_2 = \frac{[TW^{\ddagger}]}{[RW]} \; , \quad \text{and} \quad K_3 = \frac{[TW_2^{\ddagger}]}{[RW][W]} \quad ,$$

where W represents monomeric solvent water, C_W represents the total amount of all solvent water species, and $C_W \gg C_R$, C_T.

The rate (or equilibrium) constant, k, is proportional to C_T/C_R, which is given by

$$\frac{C_T}{C_R} = \frac{K_2 + K_3[W]}{1 + 1/K_1[W]} \quad . \qquad (27)$$

The slope of the appropriate log-log plot is therefore given by

$$S = \frac{d \log k}{d \log [W]} = \frac{K_3[W]}{K_2 + K_3[W]} + \frac{1}{K_1[W] + 1} \qquad (28)$$

and its curvature by

$$\frac{d\ S}{d \log [W]} = \frac{K_2K_3[W]}{(K_2 + K_3[W])^2} - \frac{K_1[W]}{(K_1[W] + 1)^2} \quad . \qquad (29)$$

The difference between the average degree of hydration of the transition-state and reactant (i.e. the number of solvent water molecules involved in the activation equilibrium) is

$$S' = \frac{[TW^{\ddagger}] + 2[TW_2^{\ddagger}]}{C_T} - \frac{[RW]}{C_R} = \frac{K_3[W]}{K_2 + K_3[W]} + \frac{1}{K_1[W] + 1} \qquad (30)$$

from which it can be seen that $S = S'$.

A kinetic order plot with respect to log[W] is therefore linear (i) if each of the quantities $K_1[W]$ and $K_3[W]/K_2$ are either much larger than or much smaller than unity, or (ii) if $K_1 = K_3/K_2$. Condition (i) corresponds to a situation in which the reactant and transition-state are each essentially in the form of one of their hydrates, while condition (ii) obtains when the balance between the two hydrates is the same for the two species. The physical significance of the slope of the kinetic order plot at any composition is independent of its curvature, the latter reflecting the change in the mean hydration number of the transition-state with solvent composition relative to the corresponding change for the reactant.

According to this treatment the inclusion of an originally unhydrated molecule of catalyst into each transition-state makes no difference to the kinetic order plots, and the formally equivalent situation in which the catalyst exists in two differently hydrated forms and the reactant is entirely unhydrated (the situation resembling that most probably existing in the present ketone hydration reactions) necessarily results in analogous behaviour. It can be shown that the above scheme can be extended to include any number of hydrates without altering the physical significance of the kinetic order slope, and that in the general case the condition for linearity of this plot is that the equilibrium constant for the conversion of the lowest reactant hydrate into the lowest transition-state hydrate must be equal to that for the interconversion of the next lowest pair, etc.

In the likely event that the solvent water is at least partly polymerised, the slope of the kinetic order plot constructed with respect to some measure C_w of the stoichiometric amount of water in the solution is given by

$$S_C = \frac{d \log k}{d \log C_w} = S \cdot \frac{d \log[W]}{d \log C_w} \qquad (31),$$

from which

$$S_C = S' \cdot \frac{d \log[W]}{d \log C_w} \quad . \qquad (32)$$

In the general case, $C_w = [W] + 2k_2[W]^2 + 3k_3[W]^3 \ldots$ where the k's are association constants,

so that

$$\frac{d \log[W]}{d \log C_w} = \frac{[W] + 2k_2[W]^2 + 3k_3[W]^3 \ldots}{[W] + 4k_2[W]^2 + 9k_3[W]^3 \ldots} \qquad (33)$$

The mean degree of polymerisation of the water, $\bar{m}$, can be defined by

$$\bar{m} = \frac{C_w}{[W]+[W_2]+[W_3]\ldots} = \frac{[W] + 2k_2[W]^2 + 3k_3[W]^3 \ldots}{[W] + k_2[W]^2 + k_3[W]^3 \ldots} \qquad (34)$$

Thus, when one polymeric water species predominates,

$$\frac{d \log[W]}{d \log C_w} = \frac{1}{\bar{m}} \qquad (35),$$

and a kinetic order plot which would be linear in log[W] will still be linear in log C_w. Its slope may be integral or fractional. In the more general case the ratio of the mean hydration change S' to the experimental slope S_C will be somewhat nearer than $\bar{m}$ to the next higher whole number, and a linear kinetic order plot is only possible if the contributions of the two factors on the right hand side of equation (31) to the curvature cancel with each other.

(3) Evaluation of the above approach

There are four important types of assumption made in explaining the variation of a rate or equilibrium constant with solvent composition in terms of specific solvation. These are:
(i) that all the solvation equilibria have been accounted for,
(ii) that the measure of composition used is the correct one,
(iii) that no long range electrostatic effects operate, and
(iv) that packing considerations may be neglected.

With regard to assumption (i), the above equations are only true if the degenerate activity coefficient of transfer for each of the reacting species between two solvent mixtures of different composition is unity, or in molecular terms if a given species interacts equally with its environment in any solvent mixture. Since to account for all possible interactions in terms of equilibria would be impossibly complicated, the solvation numbers obtained are dependent on the model assumed, and it is therefore important to consider carefully the probable relative strengths of these interactions in choosing the best simple description of the system. The usual assumption made is that the relative interactions of the various reacting species with one of the solvent components are constant with changing solvent composition. This is a fairly good assumption when, as in the present case, the proportional change in the amount of this component (dioxan) is much less than that of the other component (water) which is explicitly included in the solvation equilibria. When the solvent composition is varied over its entire range, as is often the case for reactions conducted in concentrated aqueous acid solutions, this assumption is less reliable, as has been clearly pointed out by Bunnett (117).

Turning to assumption (ii) the question arises as to the particular measure of composition to substitute in the above equations. The theoretical approach to an answer requires an appeal to the statistical theory of the entropy of mixing (ref. 118 p.246, ref. 41 p.242), which considers the molecules of a liquid mixture to be distributed over a fixed number of identical sites. According to whether each molecule occupies a number of sites depending on its relative molecular volume or just a single site, the activity of each component is proportional to its volume fraction or to its mole fraction in the solution. Since both alternatives rely on an assumed model for the liquid state, they can only be judged by their experimental consequences, but this inevitably requires some assumptions as to the acceptable form of the solvation equilibria. The evidence relevant to electrolyte and non-electrolyte solutions has been discussed by Robinson and Stokes (ref. 41 p.243).

For reactions involving ions assumption (iii) would appear to be the most tenuous. According to the Born equation, the free energy of transfer ΔG of a singly charged ion of radius r from a solvent of dielectric constant ϵ_1 to one of ϵ_2 is given by

$$-\Delta G = \frac{e^2N}{2r}\left(\frac{1}{\epsilon_1} - \frac{1}{\epsilon_2}\right) \quad .$$

where N is the Avogadro number and e the fundamental electronic charge. The predicted dependence on the dielectric constant is followed in an approximate fashion by the dissociation constants of a number of aliphatic carboxylic acids in alcohol-water and dioxan-water mixtures (ref. 41 p.365). In the sphere of kinetics Tommila (119) has shown that the ratio of the solvolysis rate of a substituted to the unsubstituted benzene derivative varies linearly with $1/\epsilon$ for a range of reactions and solvent mixture types, while Franke (120) has demonstrated a linear relation between the rate and $1/\epsilon$ in the specific acid catalysed decomposition of diazoacetic ester (after removal of the acid activity coefficient from the rate constant). In the range of solutions covered in the present work ϵ varies between about 3 and 6, so that from the Born equation the rate of a reaction in which the charge on an ion of radius 2 Å is completely dissipated would vary by about eight powers of ten. Ion-pairing should considerably reduce this variation, but it is nevertheless clear that electrostatic effects should not be neglected in interpreting the results obtained in the present work for mineral acid catalysis. The Born effect may always be regarded as a form of long range solvation and hence be included in the general interpretation of reaction orders in terms of solvation changes, but such an approach is irrelevant to the problem of transition-state constitution.

For reactions which do not involve the creation or dissipation of strong centres of charge the assumption that long range electrostatic effects are absent would appear much more reasonable. In their study of the dimethylaniline-catalysed decomposition of nitramide in a number of single component organic solvents Caldin and Peacock (121) found no correlation between rate and dielectric constant, but were obliged to consider specific solvation interactions in order to interpret the results. Bell, Lidwell, and Vaughan-Jackson (122) similarly explained the decreasing catalytic effects of trichloroacetic acid in the series of solvents benzene, anisole, and amyl acetate by an increasingly strong interaction between the solvent and catalyst. Electrostatic effects will be neglected in discussing the results of the present work for all except the mineral acid catalysts.

Finally the possibility (iv) that the degree of molecular interaction is affected by the ease with which a molecule of one component can be accommodated into the structure of the other is likely to be most important at fairly low temperatures and in regions of composition in which one solvent is considerably ordered, in particular in highly aqueous water-organic solvent mixtures. The evidence that the introduction of small amounts of alcohols increases the degree of water structure has been summarised by Franks and Ives (133) and supported by the calorimetric measurements of Arnett and co-workers (134). Glew, Mak, and Rath (135) observed that at $0^{o}C.$ the addition of 4 mole % of tetrahydrofuran to water produces a downfield shift in the p.m.r. signal of water, the direction being opposite to that expected and observed for larger additions and higher temperatures, while Clemett (136) has shown, also by p.m.r., that the self-diffusion coefficients of both water and dioxan have minima around 25 mole % of the latter. The structure-making effect of relatively small organic molecules in highly aqueous solutions might be expected to be quite general; however it cannot be accounted for in terms of equilibria between well-defined associated species and is therefore likely to complicate the interpretation of apparent kinetic orders in this region of composition. On the other hand, such effects may reasonably be neglected at the lower water mole fractions used in the present work.

It has sometimes been suggested, for example by Tommila (119) and Dolman and Stewart (124) that the basic strength of hydroxide in dimethylsulphoxide-water mixtures increases with the concentration of the organic component because decreasing hydration of the ion gives rise to species of higher reactivity. This can be shown to be thermodynamically inconsistent since, if the activity coefficient of the hydroxide can be interpreted in terms of hydration, the same is true of the transition-state (or the anionic product for a proton abstraction reaction), and the system can be represented by a scheme of the type presented in section (2). It follows that the basic strength increases because at any solvent composition the hydration of the transition-state or product is less than that of the hydroxide ion. In contrast to the above suggestion, it is the tenacity of the latter species for water molecules which accounts for the observed behaviour, while the equilibrium between the various hydrates determines the curvature of the kinetic order plot. The previous explanation neglects the thermodynamic relation between the hydration of the hydroxide ion and its basicity. Any account of the data in terms of hydration is of course subject to all the above reservations.

(4) Activity, composition, and solvent association

In accordance with the general assumption of the present chapter that the change in activity coefficients with composition can be accounted for in terms of equilibria between well-defined solvation complexes, it follows that the mole fraction of single molecules of one component should be proportional to its activity. (The mole fraction may be replaced by whatever variable is considered to be the fundamental measure of composition.) In equations (27)-(30) [W] may be put equal to $K.a_W$, where a_W is the water activity and K depends on the standard state, and the slope of a kinetic (or equilibrium) order plot constructed using log a_W can then be seen to measure the total number of solvent water molecules involved in the reaction. The result is independent of the standard state assumed for water in the condensed phase. The reaction may be regarded as heterogeneous, with the free water being supplied from the vapour phase.

Making the same substitution for [W] in equations (31)-(35), it can further be seen that the slope of a plot of log C_w (where C_w is the appropriate composition variable) against log a_w is approximately equal to the mean degree of self-association of the solvent water. A plot of log k against log C_w gives the average number of these average water polymer units involved in the reaction, while the number of water molecules involved is given by the product of these two quantities.

A number of workers, for example Bell, Millington, and Pink (6) in the hydration of sym-dichloroacetone and Edwards and co-workers (123) in the hydrogen peroxide-catalysed oxidation of thioxane, have restricted themselves to kinetic order plots in terms of mole fraction or concentration. This is partly due in the second example to the lack of activity data, but in the first it is justified in terms of the need to obtain a measure of the number of water molecules of direct mechanistic importance, i.e. those involved in the ring of the proposed cyclic transition-state. In terms of the present treatment the slope of such a plot should reflect this quantity provided that each of the water molecules taken up to form the ring has the same affinity for further hydration as if it were single. This in turn means that a linear relation between log k and log C_w should be observed even when curvature of the log C_w v. log a_w plot indicates that $\bar{m}$ is composition-dependent, provided always that all the assumptions discussed above are valid. Consideration of the behaviour of both types of plot should lead to the best understanding of the hydration phenomena in any reaction.

Before discussing the present results according to the above principles, a number of important and reasonably successful attempts to account for thermodynamic and kinetic data in several types of solvent system in terms of hydrate formation may be briefly mentioned in order to demonstrate the validity of the approach. Aqueous solutions of strong electrolytes have been dealt with by

Robinson and Stokes and by Glueckauf (ref. 41 pp.238), the latter of whom obtained physically more reasonable hydration numbers by the use of the volume fraction scale, but very little work has yet been done on equilibria and kinetics in these solutions. The acidity functions of aqueous acid mixtures have been treated in terms of the species $H^+(H_2O)_4$ by Bascombe and Bell (125), while Bunnett (117) has extended the treatment to the equilibria and kinetics of organic reactions. The work of Lane, Cheung, and Dorsey (128) on the rates of hydrolysis and carbonyl ^{18}O exchange of a number of esters in aqueous sulphuric acid, in which it was concluded that two additional water molecules are taken up in going to the transition-state, is essentially an application of Bunnett's approach. Parallel analyses have been presented by Anbar and co-workers (126,127) for concentrated aqueous hydroxide solutions, in which the species $OH(H_2O)_3^-$ was invoked, the chief difference in their treatment compared with that of Bunnett being in their use of the concentration of free water in place of its activity in the discussion of equilibria and kinetics. As pointed out above, plots involving activity will normally give higher numbers, but should be interpreted differently. The apparent proportionality between the activity and concentration of free water in the strong acid solutions considered by Bascombe and Bell indicates that the hydrate formation model cannot always account for every feature of the system.

(5) Model of dioxan-water system

The data of Goates and Sullivan (129) for the activities of the two components of the water-dioxan system show that both exhibit positive deviations from Raoult's law over the whole range of composition. This behaviour is interpretable in terms of the effect of association equilibria among like molecules as the chief cause of deviations from ideality. On chemical grounds the water molecules would be expected to be the more strongly associating, and this interaction is anyway the more important in the low water mole fraction region of concern in the present work.

If water association is regarded as the only cause of non-ideal behaviour, the degree of association at any composition should be given exactly by the ratio $x_w/(1-a_2)$ and fairly closely by the slope $\bar{m}'$ of a plot of log x_w against log a_w. (It has been assumed that the mole fraction scale is appropriate, and a_2 represents the activity of dioxan on this scale referred to the pure solvent). Table 46 shows how these quantities, obtained from adjacent pairs of values of Goates and Sullivan, vary with x_w.

TABLE 46

ASSOCIATION OF WATER FROM ACTIVITY DATA

x_w	$\bar{m}$	$\bar{m}'$
0.375	2.2	5.8
0.325	2.1	4.5
0.275	1.8	4.4
0.225	1.8	3.2
0.175	1.6	2.7
0.125	1.4	2.4

The fact that the results obtained from the water activity are larger than those obtained from that of dioxan suggests that the dioxan activity coefficient is reduced by increasing interaction with the water. However, such an interaction need not affect the interpretation of $\bar{m}'$ as a quantity fairly closely equal to the mean degree of association of the water molecules. The value of the degree of association calculated from the cryoscopic data of Bell and Wolfenden (130) is 1.6 at $x_w = 0.125$, the slightly larger magnitude than that appearing in the second column of Table 46 being perhaps attributable to the lower temperature.

Clemett (131) has summarised infra-red, dielectric relaxation, and p.m.r. evidence for the increasing degree of association of water in dioxan over the above concentration range.

For example the downfield shift of the p.m.r. water signal as its mole fraction is increased indicates a change in the environment of these protons, although a quantitative interpretation is prevented by uncertainty as to their average chemical shift in any particular water polymer. Studies of the vapour pressure of water over its dilute solution in a number of organic solvents of varying structure and basicity have been reported by Johnson and co-workers (132), and indicate mean degrees of association ranging from about 1.0 to 3.0 at $x_w = 0.10$.

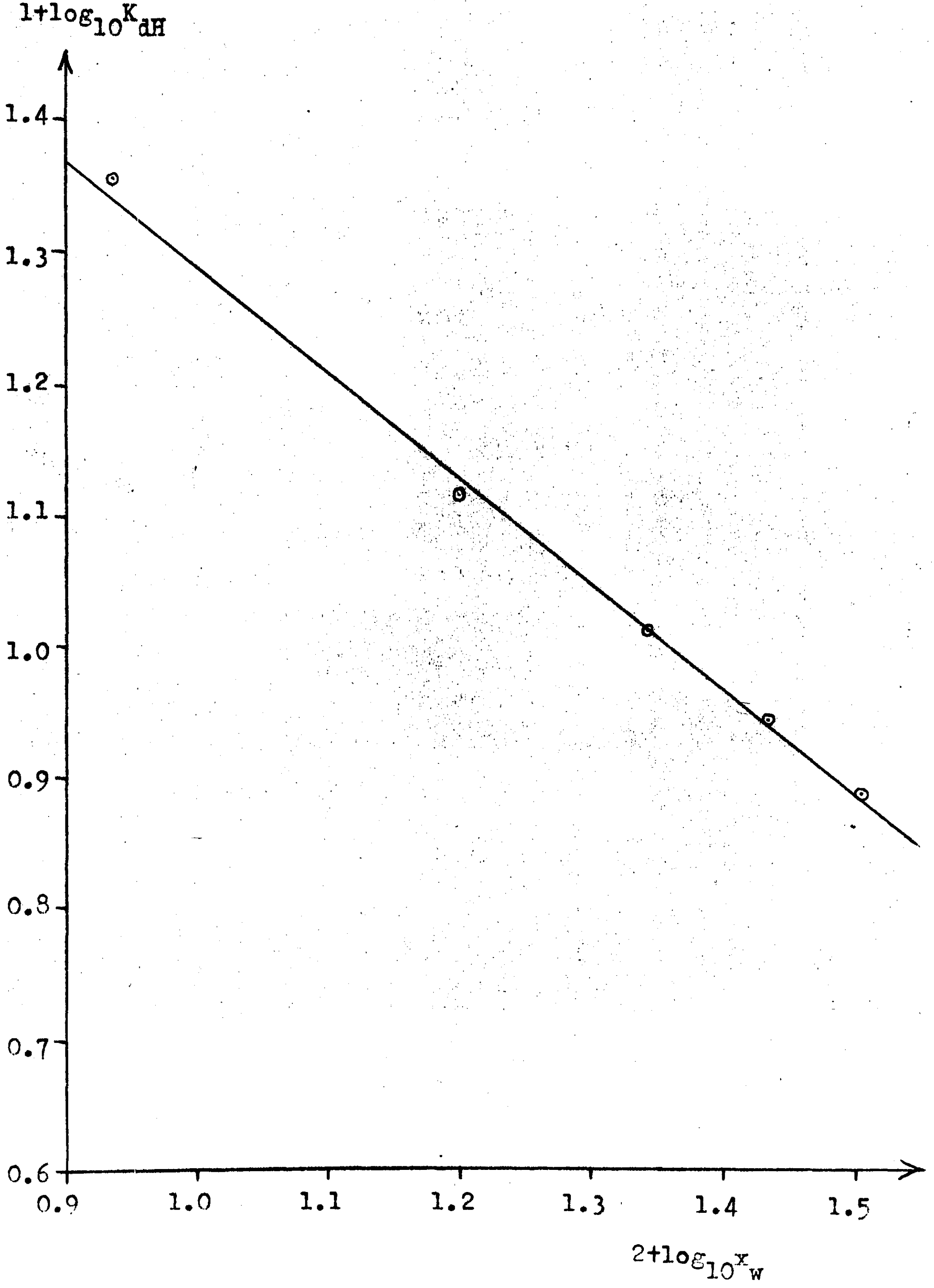
The changing value of $\bar{m}'$ with water mole fraction shows that a kinetic (or equilibrium) order plot cannot be linear with respect to both log x_w and log a_w. The slope of a plot using the latter variable will be about 4.5 times larger than that for the former at the higher concentration end and about 2.0 times larger at the lower concentration end of the region of interest in the present work. On the other hand, a plot of log c_w against log x_w (where c_w represents the concentration of water) is only slightly curved over this range, and at no point differs by more than 4% in c_w or x_w from the best straight line. Plots linear with respect to log x_w will therefore be practically linear with log c_w, but will have a 16% smaller slope, as found in the work of Bell, Millington, and Pink (6).

(6) Equilibria and kinetics in the absence of added catalysts

The simplest to interpret of the data obtained in the present work are those relating to the kinetics and equilibria of ketone hydration in the absence of added catalysts. Figure (17) shows a plot of $\log_{10} K_{dH}$ against $\log_{10} x_w$, using the mean dissociation constants K_{dH} from Table 5 p.(69). As expected from the rather good fit of these data to equation (26), the plot is slightly steeper at low x_w, but the largest deviation by any point is still only 4% in K_{dH}. This shows that in any reaction at least one of the kinetic order plots

FIGURE 17

Dependence of ketone hydration equilibrium on x_w.

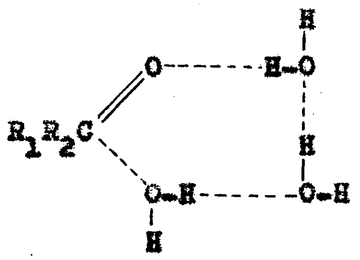


must be very slightly curved. The straight line in Figure (17) has a slope of -0.80, which as required is close to the difference between the kinetic orders for dehydration and hydration recorded for the various catalysed reactions in Chapter (V).

The above plot is considerably more linear than that between log a_w and log x_w, which suggests that the treatment of Bell, Millington, and Pink discussed in section (4) may be approximately valid and that one water molecule is taken up in an intimate way in forming the hydrate. Exact validity would require that the outer solvating water molecules of the hydrate could be removed as readily as the associated water species in the solvent could be broken down, a rather unlikely relation in view of the fact that the hydrate molecule has two equivalent hydroxylic oxygens. In addition it cannot be certain that the mole fraction scale is perfectly appropriate, especially since the use of concentration would give a slope of -0.69, so that the exact value should not be taken too seriously. The direction of the curvature is such as to give an order nearer to -1.0 at lower water concentrations as required, although the experimental accuracy hardly warrants conclusions of this type.

The results of Bell, Millington, and Pink (6) for the same system do not differ sufficiently from those of the present work to alter the above interpretation. Comparison with the results of other workers is complicated by the use of different solvent systems and different measures of composition, although all agree that some water must be taken from the solvent in forming the hydrate. Griffiths and Socrates (137) confirmed the earlier findings of Gold and co-workers (138) that in mixtures of water and pyruvic acid the equilibrium constant for hydration varies linearly with the cube of the water concentration down to $c_w \simeq 20$ moles/litre. Since the alternative use of water mole fraction would be expected to give an even larger kinetic order and since water must be fairly strongly associated in these more aqueous solutions, it appears that more water is taken up on hydration than found in the present case. Gruen and McTigue (5) concluded from a study of propionaldehyde in concentrated aqueous electrolyte solutions that on the volume fraction scale a total of three water molecules was involved in hydration, but the importance of the composition variable employed is shown by the fact that a plot of log K_d against log a_w although curved has a slope which never falls below five. Pocker (139) considers that the solvent shift with water concentration of the wavelength of maximum absorption in the near ultra-violet indicates aqueous solvation of the unhydrated ketone, but there is no way of assessing the strength of this interaction on the thermodynamic scale to which the kinetic and equilibrium orders belong.

The kinetic orders found in the present work for the rate of the water-catalysed reaction can be interpreted in the same way as for the equilibrium constant. The linearity of the hydration plot and its slope of 3.65 (or 3.14 with respect to concentration) are together compatible with a transition-state in which three or four water molecules form a ring with the ketone. Three water molecules could be accommodated in the following cyclopentane-like structure



(positions of hydrogens not specified)

in which the hydrogen-bonds are linear and the other five ring atoms are co-planar, while the stereochemistry of a cyclic complex with four ring water molecules might vary from cyclohexene-like to cyclohexane-like (chair form) as the addition reaction progressed.

Both alternatives involve cis-addition to the carbonyl bond, and the experimental evidence cannot distinguish between them. The inclusion of three or four water molecules is in accord with the familiar stability of five- and six-membered rings.

(7) Kinetics in the presence of organic acid catalysts

Leaving aside the results for catalysis by hydrochloric and perchloric acids, the remaining acid catalysts give linear kinetic order plots of positive slope, (although linearity for benzoic acid and o-dichlorophenol has only been established within a lower order of precision). Except for benzoic acid, a semi-quantitative measure of the degree of hydration of these five catalysts has been obtained, while for this one acid qualitative evidence for the phenomenon is available. The hydration numbers are independent of any conclusions regarding the exact number of water molecules involved in the ketone-ketone hydrate equilibrium, since they rely on an empirical relation between K_d and x_w. Their status is similar to that of the descriptions already put forward for the ketone hydrate and for the transition-state of the water-catalysed reaction, as all rely on the assumption that activity data can be accounted for in terms of solvation equilibria.

Two necessary thermodynamic requirements of the above interpretation of the experimental variations of K_d with catalyst mole fraction have already been tested for, namely that the hydration numbers should decrease and the fraction of bound water increase with increasing values of the relative stoichiometric mole fractions of catalyst and water, x_c/x_w^s. The results may be interpreted qualitatively in terms of equilibria of the general type

$$\text{catalyst} + \text{water} \rightleftharpoons \text{hydrated catalyst} \quad ,$$

although competitive solvation of the acids by dioxan could also be included. The cryoscopic results of Bell and Arnold (115) for equimolar mixtures of water and trichloroacetic acid in dioxan up to mole fractions of the two solutes approaching 0.05 indicate a mean hydration number close to unity in such a solution, which agrees at least qualitatively with the behaviour found in the present work, in which lower acid and higher water concentrations were studied. Their results also show that the degree of hydration increases with the two mole fractions, as would be expected on the basis of the equilibria proposed above. It is therefore clear that the catalysts are hydrated in the ground state, and that this cannot be neglected in considering the kinetic order results.

It is possible in principle to obtain the numbers of water molecules, q_T, in the various transition-states by adding the mean hydration number, q_c, of the catalyst in each case to the product of the slopes of the log k_h v. log x_w and log x_w v. log a_w plots (S_h and $\bar{m}'$, respectively). This is done in Table 47 for $x_w = 0.273$, in which rough guesses have been made as to the limiting values of q_c. The same value has been used for all the carboxylic acids on the basis of the closely similar hydration numbers found for acetic and trichloroacetic acids. Although the values of q_T are quantitatively quite unreliable, it is clear that relative to the phenol the higher hydration numbers of the carboxylic acids are at least partly able to compensate for their lower kinetic orders, and that impossibly high degrees of hydration for these acids would be required to obtain q_T values as high as that for water.

TABLE 47

HYDRATION OF TRANSITION-STATES

catalyst	q_c	S_h	$\bar{m}'$	q_T
trichloroacetic acid	5	0.91	4.4	9
monochloroacetic acid	5	0.98	4.4	9
benzoic acid	5	0.92	4.4	9
acetic acid	5	0.98	4.4	9
o-dichlorophenol	1	2.5	4.4	12
water	-	3.65	4.4	16

Two types of transition-state structure may be proposed to account for the qualitative aspects of the above results:

(A) Bell, Millington, and Pink (6) suggested that the transition-state for water-catalysis involves three water molecules in an intimate way and that two of these can be replaced by a molecule of benzoic acid. Extending this to include the present results, all the carboxylic acids must replace two water molecules while the phenol replaces one, and the catalysts keep their hydration shells intact in progressing to the transition-state. Linear log k_h v. log x_w plots are obtained because the binding of the outer water molecules to catalyst and ring water is essentially the same on both sides of the activation equilibrium. The observed kinetic orders will always depend on the structure of the catalyst.

(B) It may alternatively be proposed that all catalysts replace only one of the ring water molecules, and that on doing so lose practically all their water of hydration as a result of the involvement of their hydroxylic groups in ring bonding. According to this suggestion linear plots arise because the binding of the outer water molecules to those making up the ring is similar to that for solvent water molecules and catalyst hydration shells. The observed kinetic orders will then be the same for equally hydrated catalysts, as observed for acetic and trichloroacetic acids, and lower the more strongly hydrated is the catalyst; a general tendency for a decrease in the kinetic order with increasing acid strength might be expected.

The former model has the disadvantage that it is difficult to see how the catalyst can retain its hydration in the transition-state if catalyst-water bonding occurs chiefly through the acidic proton. Apart from this the kinetic order and hydration data alone cannot be said to distinguish between the two models, and the question is returned to after the following section.

(8) Kinetics of mineral acid catalysis

The curved kinetic order plots of negative slope obtained for hydrochloric and perchloric acid catalysis in the present work and for catalysis by sodium benzoate in the work of Bell, Millington, and Pink (6) suggest that such behaviour may be characteristic of strong electrolytes in these solutions. It is not clear to what relative extents long range electrostatic effects and specific ion hydration are responsible, but for the sake of completeness the evidence relevant to the degree of hydration of the ground states is discussed here.

Grunwald and co-workers (140) obtained values for the partial molal free energy of water in 50% by weight water-dioxan mixtures containing various salts at infinite dilution by means of vapour pressure measurements. To interpret these in terms of the Born effect it was found necessary to specify the solvation of the salts, and in particular that appreciable solvation by dioxan was often required. A method for division of the data into separate ionic contributions led to the conclusion that the cations are solvated largely by dioxan and the anions (if at all) by water. That dioxan and other organic solvents can compete (according to their basicity) with water in the solvation of ions has also been suggested by Fratiello and co-workers (141) on the basis of p.m.r. solvent shifts.

Extrapolation of the above behaviour would show ions to be insignificantly hydrated at low water concentrations. However, the conductivity data of Owen and Waters (113), relating to hydrochloric acid in dioxan solutions containing 30 and 18 weight % of water, suggest that the solute should be very largely ion-paired in the solutions of present interest, and the linear catalytic plots obtained at least for perchloric acid show that this process is essentially complete. Under these circumstances hydration might be expected to be more important since the smaller size of the water molecule should allow the best compromise between stabilisation due to ion-solvent and cation-anion interactions. Whether the anion or cation is the more hydrated is immaterial for kinetic order studies, while for the purpose of interpreting the isotope effects the usual model is permitted provided that the bare proton is solvated by at least one water molecule (a situation admitted in Grunwald's treatment).

Several pieces of evidence suggesting that these electrolytes are in fact strongly hydrated in weakly basic organic solvents containing rather little water may be mentioned. Robinson and Selkirk (108) found that the addition of small amounts of hydrogen chloride to such a solution in dioxan caused separation into two phases, of which the more aqueous one took up most of the acid, and Chantooni and Kolthoff (142) have interpreted the effect of added water on the potential of the glass electrode in solutions of tetraethylammonium benzoate in acetonitrile in terms of strong hydration of the benzoate ion. Thus, while electrostatic effects cannot be ruled out, it would be possible to explain the negative kinetic orders observed in catalysis by hydrochloric and perchloric acids at least partly by the loss of water on incorporation of the acids into the transition-state. Such an interpretation would be in accord with the expectation of lower kinetic orders for stronger acid catalysts implied by model (B).

(9) <u>Relation of catalytic effect to acid strength</u>

Table 48 shows the catalytic rate constants k^{c}_{hH} obtained in the present work at $x_w = 0.273$ together with the pK_a values for the acids at $x_w = 1.0$. The pK_a values are those used by Bell and Jensen (21), and the second order rate constant for water catalysis has been obtained by division of the first order constant by the molarity of the solution in water. As pointed out by the former workers, the rate constants for the two mineral acids are in general agreement with those expected for the formal species H_3O^+, but are

TABLE 48

CATALYTIC CONSTANTS AND pK_a's

catalyst	pK_a	k^e_{hH} (M^{-1} sec^{-1})
hydrochloric acid		9.45×10^{-1}
perchloric acid		4.66×10^{-1}
trichloroacetic acid	0.63	6.66×10^{-2}
monochloroacetic acid	2.87	1.39×10^{-2}
benzoic acid	4.20	9.81×10^{-3}
acetic acid	4.76	7.14×10^{-3}
o-dichlorophenol	6.79	2.6×10^{-4}
water	15.7	3.75×10^{-5}

presumably modified to some extent by interaction with the anion. The rate constant for catalysis by o-dichlorophenol is almost a factor of ten lower than might have been expected on the basis of its pK_a, and this may be attributable to steric hindrance.

From their study of 24 acids at a single water mole fraction Bell and Jensen found a value of 0.27 for the Brönsted exponent α_1, defined using the pK_a's for $x_w = 1.0$. However, the different kinetic orders with respect to water found in the present work indicate that α_1 is solvent-dependent, although the effect may not be large. For example, extrapolation of the linear kinetic order plots for catalysis by water and acetic acid to $x_w = 1.0$ changes the difference in the logarithms of the second order rate constants by 11%, while Bell, Rand, and Wynne-Jones (19) found a value for the acid-catalysed hydration of acetaldehyde in water identical with that obtained by Bell and Higginson (17) in 92.5% acetone. Extrapolation of the present data in the direction of very weakly aqueous systems would predict large changes in α_1, but it is doubtful whether linear kinetic order plots can be expected over large changes in composition.

There are three aspects of Brönsted behaviour relevant to the problem of transition-state strusture discussed in section (7). Firstly it can be seen that linear plots of the above type based on pK_a's at $x_w = 1.0$ can only be obtained if as required by structure (B) the kinetic orders with respect to water depend on the acidity of the catalyst; their slopes will change with the solvent composition. Secondly true Brönsted plots based on pK_a's measured at the appropriate solvent composition can be linear and of constant slope according to either postulate (A) or (B), provided that the solvation changes accompanying the acid ionisation process (in terms of which the variation of pK_a with solvent composition may be described) depend in a suitable way on the structure or the acidity, respectively, of the catalyst. Finally, regardless of the value of x_w, linear plots would normally only be expected for reactions passing through transition-states of similar structure, with noticeable positive deviations for any case in which a more favourable reaction path exists; exceptions to this would only be expected if a transition-state having the same structure as all the others were for any reason of unusually high energy. Insufficient data is available to test the first two points, but with regard to the third the well established linear Bronsted plots for carbonyl hydration reactions would appear to favour the postulate (B) of a common transition-state structure over that (A) of bifunctional (or tautomeric) catalysis by the carboxylic acids.

CHAPTER VIII

ISOTOPE EFFECTS AND TRANSITION-STATE VIBRATIONS

(A) Analysis of experimental isotope effects

(1) Equilibrium isotope effects

From Chapter IV the mean isotope effects on the dissociation equilibrium constant of the ketone hydrate in D_2O and in a 50% H_2O-D_2O mixture were found to be, respectively,

$$\frac{K_{dD}}{K_{dH}} = 0.915 \pm 0.020 \quad \text{and} \quad \frac{K_{dHD}}{K_{dH}} = 0.945 \pm 0.018 \text{ at } 25^\circ\text{C.}$$

The very small effect of the protium present in the heavy water has been neglected, and the errors quoted here are as usual the standard deviations.

Edwards and co-workers (143) also found that $K_{dD}/K_{dH} = 0.91$ for acetaldehyde at 20°C., but Gruen and McTigue (5) have reported the value 0.84 for acetaldehyde at 25°C., together with results for a number of other aliphatic aldehydes falling to 0.75. This difference is too large to be due to the different values of the extinction coefficient, ϵ°, assumed. Gruen and McTigue also found that the enthalpy of hydration has a larger negative value in light water, from which they concluded that the direction of the isotope effect is determined by an entropy difference; however, this observation rests on a comparison of small differences in large quantities, and even if experimentally justified could be attributed to an isotope effect on ϵ°.

On the assumption that a molecule of the ketone hydrate contains two equivalent exchangeable hydrogens which are vibrationally distinct from those of the solvent, and also that the total medium effect can be ignored, the present deuterium oxide isotope effect would correspond to a fractionation factor of 1.045 for these two hydrogens. Gruen and McTigue's results would similarly imply fractionation factors of up to 1.15 for aliphatic aldehydes in general.

These values are considerably lower than those of 1.48 and 1.61 calculated on similar assumptions from the dissociation constant data of Ballinger and Long (144), while the analogous experiments of Pocker (145) give the value 1.35 for D-tetra-O-methylglucose. These differences are surprising in view of the similarities in the pK_a's (1), but it is impossible to say whether they reflect differences in the vibrations of the acidic protons or in the medium effects on the two reactions.

The data obtained in the present work for the equilibrium isotope effect in a 50 mole % H_2O-D_2O mixture is in principle capable of giving information relating to the structure of the hydrate. For the above value of K_{dD}/K_{dH}, any model involving two or more equivalent hydrogen atoms would predict a value for K_{dHD}/K_{dH} between 0.955 and 0.957. The experimental value is therefore only consistent with a description in terms of at least two different fractionation factors, and would consequently appear to require the inclusion of more than one water molecule in forming the hydrate. However it is doubtful whether the accuracy of the experimental results is sufficient to justify such a conclusion.

(2) Variation of isotope effect in water catalysis with deuterium atom fraction, n, of solvent.

The much larger value of the isotope effect on the rate of the water-catalysed hydration reaction makes it more likely that useful information can be gained from its variation with the deuterium atom fraction, n, of the solvent. Before considering the results, three relevant theorems derived from the basic isotopic solvent mixture theory of Gold, Kresge, and Long are proved.

I. That $\prod_i (1-n+n\phi_i) > \prod_i \phi_i^n$,

where $0<\phi_i<2$, at least one $\phi_i \neq 1$, and i is any finite number.

The approximate equality of these two factors was pointed out by Goodall and Long (70). The theorem follows from the binomial expansion:

$$\phi_i^n = [1+(\phi_i-1)]^n$$

$$= 1+n(\phi_i-1)+\frac{n(n-1)}{2}(\phi_i-1)^2+\frac{n(n-1)(n-2)}{6}(\phi_i-1)^3+\ldots \qquad (36).$$

Since the third term is always negative and the fourth and succeeding terms may be neglected,

$$1 - n + n\phi_i > \phi_i^n,$$

the difference increasing with the difference between ϕ_i and unity. The inequality must hold also for the product of such factors.

II. That $\prod_i (1-n+n\phi_i)$ has a minimum value for a given i and $\prod_i \phi_i$ when all the ϕ_i's are equal.

This follows from the above since the factor $(\phi_i-1)^2$ in the third term increases rapidly with the difference between ϕ_i and the common point, unity.

III. That the minimum value of $\prod_i (1-n+n\phi_i)$ for a given $\prod_i \phi_i$ decreases with an increase in i.

This also results from the quadratic dependence of the third term on ϕ_i.

According to equation (12), and assuming for the moment that medium effects are negligible, for the water-catalysed hydration of sym-dichloroacetone

$$\frac{k_{hn}}{k_{hH}} = \prod_t (1-n+n\phi_t) \quad ,$$

where the ϕ_t's are the fractionation factors for the t vibrationally distinct protons of the transition-state. For a series of assumed values of t there is a series of progressively decreasing minimum values of k_{hn}/k_{hH}, for each of which all the ϕ_t's are equal, and these are calculated in Table 49 for each of the solvent compositions studied. The calculations were performed remembering that the experimental results refer to n = 99.2% and n = 49.6%.

Making use of the above principles, it can be seen from the table that the data cannot be fitted by a two-proton transition-state. A four-proton model is just acceptable in three of the cases but falls just outside the limits set by the other two; however, such a model imposes the almost certainly unreasonable requirement that all the transition-state protons must have practically identical fractionation factors. It can therefore be concluded from these results that at least three water molecules must be taken up in forming the transition-state of the water-catalysed hydration reaction.

TABLE 49

WATER-CATALYSED HYDRATION IN MIXED H_2O-D_2O SOLUTION

x_w	0.320	0.297	0.273	0.247	0.220
experimental values:					
$\frac{k_{hD}}{k_{hH}}$	0.256	0.251	0.253	0.248	0.249
$\frac{k_{hHD}}{k_{hH}}$	0.539	0.534	0.532	0.532	0.528
calculated minimum values of k_{hHD}/k_{hH} for different t:					
t=2	0.567	0.563	0.564	0.561	0.562
t=4	0.536	0.532	0.533	0.529	0.530
t=6	0.526	0.521	0.523	0.518	0.519
t=8	0.521	0.516	0.518	0.513	0.514
t=∞	0.506	0.501	0.503	0.498	0.499

These must be involved fairly intimately since their protons suffer appreciable changes in their vibrational behaviour, and it is suggested that they form the ring in the proposed cyclic structure. The 2% difference separating the minimum values of k_{hHD}/k_{hH} for the four- and six-proton models should be only just outside the accumulated errors in the kinetic and equilibrium measurements used in evaluating the two isotope effects, but the similarity in the results obtained independently for the five solutions suggests that the above conclusions are experimentally justified. Since the sensitivity of the minimum value of k_{hHD}/k_{hH} to t is greatest at n = 50%, it was considered more profitable to carry out a number of experiments at this one deuterium atom fraction than to distribute them over a range of n. The results of the above isotope effect analysis support the interpretation of the kinetic order of the hydration reaction with respect to water mole fraction presented in the previous chapter.

Mention should be made of the analogous work of Huang, Robinson, and Long (98) on the water-catalysed mutarotation of α-D-tetra-O-methylglucose. Although unaware of the simplifications introduced by the above theorems, these workers were unable to reproduce their experimental isotope effect in the 50% mixture by any combination of fractionation factors for a transition-state in which only two water molecules had been taken up, the predicted result for all fractionation factors equal falling 2% higher than the measured value. Since the glucose derivative is comparable in structure with the hydrated ketone of the present work, it would appear that more water molecules may be involved in this case. It should be added, however, that the interpretation of their results differs from that used in the present work in requiring knowledge of the fractionation factor of the hydroxylic proton in the reactant, and although this does not have a large effect on the shape of the rate versus n curve, the discussion in the previous section indicated the need for further investigations into fractionation factors in such systems.

Application of the above theorems to the results of Gold and Lowe (77) for the isotope effect on the ionic product of water shows without any assumptions as to the values of the fractionation factors that the hydronium and/or hydroxide ions must give rise to additional fractionation effects in the solvent molecules around them. Similarly the data of Batts and Gold (97) for the water-catalysed hydrolysis of acetic anhydride can be shown to require the incorporation of two water molecules, and hence to need interpretation by some scheme such as that presented by the authors.

Finally it is necessary to investigate to what extent the above conclusions depend on the neglect of the medium effect. As explained in the Introduction, small degrees of fractionation at an unspecified number of sites in the solvent may be represented by a linear dependence of the free energy of transfer on n, and this is justified in terms of equation (36) by the fact that the third term becomes negligibly small as ϕ_i approaches unity. The equation for the present case therefore becomes:

$$\frac{k_n}{k_H} = Y^n \prod_t (1-n+n\phi_t) \quad .$$

When $Y = 0.9$, the predicted minimum k_{nHD}/k_{nH} is lowered by 2% for $t = 2$ and 1% for $t = 4$, while for $Y = 1.1$ the changes are similar in magnitude but occur in the opposite direction. Since the evidence currently available suggests that medium effects of this magnitude are restricted to reactions in which modification of centres of negative charge occurs (70,89,90), the above interpretation is probably still valid.

(3) Transition-state structures for other catalysts from kinetics in H_2O-D_2O mixtures

The results obtained for the variation with n of the second order rate constants for the hydration reaction catalysed by water, acetic acid, and trichloroacetic acid at $x_w = 0.273$ are shown in Figure (18). Since the data relating to the two carboxylic acids are probably not accurate to better than 1%, the impurity of protium in the heavy water has been neglected. The curve for trichloroacetic acid differs from the other two in being marginally concave to the composition axis.

In order to perform the same type of analysis as above it is necessary to know the ground state fractionation factors of the catalysts. The only available data relating to dioxan-water mixtures are those obtained by the p.m.r. method by Gold and Tomlinson (92), which show that l (the fractionation factor for the protons of the hydrogen ion) changes from 0.69 in water to 0.80 in a solution of $x_w = 0.14$. This difference could be due as much to a weakening of the vibrations of the solvent water molecules as to any change in the solvation and vibrations of the acidic proton, and to the extent to which this is true the fractionation factors of all other species solvated largely by water will be increased by a similar factor. For want of any other information it has been assumed in the present work that all fractionation factors have the same value as in water, but the less demanding assumption that the isotope effects are unchanged in going to 100% aqueous solution is entirely equivalent as far as the validity of the conclusions are concerned. Medium effects have also been neglected.

In Table 50 the minimum values of k_{hHD}/k_{hH} have been calculated for the inclusion of none ($t = 1$), one ($t = 3$), and two ($t = 5$) solvent water molecules into the transition-states of the two carboxylic acid reactions for which the corresponding experimental data exist. The fractionation factor for acetic acid has been taken as 0.96 from Gold and Lowe (79). That for trichloroacetic acid in water is not known, but for monochloroacetic acid Lewis and Schutz's value of 2.74 for the isotope effect on the acid dissociation constant (146) leads to the value 0.90, or 0.80 if Gold and Lowe's correction for the medium effect is applied. The figure for trichloroacetic acid might be expected to lie between this and 0.69,

TABLE 50

CATALYSIS BY CCl_3COOH AND CH_3COOH in H_2O-D_2O MIXTURES

	CCl_3COOH		CH_3COOH
	$\phi_c = 0.60$	$\phi_c = 0.82$	$\phi_c = 0.96$
experimental values:			
$\frac{k_{hD}}{k_{hH}}$	0.412		0.337
$\frac{k_{hHD}}{k_{hH}}$	0.714		0.641
calculated minimum values of k_{hHD}/k_{hH} for different t:			
t = 1	0.780	0.735	0.709
t = 3	0.674	0.671	0.647
t = 5	0.652	0.657	0.634
$t = \infty$	0.621	0.639	0.580

and calculations have been performed with the arbitrary choices $\phi_c = 0.60$ and $\phi_c = 0.82$ in order to show the relative insensitivity of the results to its value. The subscript HD for acetic acid refers to n = 44.8%. The isotope effect data all refer to solutions of $x_w = 0.273$, the k_{hD}/k_{hH} values obtained from the catalytic plots for the two carboxylic acids being probably more reliable than those obtained from single runs at a variety of water mole fractions.

From the figures in Table 50 it can be seen that for any reasonable value of the fractionation factor for trichloroacetic acid a three-proton transition-state is quite adequate. On the other hand, for acetic acid catalysis the data would appear to require at least five protons, and thus to rule out structure (A) in which two water molecules in the transition-state for water catalysis have been replaced by a single molecule of acetic acid acting bifunctionally (or tautomerically). Consideration of the probable experimental errors, variation of the ground state fractionation factor for the catalyst, and allowance for a medium effect could change the figures by the few percent necessary to allow a three-proton model, and although this would require the fractionation factors to be fairly similar, such a possibility cannot be excluded. It is therefore merely tentatively concluded on the basis of this evidence that structure (A) is rather less probable. When considered with the difficulty of reconciling it with a linear Brönsted plot and of explaining the retention of water of solvation by the catalyst on incorporation into the transition-state, the weight of the evidence would appear to favour the alternative structure (B).

(4) Transition-state fractionation factors

Although a complete analysis of the type undertaken by Gold's school (89,90,77,79) is obviously excluded by the large difference between the number of exchangeable protons involved and the two independent experimental results, it is nevertheless of interest to inquire whether anything can be learnt about the contribution to $\prod_t \phi_t$ of the individual transition-state fractionation factors ϕ_t. The range allowed for the lowest value, ϕ_{low}, in any reaction can be obtained fairly simply by the use of a fourth theorem:

IV. That the minimum and maximum values of ϕ_t (ϕ_1 and ϕ_2, respectively) allowed by the data occur when all the other ϕ_t's are equal (at ϕ_3 and ϕ_4, respectively), and that the range of the lowest value, ϕ_{low}, is between ϕ_1 and ϕ_4.

This again follows from equation (36), which shows that in order to reproduce the rate both at some intermediate deuterium atom fraction and in the isotopically pure solvents it is necessary not only that the geometric mean of the fractionation factors should be constant but that there should also be a balance between their values according to their difference from unity. Since the extreme values of ϕ_t give rise to particularly large $(\phi-1)^2$ terms, the most extreme value possible requires all the others to be equal in order to minimise their contributions. Any increase of ϕ_{low} above the minimum requires the remaining ϕ_t's to spread out in both directions from the common value ϕ_3, and similarly if the largest value ϕ_{big} is less than the maximum ϕ_2, the others must lie above and below ϕ_4. It therefore follows that the lowest fractionation factor must be between ϕ_1 and ϕ_4, which may in turn be calculated from the experimental data. The truth of this theorem has been checked by trial calculations for a five-proton transition-state, using the results for acetic acid catalysis.

The allowed ranges of the lowest and highest fractionation factors in the transition-states for catalysis by trichloroacetic acid, acetic acid, and water are given in Table 51. The results for water catalysis at $x_w = 0.273$ have been used, and for trichloroacetic acid calculations have been performed for three possible ground state fractionation factors, $\phi_c = 0.60$, 0.82, and 1.00. A six-proton model is assumed for the water-catalysed reaction, and a five-proton model for the other two.

TABLE 51

ALLOWED RANGES OF LARGEST AND SMALLEST TRANSITION-STATE FRACTIONATION FACTORS

	range of ϕ_{low}		range of ϕ_{big}	
	ϕ_1	ϕ_4	ϕ_2	ϕ_3
CCl_3COOH ($\phi_c = 0.60$)	0.35	0.62	1.62	0.92
CCl_3COOH ($\phi_c = 0.82$)	0.38	0.67	1.67	0.97
CCl_3COOH ($\phi_c = 1.00$)	0.39	0.69	1.77	1.01
CH_3COOH ($\phi_c = 0.96$)	0.60	0.75	1.05	0.86
H_2O ($\phi_c = 1.00$)	0.57	0.75	1.07	0.85

The results in Table 51 show that at least one of the transition-state protons has a rather low fractionation factor, and particularly in the case of trichloroacetic acid this is in the range normally found only for protons which are involved in the reaction coordinate. However, the allowed range lies very much at the upper end of that found in primary isotope effect studies with carbon acids. Further calculations showed that changes in the assumed number of protons were felt almost exclusively in the common values, ϕ_3 and ϕ_4. These conclusions are all that can be drawn without making further assumptions concerning the various transition-states.

More detailed information can be gained regarding the fractionation factors if it is assumed that values much larger than unity can be excluded. This is a reasonable assumption on the basis of the general correlation between ϕ and acidity noted in the Introduction, the non-observation of inverse primary hydrogen isotope effects, and the value $\phi = 1.04$ found for the hydroxylic protons of the ketone hydrate. Inspection of the limiting values for trichloroacetic acid in Table 51 shows that as ϕ_{low} increases from ~ 0.38 to ~ 0.67, ϕ_{big} must also increase from ~ 0.97 to ~ 1.67; restriction of ϕ_{big} to values $\leqslant 1.04$ confines ϕ_{low} to the lower end of its allowed range. Calculation of possible sets of values (by fixing three and then solving for the other two) in fact showed that by making ϕ_{low} only 0.02 larger than the limiting value ϕ_1 at least one fractionation factor was forced to take on values higher than 1.04, so that for this catalyst $\phi_{low} \simeq \phi_1$. The high sensitivity of the spread of the other four fractionation factors to the value of ϕ_{low} in this case can be understood from equation (36), since the $(\phi-1)^2$ term is particularly large for the latter proton. A similar further restriction on the value of ϕ_{low} for the other two catalysts cannot be made, as their ϕ_{big} values fall in a lower range. The conclusion that ϕ_{low} for the trichloroacetic acid catalysed reaction lies between 0.35 and 0.41 is subject to some uncertainty arising from experimental error, but it can be shown to have a value below those for the acetic acid- and water-catalysed reactions provided that the comparison of the data is justified to better than 7%. This requirement should certainly be met for trichloroacetic acid and water, although the validity of the results for acetic acid may be more in question as a result of the corrections which had to be applied to the primary data.

The analysis so far presented in this chapter illustrates how useful information may be obtained from kinetic studies in H_2O-D_2O mixtures even when the possible number of exchangeable protons in the transition-state far outweighs the number of independent data. The number of such protons is easier to define the smaller the differences between their fractionation factors, but on the other hand if this number is assumed the fractionation factors are more closely specified the wider their variation. For this type of treatment, which is concerned with obtaining data most sensitive to t and the ϕ_t's rather than with testing the theory over the widest possible range, it would appear better to concentrate experimental measurements at the ends and centre of the rate versus n curve. Finally, the analysis is greatly simplified by the use of a number of related theorems describing qualitatively some of the features of isotopic solvent mixture theory.

(5) Magnitude of the isotope effects

The observed values of the isotope effects on the rate of acid-catalysed hydration of sym-dichloroacetone are listed in Table 52 in order of decreasing catalytic constants at $x_w = 0.273$. Since the drawing of fine distinctions between values is not intended, the isotope effects given are those obtained by averaging all the measured values. The ground state fractionation factors, ϕ_c, of the acids in water are given in the fourth column, that for benzoic acid having been obtained from the acid dissociation data of Rule and La Mer (147), combined with the medium effect found for the ionisation

TABLE 52

MAGNITUDE OF KINETIC ISOTOPE EFFECTS

catalyst	k^{e}_{hH} (M^{-1} sec.$^{-1}$)	k^{e}_{hH}/k^{e}_{hD}	ϕ_e	$\prod_t \phi_t$
HCl	9.45×10^{-1}	1.23	0.69	0.27
$HClO_4$	4.66×10^{-1}	1.29	0.69	0.25
CCl_3COOH	6.66×10^{-2}	2.46	0.75	0.30
$CH_2ClCOOH$	1.39×10^{-2}	2.92	0.80	0.27
PhCOOH	9.81×10^{-3}	2.76	0.91	0.33
CH_3COOH	7.14×10^{-3}	2.94	0.96	0.33
H_2O	3.75×10^{-5}	3.97	1.00	0.25

of acetic acid by Gold and Lowe (79). The value for trichloroacetic acid has been arbitrarily taken as the mean of those for monochloroacetic acid and the hydronium ion, and the origin of the other values has already been discussed. The last column gives the calculated fractionation factor product for the transition-states on the assumption of a zero net medium effect in all cases and the structure H_3O^+ for the mineral acid catalysts.

It can be seen from the table that the general correlation of isotope effect with acid strength can be attributed almost entirely to the variation of catalyst fractionation factors in the ground states. The range of 320% in the isotope effects has been reduced to one of only 30% in the transition-states. An even closer similarity can be demonstrated if the extra secondary protons in the structure (B) transition-states for water- and hydronium ion-catalysis are allowed for, but the assumptions made in obtaining the $\prod \phi_t$ values hardly warrant detailed consideration of such small differences. The similarity of these results lends further circumstantial support to the view that all the transition-states have similar structures.

A number of the isotope effects found in the present work may be compared with those found for the hydration of acetaldehyde (165) and the mutarotations of tetramethylglucose (98) and glucose (114). Table 53 shows that there is a fairly close similarity with the results of the present work, although rather less close than that between the data for acetaldehyde and the two mutarotations. The difference may reflect the change of either substrate or solvent.

TABLE 53

ISOTOPE EFFECTS IN RELATED REACTIONS

catalyst	H_3O^+	AcOH	H_2O
hydration of sym-dichloroacetone	1.23-1.29	2.94	3.97
hydration of acetaldehyde	1.30	2.59	3.61
mutarotation of tetramethylglucose	1.34	2.46	3.58
mutarotation of glucose	1.37	2.59	3.80

****

(B) Hydrogen vibrations in the transition state

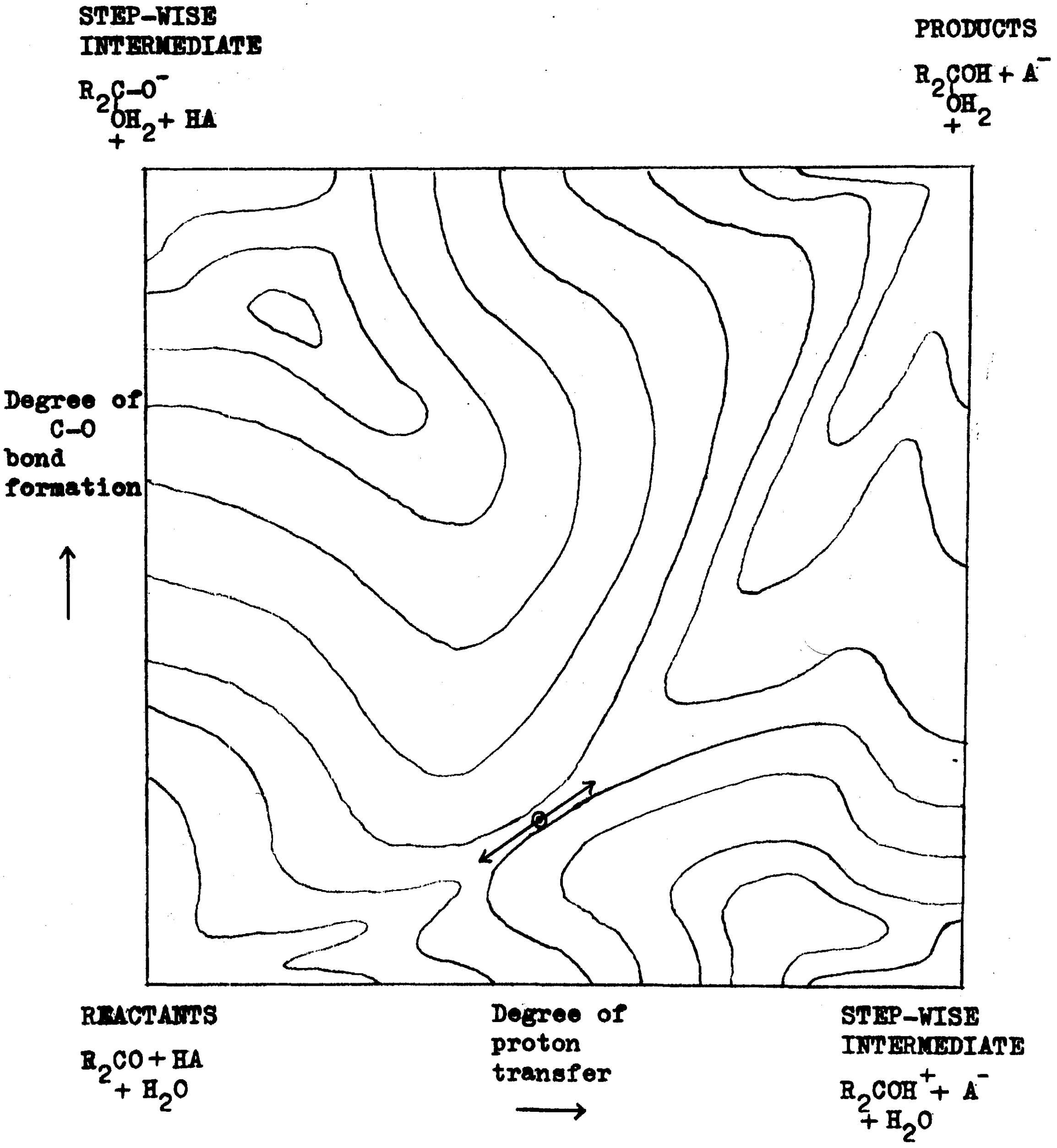
It was established in the Introduction that on the basis of the rates and general acid-base catalysis of carbonyl hydration reactions there is good evidence for a concerted mechanism passing through a cyclic transition-state, although nothing could be said concerning its configuration. It follows that even if a three-centre model is adequate to explain the isotope effects in proton transfers from carbon atoms (about which there is some doubt) it certainly cannot be so in the present case, in which nucleophilic attack of oxygen on carbon and the transfer of several hydrogens may be occurring concurrently. The remainder of this chapter is devoted to a discussion of the factors affecting the hydrogen isotope effect in concerted reactions.

(6) Concerted proton transfer and nucleophilic attack

It is proposed to discuss a simplified model of a reaction in which the products differ from the reactants both in the transfer of a proton from a general acid catalyst to an oxygen atom and the formation of a carbon-oxygen bond. The reaction is regarded as concerted, (i.e. the transition-state contains all the participating species), but the configuration could be described by any degree of completion of the two processes. A typical example is depicted by the potential energy surface in Figure (19), which is similar to those used by Albery (42) and More O'Ferrall (148) in a discussion of solvent bridges and E2 eliminations, respectively. The two axes represent the degrees of completion of the two processes, with the implicit assumption that the main features of the reaction may be expressed adequately in terms of two configuration variables. The chemical species depicted at the corners of the diagram refer to the example of general acid-catalysed carbonyl hydration in which the cyclic nature of the transition-state has been disregarded, but the surface could serve equally well for a variety of reactions. It

FIGURE 19

Potential energy surface for partly synchronous reactions.



shows a case in which a partly synchronous reaction path is favoured over a completely step-wise sequence, the transition-state having a configuration in which the proton is roughly half transferred, while carbon-oxygen bond formation is rather less far advanced.

It is now possible to discuss the vibrational behaviour of the transition-state, and hence the hydrogen isotope effect, in terms of the potential energy surface. Bending vibrations are considered to behave as in an analogous non-concerted reaction, and are therefore ignored. The direction of the double arrow located at the transition-state shows the direction of maximum negative curvature, which may for convenience be termed the 'reaction path' without implying that all complexes decompose exactly along it. The first point to make is that in general this direction is not determined by the configuration; in the present case it lies along a tangent to a smooth curve drawn through the transition-state and the end-points, but there is no physical reason for such a path, which would in any case depend on the choice of variable used to define the configuration. The second point is that the normal modes of vibration depend not only on the curvature of the potential energy surface in all directions but also on the masses of the atoms, so that in general the reaction coordinate makes an angle with the reaction path.

Although a rigorous discussion of the isotope effect can be seen to require a knowledge of the force constants and atomic masses for every part of the system undergoing modification during the reaction, a fairly good approximate treatment can be carried out if use is made of the principle of the separability of hydrogenic vibrations. It can in fact be shown by a very similar method to that used by Bigeleisen and Goldstein (67) in their demonstration of the rule of the geometric mean for systems with large quantum corrections that this principle is particularly valid for the purpose of calculating an isotope effect, provided that the tunnel correction can be expressed by Bell's equation (equation 4) expanded to its first approximation. Using this simplification, the hydrogen isotope effect may be assessed from the frequency of vibration of the hydrogen atom constrained to move parallel to the horizontal axis in Figure (19). It can therefore be seen that unless the reaction path is perpendicular to the C-O bond formation axis the isotope effect will be lower than for a non-concerted reaction.

A more thorough treatment would require the addition of a third dimension to the potential energy surface to allow the proton transfer coordinate to be resolved into one for the motion of the proton and another for the relative motion of its donor and acceptor sites, just as in the usual three-centre treatment of simple proton transfer reactions. The reaction path would then make an increasingly large angle with the axis for motion of the proton the more the extent of proton transfer in the transition-state differed from one half and the more the carbon-oxygen bond formation process took part in the reaction path. Provided that the curvature of the potential energy surface in the neighbourhood of the transition-state for a concerted reaction is not enormously different from that for other types of reaction, the hydrogen isotope effect for any extent of proton transfer should be lower than if the reaction were not concerted, the difference depending on the particular route taken by the reaction in going over the surface.

Mention should be made of the 'solvation rule' of Swain, Kuhn, and Schowen (149), which states that any reaction in which proton transfer between oxygen atoms is concerted with the formation or rupture of other bonds proceeds by an essentially stepwise mechanism, and passes through a transition-state in which the proton transfer process has either been almost completed or hardly begun. Their evidence rests on the low value of the solvent hydrogen isotope effect in many such reactions, for example in the base catalysed formation of tetrahydrofuran from 4-chlorobutanol $k_H/k_D = 1.28$ for the water-catalysed and 0.93 for the hydroxide ion-catalysed reaction. However, in terms of the above treatment some of these low values may be due to strong participation of the heavy atom changes in the reaction path even when the proton is partly transferred, as has been pointed out by Cordes (150), and this would offer a somewhat more convincing explanation of the general acid and base catalysis observed for many of these reactions. Isotope effect studies would appear to be a rather less reliable indication of configuration in concerted reactions than in simple proton transfers. A less defensible argument has been put forward by Williams and Kreevoy (96), who suggest that A-S_E2 reactions are likely to be step-wise on the grounds that hydrogenic and heavy atom motions are not usually well coupled; this overlooks all the distinctions made here between reaction coordinate, reaction path, and transition-state configuration.

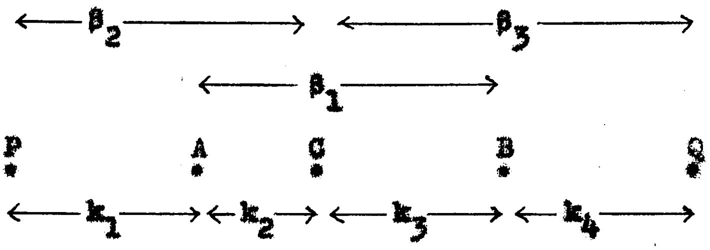
The hydrogen isotope effects observed in base catalysed E2 eliminations are often rather lower than those found in proton abstractions from carbon acids, and it is possible that this is due to significant participation of other aspects of the process in the reaction path. These ideas may also be tentatively extended to the latter class of reactions to explain the fact that quantum mechanical tunnelling does not appear to be large in many reactions passing through symmetrical transition-states. However, detailed assessment of the influence of participation by the activating group on the isotope effects in less symmetrical transition-states requires assumptions concerning a number of force constants, i.e. the problem is essentially that discussed above for reactions which are strongly concerted.

(7) Isotope effects for concerted transfer of two hydrogen atoms

The cyclic mechanism for carbonyl hydration envisages that, in addition to the concurrent transfer of a proton and formation of the carbon-oxygen bond, other proton transfers may also be taking place. The reaction could be described by a multi-dimensional potential energy diagram in which could be specified the configuration of the transition-state and the angle made by the reaction path at this point with the various displacement coordinates. The magnitude of the solvent isotope effect depends not only on the extent to which the heavy atom changes participate in the reaction but also on the relative participation of the hydrogen atoms.

Murrell and Laidler (151) have shown that it is impossible for one point on a potential energy diagram to represent the transition-state for more than one reaction. It follows therefore that, irrespective of the number of hydrogen atoms undergoing transfer, only one vibrational mode may be imaginary, and the isotope effect will to a first approximation be normal in magnitude. Any further conclusions must depend on the choice of a particular model for the transition-state, making assumptions regarding the masses and force constants. An electrostatic model, in which three centres of negative charge were fixed on a ring and three protons were allowed to move between them, was investigated by Bell, Millington, and Pink (6), but this only satisfied the requirement of a single imaginary vibration frequency when not more than one proton was partly transferred in the transition-state, and is therefore unsatisfactory for the present purpose. A purely electrostatic force field emphasises the effect of nearest neighbour interactions, and so is less useful for discussing concerted reactions in which a partly synchronous route may be followed because of the effect of interactions between more distant parts of the molecule.

A brief discussion is presented here based on a simple linear system involving the transfer of two hydrogen atoms, A and B, between three heavy atoms P, C, and Q. Stretching vibrations are dealt with first.



Using the four simple force constants (k's) and three interaction force constants (β's) depicted above, the change in potential energy for small displacements, x, along the line of centres is given by

$$\Delta V = \tfrac{1}{2}\, k_1(x_A - x_P)^2 + \tfrac{1}{2}\, k_2(x_C - x_A)^2 + \tfrac{1}{2}\, k_3(x_B - x_C)^2 + \tfrac{1}{2}\, k_4(x_Q - x_B)^2$$

$$+ \beta_1(x_C - x_A)(x_B - x_C) + \beta_2(x_A - x_P)(x_C - x_A) + \beta_3(x_B - x_C)(x_Q - x_B)$$

The usual treatment results in a rather unwieldy quartic expression which is not reproduced here, but application of the principle of separability of hydrogenic vibrations by assigning infinite masses to the heavy atoms gives the simpler equation:

$$\lambda^2 - \lambda\left[\frac{(k_1 + k_2 - 2\beta_2)}{m_A} + \frac{(k_3 + k_4 - 2\beta_3)}{m_B}\right]$$

$$+ \frac{1}{m_A m_B}\,(k_2k_3+k_1k_4+k_1k_3+k_2k_4-\beta_1{}^2-2k_1\beta_3-2k_3\beta_2-2k_2\beta_3-2k_4\beta_2+4\beta_2\beta_3) = 0 \qquad (37)$$

in which m_A and m_B are the atomic masses, $\lambda = 4\Pi^2\nu^2$, and ν represents a normal vibration frequency.

It was not considered worthwhile to solve the above equation for all possible relative values of the seven constants, but a few sample calculations were performed for the system corresponding to synchronous half transfer of the two atoms. Such a configuration is characterised by the relations:

$$k_1 = k_2 = k_3 = k_4 = k_A, \text{ and } \beta_2 = \beta_3 = \beta_0$$

The results are shown in Table 54, in which ν' is a non-dimensional quantity given by

$$\nu'^2 = \lambda \frac{m_H}{k_A}$$

m_H being the atomic mass of hydrogen. ν'_s is the frequency of the symmetric stretching mode, while ν'_a refers to the asymmetric vibration, and both are calculated for the di-proto species.

TABLE 54

VALENCY FORCE FIELD CALCULATIONS

	β_0/k_A	β_1/k_A	ν'_s	ν'_a
(a)	1.0	1.0	1.00	i 1.00
(b)	1.0	2.0	1.41	i 1.41
(c)	2.0	2.0	0.00	i 2.00
(d)	2.0	1.0	i 1.00	i 1.73
(e)	0.5	1.0	1.41	0.00
(f)	0.5	2.0	1.73	i 1.00

These figures show the dependence of the vibrational behaviour on the relative magnitudes of the interaction force constants. Cases (a) and (b) both have equally important real and imaginary frequencies, (f) and (c) represent situations in which the former and latter predominate, respectively, while systems (d) and (e) can be excluded as transition states. The frequencies of the di-deutero species will be lower by a factor of $2^{\frac{1}{2}}$ in all cases. The isotope effects depend also on the ratio of k_A to the bond force constants in the ground state, but provided that excessive weakening does not occur in going to the transition-state it can be seen that the condition for an isotope effect similar in magnitude to that for a simple symmetrical proton transfer is

$$\beta_o < k_A < \beta_1$$

It would be expected that any less symmetrical configuration would lead to lower values. Since the 'a priori' prediction of transition-state force constants must be very hazardous, it can merely be concluded that large or small isotope effects are possible, and that the magnitude of an isotope effect is likely to be an uncertain measure of transition-state configuration. The principle of the separability of hydrogenic vibrations was shown to be a good approximation by solving the quartic expression for case (a) in which the heavy atom masses were put at $16m_H$; two frequencies differing from those quoted above by no more than 5% were found, together with two lower real frequencies which showed practically no sensitivity to isotopic substitution.

Apart from the possible occurrence of large isotope effects, the synchronous transfer of two hydrogen atoms may also lead to special effects resulting from the breakdown of the rule of the geometric mean for the transition-state. In a situation in which the symmetric stretching mode has a numerically much larger frequency than the asymmetric vibration, the transition-state resembles the hydrogen molecule and exhibits the largest possible deviations from the rule. These are offset by identical deviations occurring in the isotope effect on the asymmetric vibration, but complete cancellation can only occur when the two frequencies are numerically equal and the tunnel correction is adequately accounted for by the first approximation to Bell's equation (equation 4). Highly synchronous proton transfer should therefore give either large isotope effects or large deviations from the rule of the geometric mean.

Since these deviations may be much larger than those occurring in water, the latter may be neglected and a fairly simple account given of the consequences of the former. This treatment therefore differs from those mentioned in the Introduction, which show that small deviations from the rule tend to cancel between the two sides of an equilibrium. The total amount of an activated complex XL_AL_B in which the hydrogens at the two distinct sites A and B are undergoing synchronous transfer is related to the amount of the di-proto species through the fractionation equilibria:

$$XH_AH_B + \tfrac{1}{2}D_2O \rightleftharpoons XD_AH_B + \tfrac{1}{2}H_2O \qquad \phi_{BH}$$

$$XH_AH_B + \tfrac{1}{2}D_2O \rightleftharpoons XH_AD_B + \tfrac{1}{2}H_2O \qquad \phi_{AH}$$

$$XD_AH_B + \tfrac{1}{2}D_2O \rightleftharpoons XD_AD_B + \tfrac{1}{2}H_2O \qquad \phi_{AD}$$

The subscripts under the fractionation factors refer to the nature of the isotope not undergoing substitution. Thus,

$$[XL_AL_B] = \frac{[XH_AH_B]}{(1-n)^2}\left[(1-n)^2 + \phi_{AH}n(1-n) + \phi_{BH}n(1-n) + \phi_{BH}\phi_{AD}n^2\right] \qquad (38)$$

When the rule of the geometric mean is obeyed, $\phi_{AH} = \phi_{AD}$, and the expression reduces to the more familiar one:

$$[XL_AL_B] = \frac{[XH_AH_B]}{(1-n)^2}(1-n + n\phi_{AH})(1-n + n\phi_{BH}) \qquad (39)$$

Under particularly favourable conditions (for example in acid-catalysed hydride transfer reactions) it might be possible to show that equation (38) is followed rather than (39). This is ruled out in the present case by the large number of exchangeable protons involved, but the inapplicability of equation (39) nevertheless cannot be ignored as it can be shown that appreciable errors can arise in the measured values of the two fractionation factors. For example if $\phi_{BH} = \phi_{AH} = 0.55$ and $\phi_{AD} = 0.45$, their substitution into equation (38) at $n = \frac{1}{2}$ and $n = 1$ followed by solution of equation (39) at these two values of n leads to the result $\phi_{AH}, \phi_{BH} = 0.78, 0.31$. Any description of a reaction in terms of a highly synchronous transfer of two protons must therefore take account of this effect.

Bending vibrations can be discussed much more briefly. Calculations were performed using a linear 5-centre model with equal bending force constants opposing angular deformation at all five centres, and gave two frequencies above and below those calculated for single transfers with similar assumptions as to the force constant. The principle of separability of hydrogenic vibrations was shown to be a good approximation, and the rule of the geometric mean was obeyed well for the sum of the two vibration frequencies. It therefore appears that, as was assumed in the case of synchronous hydrogen transfer and heavy atom bond formation, any special features in the isotope effects for such reactions can be attributed to the character of vibrations which involve the greatest degree of motion along the chemical bonds.

CHAPTER IX

CONFIGURATION OF THE TRANSITION-STATE

The first two chapters of the Discussion were concerned largely with interpreting the kinetic orders with respect to water, catalyst hydration numbers, linear Brönsted plot, and variation of the rate with the solvent deuterium atom fraction in terms of the composition of the transition-state. Although the inclusion of several water molecules in an intimate manner was shown to be supported by a number of observations, the postulate that these molecules form a ring structure still rests solely on the argument of Eigen presented in the Introduction. An important requirement that can be made of this postulate is that it should permit a description of the configuration of the transition-states which is able to explain further aspects of the experimental data, chiefly the Brönsted exponent and the kinetic isotope effects. As pointed out in the last chapter, the magnitude of the isotope effect in a concerted reaction cannot be related unambiguously to any unique configuration, and a similar point may be made for the Brönsted exponent, which is a measure of the influence of changes in the catalyst on the energy of the whole reacting system. There is therefore no alternative to the use of some theory which can predict the configuration of a transition-state of assumed structure, both the theory and structure being judged together by the success of these predictions.

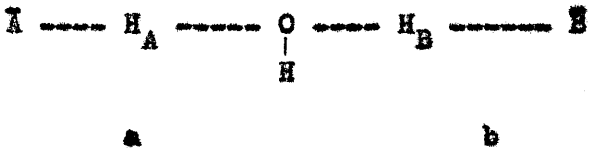
The most widely used measure of transition-state configuration is provided by the total free energy change in the reaction step through the Hammond postulate (52), but its application to a concerted process is uncertain since more than one bond is undergoing modification. The 'solvation rule' of Swain, Kuhn, and Schowen (149) regards reactions in which proton transfers between atoms having unshared pairs of electrons are concerted with changes in the bonding of heavy atoms as passing through transition-states in which the proton transfers have either hardly begun or are practically complete, but Kurtz and Coburn (20) were unable to reconcile this with the relative activation parameters found in the water- and hydronium ion-catalysed hydrations of acetaldehyde. As pointed out in the previous chapter and by Cordes (150), the experimental basis for the solvation rule may be questioned, and there seems no reason why it should apply in every case. A similar type of objection may be made to the use of an electrostatic model, since this is equivalent to the prior assumption that the reaction proceeds by a step-wise mechanism.

Thornton's modification (152) of the 'reacting bond' rule of Swain and Thornton (153) is capable of dealing with reactions in which the concerted processes occur synchronously or in a step-wise manner, although it can only predict the changes which occur in an assumed configuration when some small change is made in the electron-donor power of a substituent. A related but more easily applicable treatment has recently been given by More O'Ferrall (148) and applied to E2 eliminations, in which changes in the transition-state are assessed from changes in the stability of the intermediates which would have been formed in the corresponding hypothetical step-wise processes. Both these treatments depend on the principle, justified by Thornton, that applied perturbations have a different effect on changes in configuration occurring along the reaction path than those occurring at right angles to it.

While the above approaches are very valuable in correlating observations for a wide range of reactions, they have the disadvantage that they are necessarily only qualitative and give no indication of the nature of the transition-state in any one reaction. In the present chapter a semi-quantitative model is developed which deals with situations such as the present one in which one bond change involving heavy atoms is concerted with a number of proton transfers. The potential energy surface, and hence the position on it of the transition-state, is calculated by means of an assumed energy function in which the coefficients are obtained from the energies of the intermediates of the hypothetical step-wise processes. In this respect there is a close resemblance to More O'Ferrall's approach, but by restricting attention to reactions in which all but one of the internal bonding changes concern proton transfers use can be made of the considerable amount of available data on proton transfer equilibria and the simple relations between them. This allows a semi-quantitative application, with the consequent prediction (at least in principle) of absolute configuration.

(1) <u>Description of the model</u>

The mode of application and chief assumptions of the model may be illustrated by reference to the simple case of a hypothetical concerted transfer of two protons:



$$\bar{A} \cdots H_A \cdots \underset{\displaystyle H}{\overset{}{O}} \cdots H_B \cdots \bar{B}$$

The total reaction

$$AH + \bar{B} \longrightarrow \bar{A} + HB$$

is considered to proceed through the intermediacy of a water molecule, and the charge type of the reaction is not important. The configuration at any point on the potential energy surface may be represented by the coordinates a and b, which may be expressed by the method used by Albery (42) in terms of the ratios of the partial bond lengths,

$$a = \frac{AH_A}{AO} \;, \quad \text{and} \quad b = \frac{OH_B}{OB} \quad .$$

As pointed out by Bell, Millington, and Pink (6), a synchronous mechanism will be preferred only if the transfer of one proton produces a sufficient lowering of the energy required to transfer the other. That there is such an interaction, at least in the energy of the total reaction, can readily be seen from the fact that transfer of H_B from H_3O^+ is much easier than from H_2O. If the single transfer of H_A or H_B requires an energy E_A or E_B, respectively, the energy required for the second process after completion of the first can be written $E_B - E_1$, and the total energy for the whole reaction irrespective of the sequence is given by

$$E = E_A + E_B - E_1 \quad .$$

The model proposed here makes the simplest possible assumptions, namely (i) that the energy required for either process occurring separately is a linear function of its degree of completion, and (ii) that if H_A is transferred to an extent a, the total energy for the transfer of H_B is given by $E_B - aE_1$. These may be combined in the complete energy function

$$E_{ab} = aE_A + bE_B - abE_1 \quad . \qquad (40)$$

Eigen (34) has shown that the assumption of non-activated transfer between oxygen atoms is a good one for pK_a differences of more than 2 or 3 units, while the results of Grunwald and co-workers (154) indicate that even for a zero pK_a difference the reaction is still very fast. A more realistic approach might therefore be to define new parameters a' and b' in terms of the energy changes, so that the only assumption is that relating to the form of the interaction term; since the true potential energy profile for a single hydrogen transfer is almost certainly concave to the reaction coordinate, the transition-state configuration will be described by values of a and b which are smaller than the calculated values a' and b'. This should be borne in mind when interpreting the results.

The coefficients E_A, E_B, and E_1 may be obtained from the pK_a's of AH, BH, H_2O, and H_3O^+ by putting in three of the conditions a,b = 0,1. In the present example

$$E_A = pK_a(AH) - pK_a(H_3O^+)$$
$$E_B = pK_a(H_2O) - pK_a(BH)$$
$$E_1 = pK_a(H_2O) - pK_a(H_3O^+) \quad ,$$

where the energies are expressed in the reduced units of $moles^{-1}$ after division by RT. The use of pK_a differences to measure the energy of transfer of a proton from one stable hydrogen-bonded state to the other involves the assumption that the formation of each of these states from that in which the acidic and basic components are solvated by water requires a similar change in free energy. Provided that hydrogen bond energies vary in a fairly uniform manner with the strength of the acid or base, the error involved in this assumption should increase with the pK_a difference, and should therefore not affect predictions of transition-state configuration.

Figure (20) shows the potential energy surface calculated according to equation (40) for the above concerted proton transfer when $pK_a(AH) = 5.0$ and $pK_a(BH) = 3.0$. The figures on the surface indicate the energies of the respective contours. Since $pK_a(H_2O) = 15.7$ and $pK_a(H_3O^+) = -1.7$, $E_A = 6.7$, $E_B = 12.7$, and $E_1 = 17.4$. The configuration of the transition-state is obtained from the requirement that the change in energy caused by a small change of configuration should be zero at this point. Thus,

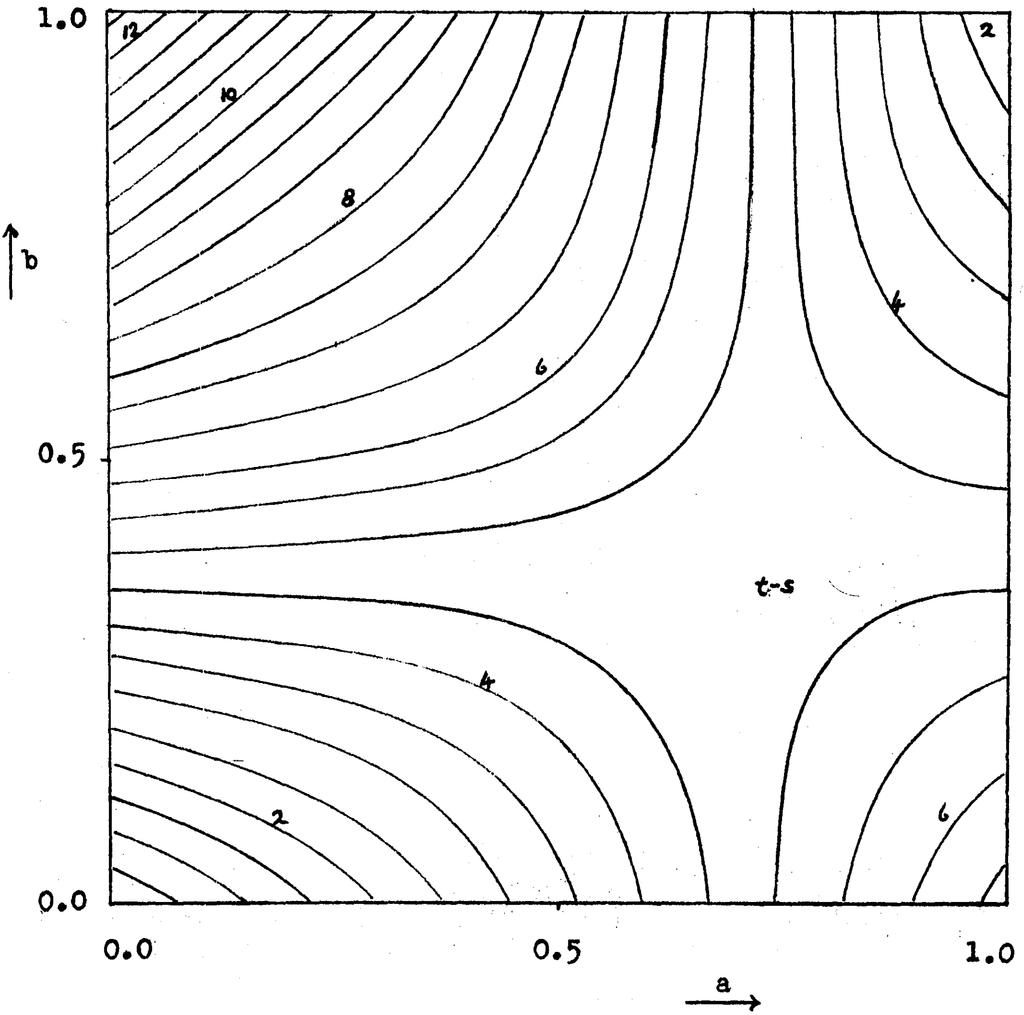
$$\left(\frac{\partial E}{\partial a}\right)_b = E_A - bE_1 = 0 \qquad (41.a)$$
$$\left(\frac{\partial E}{\partial b}\right)_a = E_B - aE_1 = 0 \qquad (41.b) \quad ,$$

from which the configuration is specified by

$$(a_{ts}, b_{ts}) = \left(\frac{E_B}{E_1}, \frac{E_A}{E_1}\right) = (0.73, 0.38) \quad .$$

FIGURE 20

Calculated potential energy surface for concerted proton transfers.



The easier of the two transfers can be seen to be the further advanced. The energy of the transition-state, measured relative to $E_{0,0} = 0$, is given by

$$E_{ts} = \frac{E_B}{E_1} \cdot E_A + \frac{E_A}{E_1} \cdot E_B - \frac{E_B}{E_1} \cdot \frac{E_A}{E_1} \cdot E_1 = \frac{E_A E_B}{E_1} \qquad (42)$$

$$= 4.9,$$

while the energy of the product is 2.0. If for any reason the reaction were obliged to proceed through a solvent bridge of this type, the fairly synchronous path described here would appear to offer a more facile route than either of the two intimate step-wise mechanisms proceeding through intermediates represented by the top left- and bottom right-hand corners of Figure (20).

Comparison of Figures (19) and (20) reveals some of the over-simplifications brought about by equation (40). The differences are largely related to the fact that in Figure (20) the intermediates of the two hypothetical step-wise processes do not lie in stable potentials; reduction of the energy at the appropriate corners will convert the surface to one more similar to that in Figure (19).

If a change is made in the strength of the acid AH, a corresponding change is brought about in E_A, but E_B and E_1 are unaltered. The Brönsted exponent α is therefore given by

$$\alpha = \left(\frac{\partial E_{ts}}{\partial E_A}\right)_{E_B, E_1} = \frac{E_B}{E_1} = a \qquad (43.a),$$

and the corresponding quantity β for substitution of B by

$$\beta = \left(\frac{\partial E_{ts}}{\partial E_B}\right)_{E_A, E_1} = \frac{E_A}{E_1} = b \qquad (43.b)$$

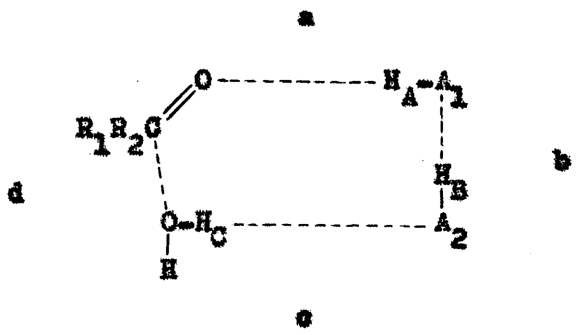
The model can be seen to predict linear Brönsted plots over a large range of acid and base strength, the value of the slope corresponding to the degree of completion of the proton transfer which occurs from or to the acid or base undergoing substitution. The latter interpretation of the Brönsted exponent has often been assumed in discussions of transition-state configuration for reactions in which a proton transfer is concerted with some other process, for example by Cordes (155).

Finally it is necessary to discuss the application of the model when one or both of E_A and E_B are either negative or greater than E_1. The energy function (equation 40) is clearly unsatisfactory outside the ranges $0 \leqslant a,b \leqslant 1$, where in reality it should rise steeply, and the simplest remedy for this is to make it infinite at all points outside the potential energy diagram of Figure (20). If there is no solution to equations (41) inside the allowed range, at least one of the coordinates must be zero or unity in the transition-state. For a two coordinate system inspection of the potential energy diagram shows that the whole process is then non-activated, but this is not a necessary result in other cases.

The particular problem of the mechanism adopted in single proton exchanges proceeding through solvent bridges is returned to after the discussion of carbonyl additions.

(2) Application to the acid-catalysed hydration of sym-dichloroacetone

In this section the above model is applied to a cyclic complex of the structure (B) type, as depicted below:



The reaction consists of the transfer of H_A, H_B, and H_C, and the formation of the C–O bond, the degrees of completion of these processes at any stage being described by the four coordinates a,b,c, and d. When the general acid is represented by A_1H_A, A_2H_B being a water molecule, the mechanism is one of 'true' general acid catalysis and is essentially a cyclic modification of that proposed by Bell and Higginson (17). The kinetically indistinguishable variation put forward by Gruen and McTigue (35), which may be described as 'specific acid + general base' catalysis, is obtained by making A_2H_B the acid catalyst and A_1H_A a water molecule. As Jencks has pointed out (156), although the first alternative might intuitively be preferred for the hydration reaction, the opposite is true in the reverse direction, for which the labels put in inverted commas must be interchanged. Calculations were performed for both types to investigate whether the present model can distinguish between them.

The energy function is constructed using the same principles as in the simple example discussed above. The choice of interaction terms is decided by the requirement that the function must be able to reproduce the experimental free energy change for any combination of completed single processes. This leads to the following expression:

$$E_{a,b,c,d} = aE_A + bE_B + cE_C + dE_D - abE_1 - bcE_2$$
$$- cdE_3 - daE_4 - adcE_5 \qquad (44)$$

The last term accounts for the fact that when d = 1 the energy for transfer of H_C depends on whether a = 0 or 1, and vice versa. No attempt has been made to account separately for the change in bond order of the carbonyl group, or for any other internal bonding changes in any of the participating species, since the relevant single and interaction energy terms are not available.

The values of the coefficients are related to experimental free energy changes by putting the coordinates equal to zero and unity in various combinations. This leads to the following relations:

$$E_A = pK_a \text{ of } A_1H - pK_a \text{ of } R_1R_2COH^+$$

$$E_B = pK_a \text{ of } A_2H - pK_a \text{ of } A_1H_2^+$$

$$E_C = pK_a \text{ of } H_2O - pK_a \text{ of } A_2H_2^+$$

$$E_D = -\log_{10}K \text{ for the reaction}$$

$$R_1R_2CO + H_2O \rightleftharpoons R_1R_2C(\overset{-}{O})\overset{+}{O}H_2$$

$$E_1 = pK_a \text{ of } A_1H - pK_a \text{ of } A_1H_2^+$$

$$E_2 = pK_a \text{ of } A_2H - pK_a \text{ of } A_2H_2^+$$

$$E_3 = pK_a \text{ of } H_2O - pK_a \text{ of } R_1R_2C(\overset{-}{O})\overset{+}{O}H_2$$

$$E_4 = pK_a \text{ of } R_1R_2C(\overset{+}{O}H_2)OH - pK_a \text{ of } R_1R_2COH^+$$

$$E_5 = pK_a \text{ of } R_1R_2C(\overset{-}{O})\overset{+}{O}H_2 - pK_a \text{ of } R_1R_2C(OH)\overset{+}{O}H_2$$

In the expressions for E_4 and E_5 the pK_a's refer to the ionisation of the proton appearing outside the bracket. It will be noticed that E_D has been put equal to the experimental free energy change in a reaction in which a change occurs in the number of molecules, and that its value therefore depends on the standard state chosen for water. This problem can be overcome by making the reasonable assumption that in 100% aqueous solution the ketone is very loosely coordinated to a molecule of water; the constant

$$K = \frac{[R_1R_2C(\overset{-}{O})\overset{+}{O}H_2]}{[R_1R_2CO]}$$

measured in such a solution then gives the required free energy change for the process $d = 0 \longrightarrow 1$.

All the coefficients in equation (44) are in principle measurable, although some must be assessed because of the lack of appropriate data. The origins of E_D and the pK_a values chosen are described below.

A_1H, A_2H, H_2O:

The pK_a value of water is taken as 15.7, and those for other acid catalysts are known.

$A_1H_2^+$, $A_2H_2^+$, $R_1R_2C(OH)\overset{+}{O}H_2$:

In the assumed structure (B) type complexes the proton H_B is donated to the same oxygen atom from which H_A is lost. The corresponding basic pK_a's are known for a number of phenols, alcohols, and water, and a few examples taken from Arnett's review (157) are reproduced in Table (55).

TABLE 55

ACIDIC AND BASIC pK_a's

Substance	pK_a (acidic)	pK_a (basic)	difference, ΔpK_a
Methanol	14	-2	16
Water	15.7	-1.7	17.4
Phenol	10.0	-6.7	16.7
Acetic acid	4.8	-6.1	10.9
Benzoic acid	4.2	-7.2	11.4

pK_a (acidic) for methanol is taken from Ballinger and Long (144), and for other acids from Robinson and Stokes (ref. 41 p.527)

There is good evidence (158,159) that the carboxylic acids are protonated at the carbonyl oxygen, so that ΔpK_a for protonation of the hydroxyl group will be higher than the values given in the table. It has accordingly been assumed that ΔpK_a for all oxygen acids is the same as for water.

The pK_a (acidic) of sym-dichloroacetone hydrate has been taken as 11.6 by interpolation from the Taft correlation established by Bell (1) for the hydrates of a number of aliphatic aldehydes; this assumes that steric effects can be neglected.

$R_1R_2COH^+$:

Campbell and Edward (160) found that a number of methyl alkyl ketones have pK_a's (basic) close to −7.0, but no halo-derivatives were studied. The value for sym-dichloroacetone has been taken as −9.0, a rather arbitrary allowance having been made for the expected smaller basicity.

$R_1R_2C(\overset{+}{O}H_2)OH$ (for ionisation of proton outside bracket):

Since this is probably the least well-known quantity, calculations have been performed using a range of values. It is expressed in the form

$$pK_a = pK_a \text{ of } R_1R_2C(OH)_2 - \Delta x = 11.6 - \Delta x$$

where Δx is a positive quantity reflecting the greater inductive effect of the $-\overset{+}{O}H_2$ compared with the $-OH$ group.

$R_1R_2C(\bar{O})\overset{+}{O}H_2$:

This is related to the above by the equation

$$\frac{[R_1R_2C(OH)\overset{+}{O}H_2]}{[R_1R_2C(OH)OH]} \cdot \frac{[R_1R_2C(OH)OH]}{[R_1R_2C(\bar{O})OH]} = \frac{[R_1R_2C(OH)\overset{+}{O}H_2]}{[R_1R_2C(\bar{O})\overset{+}{O}H_2]} \cdot \frac{[R_1R_2C(\bar{O})\overset{+}{O}H_2]}{[R_1R_2C(\bar{O})OH]} ,$$

from which

$$-pK_a = -(11.6 - 17.4) - 11.6 + (11.6 - \Delta x) = 5.8 - \Delta x \quad .$$

E_D:

This is also related to Δx, since

$$\frac{[R_1R_2C(\overset{-}{O})\overset{+}{O}H_2]}{[R_1R_2CO]} = \frac{[R_1R_2C(OH)_2]}{[R_1R_2CO]} \cdot \frac{[R_1R_2C(OH)\overset{+}{O}H_2]}{[R_1R_2C(OH)_2]} \cdot \frac{[R_1R_2C(\overset{-}{O})\overset{+}{O}H_2]}{[R_1R_2C(OH)\overset{+}{O}H_2]}$$

Thus,

$$E_D = \log_{10}K_d - (11.6 - 17.4) + (11.6 - \Delta x) = 16.4 - \Delta x \quad ,$$

taking K_d as approximately equal to 0.1.
An upper limit can be placed on Δx, since the zwitterion, $R_1R_2C(\overset{-}{O})\overset{+}{O}H_2$, must be less stable than the neutral hydrate, $R_1R_2C(OH)_2$.

$$\text{i.e.} \quad \Delta x < 17.4$$

(3) <u>Method of computation</u>

The transition state was located for each combination of a range of values of Δx and the pK_a of either A_1H or A_2H. Calculations were performed in the following stages, using an Elliot 4130 computer and a program written in FORTRAN IV.

(i) The simultaneous partial differential equations ,

$$\left(\frac{\partial E}{\partial a}\right)_{b,c,d} = E_A - bE_1 - dE_4 - deE_5 \qquad (45.a)$$

$$\left(\frac{\partial E}{\partial b}\right)_{a,c,d} = E_B - aE_1 - cE_2 \qquad (45.b)$$

$$\left(\frac{\partial E}{\partial c}\right)_{a,b,d} = E_C - bE_2 - dE_3 - adE_5 \qquad (45.c)$$

$$\left(\frac{\partial E}{\partial d}\right)_{a,b,c} = E_D - cE_3 - aE_4 - acE_5 \quad , \qquad (45.d)$$

were solved. For acid catalysis each set of energy data always led to pairs of solutions which were either imaginary or lay outside the permitted range, $0 \leqslant a,b,c,d \leqslant 1$. This established that any transition-state must be defined by a set of coordinates at least one of which must be either zero or unity, i.e. the reaction is at least partly step-wise.

(ii) One of the coordinates (c) was allowed to increase by increments of 0.1 from zero to unity, and, for each of these, that combination of the other three which gave the minimum energy was found by trial. Since these minima initially increased while the total energy of reaction was negative, it could be seen that a transition-state must exist somewhere in the allowed region. It was hoped that this procedure might give the required transition-state configuration, but this was prevented by the nature of the potential energy 'surface', which was shown to have low energy 'cul-de-sacs' running along the edges defined by three zero or unit values of the coordinates.

(iii) Because of the inapplicability of these analytical and search methods an approach was adopted which combined some features of both without making any assumptions about the nature of the potential energy surface. Since the above tests showed that there must be a transition-state (although it may not be unique) and that this must occur at a configuration having a zero or unit value for at least one of the coordinates, a partly analytical solution is possible with respect to those coordinates which are not fixed merely by the restrictions imposed on their range of values. For example, a transition-state can occur at $b = 0$ if there is a set of the other three values which makes $(\partial E/\partial b)_{a,c,d}$ positive and the other three partial differential expressions zero, and which lies in the allowed range and at a saddle point on the potential energy surface. These conditions must be tested for all combinations of initially fixed values, and, if only one satisfies all the conditions, that defines the transition-state. If more than one solution is obtained, no decision is possible without inspection of the whole 'surface', since it may be necessary to pass through one of the higher energy points in order to reach that of lowest energy. For a four coordinate system such as the present one, the problem would then be insoluble.

The above method was used to analyse for the transition-state, solving the partial differential equations which remained when one or two of the coordinates were made zero or unity. Some of these could be excluded without carrying out any calculations, since it can be shown that for example if a alone is put equal to zero or unity, equations (45.b) and (45.d) are only simultaneously soluble for particular values of the coefficients. For the same reason no more than two coordinates can be restricted. The test for a maximum, minimum, or saddle point in each case was made by calculating the sign of the energy change on undergoing a small displacement in a direction not parallel with any of the coordinate axes, this being necessary because, as can be seen from equations (45), the second derivative of the energy with respect to a single coordinate is always zero. Of the 21 possible sets of initial restrictions, no more than two were ever found to fulfil all the conditions, and fortunately in many cases only one was found satisfactory; as indicated by the results of test (ii), there was always at least one allowed solution.

(4) Results

The results obtained for acid catalysis with the acid at the positions occupied by A_1H or A_2H are given in Tables 56 and 57, respectively. The pK_a's have been varied by intervals of 4.0, starting at 15.6 and 15.8 rather than 15.7 in order to avoid complications arising from division by zero. Transition-state energies are listed in the sixth column, and in the last one are given the values of the Brönsted coefficients, α, as calculated from the points immediately above and below. Three values of Δx have been used, of which the second and third seem physically more reasonable than the first or higher guesses.

Although too much weight should not be put on the detailed aspects of these results, a number of general features are apparent from the two tables. It can be seen that the Brönsted coefficients for A_1H catalysis are fairly closely equal to (a-b), which measures the extent to which A_1 resembles the conjugate base, while similarly in Table 57 $\alpha \simeq$ (b-c). The usual physical interpretation of the Brönsted coefficient is therefore preserved in this more complicated system. The least satisfactory feature of the results for A_2H catalysis is the initial rise in the transition-state energy for acids only a little stronger than water, and, because of this and the related prediction of higher energies throughout the range of pK_a, the model suggests that 'true' general acid catalysis (Table 56) is the mechanism followed by the hydration reaction. This mechanism bears a closer resemblance to that of Bell and Higginson (17) than to the alternative suggestion of Gruen and McTigue (35). The two mechanisms necessarily involve equal energies when the catalyst is H_2O or H_3O^+, since in these extreme cases the two structures are indistinguishable.

If the mechanism is one of A_1H catalysis and $\Delta x = 10.0$ is regarded as a reasonable assumption, the model predicts a fairly constant Brönsted coefficient of 0.5-0.6 over most of the pK_a range. This should be compared with the constant value 0.27 found experimentally in the aqueous dioxan solutions, but as pointed out earlier the assumption that the energy depends linearly on the extent of proton transfer is likely to lead to values of the coordinates which are too high. For catalysis by water all three proton transfers are only partly complete in the transition-state, while the C-O bond is

TABLE 56

MODEL CALCULATIONS FOR A_1H ACID CATALYSIS

A_1H varying, $A_2H = H_2O$, $\Delta x = 4.0$.

pK_a	a	b	c	d	E_{ts}	α
15.6	0.00	0.00	0.71	0.99	12.3	
	0.01	0.23	1.00	1.00	12.2	
						0.00
11.6	0.00	0.00	0.71	0.99	12.3	
	0.24	0.00	1.00	1.00	12.2	
						0.10
7.6	0.33	0.00	0.37	0.92	11.8	
						0.60
3.6	0.75	0.00	0.00	0.76	9.4	
						0.75
-0.4	0.75	0.00	0.00	0.52	6.4	

$\Delta x = 7.0$

pK_a	a	b	c	d	E_{ts}	α
15.6	0.01	0.23	1.00	1.00	12.2	
						0.00
11.6	0.32	0.03	0.92	1.00	12.2	
						0.40
7.6	0.40	0.00	0.43	1.00	10.6	
						0.47
3.6	0.64	0.00	0.03	0.91	8.7	
						0.70
-0.4	0.69	0.00	0.00	0.63	5.9	

$\Delta x = 10.0$

pK_a	a	b	c	d	E_{ts}	α
15.6	0.10	0.28	0.92	1.00	12.2	
						0.07
11.6	0.41	0.10	0.83	1.00	11.9	
						0.50
7.6	0.58	0.00	0.60	1.00	9.9	
						0.57
3.6	0.58	0.00	0.20	1.00	7.6	
						0.60
-0.4	0.60	0.00	0.00	0.81	5.2	

TABLE 57

MODEL CALCULATIONS FOR A_2H ACID CATALYSIS

A_2H varying, $A_1H = H_2O$, $\Delta x = 4.0$.

pK_a	a	b	c	d	E_{ts}	α
15.8	0.00	0.00	0.71	0.99	12.3	
	0.12	0.23	1.00	1.00	12.2	
						-0.80
11.8	0.00	0.22	0.78	1.00	15.4	
						0.12
7.8	0.46	1.00	0.25	0.41	14.9	
						0.97
3.8	0.75	1.00	0.00	0.43	11.0	
						1.00
-0.2	0.75	1.00	0.00	0.43	7.0	

$\Delta x = 7.0$

pK_a	a	b	c	d	E_{ts}	α
15.8	0.01	0.23	1.00	1.00	12.2	
						-0.62
11.8	0.09	0.35	0.69	1.00	14.7	
						0.10
7.8	0.36	1.00	0.27	0.46	14.3	
						0.92
3.8	0.69	1.00	0.00	0.53	10.6	
						1.00
-0.2	0.69	1.00	0.00	0.53	6.6	

$\Delta x = 10.0$

pK_a	a	b	c	d	E_{ts}	α
15.8	0.10	0.28	0.92	1.00	12.2	
						-0.37
11.8	0.18	0.46	0.60	1.00	13.7	
						0.10
7.8	0.27	0.64	0.29	1.00	13.3	
						0.82
3.8	0.60	1.00	0.00	0.68	9.9	
						1.00
-0.2	0.60	1.00	0.00	0.68	5.9	

already fully made. As the acid becomes stronger the extent of transfer of H_B rapidly falls to zero, followed by H_C, until for the strongest acids only a and d have fractional values. Thus as the reaction rate increases the extent of reaction in these three coordinates becomes less product-like in a way which can be understood from the acidic character of the catalysis. Throughout most of the pK_a range the degree of proton transfer from the acid catalyst is constant, leading to a linear Brönsted plot. It is interesting that just as Eigen's arguments in favour of a cyclic transition-state apply most directly to weakly acid catalysts, the present model requires this type of structure only in such cases.

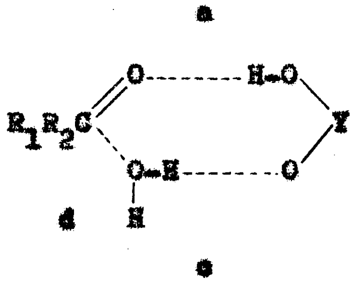
The calculated transition-state energies refer strictly to the cyclic system in its initially weakly hydrogen bonded state as zero, but if the free energy required to obtain this from randomly dissolved ketone in pure aqueous solution is neglected, the water-catalysed rate is predicted to be around 10 sec^{-1}. A rough experiment in a 50 volume % mixture of dioxan and heavy water showed that under these conditions the half-life for hydration is about 2 minutes, which might indicate a rate in 100% light water of about 10^{-1} sec^{-1}, i.e. a hundred times slower than the predicted value.

The question of whether the model accounts for the observed isotope effects is more difficult to resolve, since as shown in part (B) of Chapter VIII no universal relation between the magnitude of this quantity and the configuration can be expected for a partly synchronous mechanism. The simple potential energy function used in the present model is not applicable for this purpose on account of its lack of square terms, and any modification would require the assumption of additional coefficients. According to the model, it is possible to exclude from making any contribution to the reaction path a displacement along any coordinate which has a value of zero or unity in the transition-state, since motion along such a coordinate in one direction would inevitably take the configuration outside the allowed range, although this probably applies somewhat less strictly to a real system in which the energy varies in a continuous manner. The isotope effect should therefore be determined for most of the catalysts largely by the vibrational properties of two hydrogen atoms, as discussed in the previous chapter. Since high isotope effects are not observed, it follows that there must be large deviations from the rule of the geometric mean and that the conclusions previously drawn concerning the values of the smallest fractionation factors and the minimum number of water molecules in the transition-state are invalidated.

A more constructive interpretation is permitted if the general characteristics of the above model, but not its detailed numerical values, are considered. Just as the predicted Brönsted coefficient was found to be too high, it might similarly be assumed that the degree of product-like character exhibited by the three coordinates b, c, and d is too large. This would lead to a set of transition-states in which b and c are both small or zero and d becomes progressively smaller as the strength of the catalyst increases. The isotope effect is then chiefly due to a primary contribution from H_A and a secondary effect from both H_C and the other proton attached to the same oxygen atom. The transition-state fractionation factor associated with the latter will increase towards unity with increasing strength of the catalyst, but the primary factor may decrease either because it is partly bonded to a weaker base or because of a decreasing participation by the C-O bond formation process in the reaction path. The other protons will make small contributions, since the observation of medium effects in isotopic solvent mixture work indicates that fairly small changes in the hydrogen bonding state of a proton can alter its fractionation factor, but these effects should be relatively independent of the catalyst. This description accounts for both the constant transition-state contribution to the isotope effect and the decrease (if real) of its lowest fractionation factor with increasing acid strength. However, it must be stressed that, although a qualitative application of the model can be made to rationalise the observed isotope effect, it is not impossible that other descriptions might be equally satisfactory.

(5) Bifunctional catalysis

It was considered of interest to investigate whether a transition-state of the structure (A) type, in which a catalyst of suitable structure replaces two water molecules in the ring, could provide a lower energy path for the reaction. The cyclic system shown below



can be described by three coordinates, a, c, and d, and its energy expressed by the function

$$E = aE_a + cE'_c + dE_d - acE_6 - cdE_3 - daE_4 - adcE_5 \ . \qquad (46)$$

The coefficients are as in the previous case, except that

$$E'_c = pK_a \text{ of } H_2O - pK_a \text{ of } Y(OH)_2^+$$

and $$E_6 = pK_a \text{ of } YO.OH - pK_a \text{ of } Y(OH)_2^+$$

The transition-state was located as before for the same values of Δx. For each of the five catalyst acid strengths, pK_2, the pK_a of the conjugate acid, pK_1, was allowed to vary by unit intervals from pK_2 to $(pK_2 - 20)$. In contrast with the previous case, it was found that there were ranges of pK_1 for which a single completely analytical solution and no partial analytical solution existed within the allowed configuration range; continuity in the variation of the coordinates was found on passing to a region in which only a partial analytical solution was obtained, and this was considered to provide a good test of the methods of analysis.

It was found in general that the activation energy for this bifunctional (or tautomeric) mechanism was never significantly higher than for the model assumed previously, and that a lowering of energy occurred when (pK_2 - pK_1) was small. The decrease was particularly marked at small (pK_2 - pK_1) and when pK_2 was itself high, but the value of Δx made little difference. This may be illustrated by a few results for $\Delta x = 10.0$ presented in Table 58.

TABLE 58

BIFUNCTIONAL CATALYSIS

pK_2	pK_1	a	c	d	E(bi)	E(mono)
11.6	11.6	0.00	0.56	0.36	2.3	11.9
	7.6	0.00	0.56	0.70	4.5	
	3.6	0.03	0.56	1.00	6.7	
	-0.4	0.21	0.45	1.00	8.5	
3.6	3.6	0.19	0.33	0.91	6.3	7.6
	-0.4	0.36	0.17	0.97	7.0	
	-4.4	0.48	0.11	1.00	7.4	
	-8.4	0.57	0.09	1.00	7.5	

It would therefore appear that bifunctional catalysis is more likely when the catalyst is moderately strong both as an acid and as a base. The last two lines of the table show that for a carboxylic acid there is little to choose between the two structures. A final decision would require some estimate of the relative entropies of formation of the two weakly hydrogen bonded initial states, which is made difficult by the fact that the catalyst is hydrated in the ground state.

On the reasonable assumption that the above entropy term is small, the model offers a qualitative explanation for the positive deviations from the Brönsted plot found in catalysis by species such as the dihydrogen phosphate anion (p.10), and attributes these to bifunctional catalysis. It also predicts different (and probably higher) isotope effects in these cases, but not for catalysts such as carboxylic acids for which no decrease in the activation energy is obtained. Bifunctional catalysis in the mutarotation of tetramethylglucose has been demonstrated by Swain and Brown (161) for benzoic acid and 2-hydroxypyridine in non-aqueous solvents.

(6) Other aspects of carbonyl hydration reactions

An important test of the model is whether it can account for the differences in the kinetic behaviour of the aldehydes and ketones which have been studied. The different coefficients were not considered to be well enough known for a reliable quantitative application to the problem of fairly small differences, but qualitative conclusions can be drawn if it is assumed that only the coordinates a and d have fractional values, and if certain assumptions are made as to which energy terms vary most from one compound to another. Therefore,

$$E_{ts} = aE_A + dE_D - adE_4 \quad ,$$

from which follow relations analogous to those of section (1).

The series formaldehyde, acetaldehyde, and acetone may be discussed with the assumption that the differences between them are related essentially to the increasing value of E_D. This is reasonable on the basis of their similar inductive effects, and receives some support from the fact that the difference between the acidic pK$_a$'s of $CH_2(OH)_2$ and $MeCH(OH)_2$ is only 0.3 (1). The simplified model accordingly predicts an increase in the Brönsted coefficient α on ascending the series, and this is borne out experimentally (1,29) by the results:

$$HCHO : 0.23, \quad CH_3CHO : 0.54, \quad CH_3COCH_3 : \sim 0.7$$

The figure for acetone is based on the rates for catalysis by the hydronium ion and acetic acid. The value 0.27 for sym-dichloroacetone puts this compound in the expected position in the series, but the change of solvent makes this a less satisfactory comparison. It is tempting to suggest that the specific acid catalysis observed in ester hydrolysis is due to the very high resistance of the ester carbonyl group to hydration.

Whereas the change in rate with catalyst depends on the value of E_D, the effect of substitution in the ketone for a series of similarly catalysed reactions is a little more complicated. An increase in the electron-withdrawing power of the substituent causes changes of δ_A in E_A and $-\delta_D$ in E_D. Thus, if E_4 is approximately unchanged,

$$\delta E_{ts} = \frac{\delta_A E_D - \delta_D E_A}{E_4} = \delta_A a - \delta_D d \quad , \qquad (46)$$

showing that a decrease in rates is more likely for large a and small d, i.e. for catalysis by a strong acid of substrates in which E_D is relatively large. This explains the 'basicity effect' described in the Introduction (p.11) for hydronium ion catalysis in the hydration of substituted ketones. It can be regarded in the usual way as giving a measure of the amount of positive charge developed on the carbonyl carbon atom in the transition-state, and the above expression shows how the Taft equation parameters, ρ^*, for C-O bond formation and proton transfer equilibria combine to give the measured ρ^* for the hydration rates. When alkyl groups replace hydrogen atoms, the change in E_A is probably much less than that in E_D, with the result that the order

$$HCHO > CH_3CHO > CH_3COCH_3$$

is found to be maintained even for catalysis by very strong acids. The second order hydration rate constants for hydronium ion catalysis are (11,19,29):

$$HCHO : 5400, \quad CH_3CHO : 930, \quad CH_3COCH_3 : 33\ M^{-1}sec.^{-1}.$$

The model can therefore give a satisfactory qualitative account of the dependence of the rate on both the catalyst and the substrate. This lends further support to the modified description of the transition-state, which was proposed to account for the observed isotope effects. The specific solvation effects invoked by Ahrens (13) would appear to be unnecessary.

An attempt was made to apply the model quantatively to catalysis of the hydration of sym-dichloroacetone by bases which have a labile proton at the basic centre (e.g. primary and secondary amines). The same structures as for acid catalysis were assumed, but unfortunately the analysis invariably located two possible transition-states in each case. It could merely be concluded that location of the base at A_2 gave the lower set of activation energies, and that, in contrast to the result for acid catalysis, these decreased with increasing pK_a of A_2H, i.e. with increasing base strength. In connection with base catalysis it should be mentioned that Huang, Robinson, and Long (98) found an almost linear dependence on solvent deuterium atom fraction for the rate of the acetate ion-catalysed mutarotation of tetramethylglucose, and that similar behaviour has recently been found by Huang (162) for catalysis by a series of pyridine bases. These results indicate that only one proton is appreciably involved in the transition-state, and has a fractionation factor indicative of primary character. This is as would be expected if, by analogy with the acid-catalysed mechanism proposed here, only c and d have fractional values in the transition-state, and such an explanation is further supported by a change in the overall isotope effect, k_D/k_H, with base strength,

e.g. acetate : 0.449, pyridine : 0.356

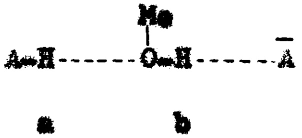
In conclusion, the data for catalysis by acids and bases which are somewhat stronger than water can be satisfactorily explained by transition-states in which one proton transfer and the process of carbon-oxygen bond formation or rupture are partly complete. For the water-catalysed reaction the variation of the isotope effect with the solvent deuterium atom fraction suggests that more proton transfers may be involved, and such a situation is in fact expected, since on passing from acid catalysts somewhat stronger than water to weakly basic catalysts a transition is required between partial transfer of H_A and of H_C. Eigen's postulate of a cyclic solvent-bridged structure therefore still rests for most reactions on the original kinetic evidence.

(7) Application of the model to other reactions

The main kinetic features of the formation of addition products (or intermediates) between carbonyl compounds and other nucleophiles can be accounted for in the same way as for the special case of the addition of water and the related mutarotation reactions. These have been discussed by Jencks (156) and others in terms of the product- or reactant-like character of the transition-states, and the model developed here merely adds further precision and simplicity to these interpretations by specifying the individual degrees of completion of the various processes. The reactions often exhibit good linear Brönsted plots over a wide range of pK_a, for example in the acid-catalysed addition of semicarbazide to p-chlorobenzaldehyde (163), and both Cordes and co-workers (155) and Jencks (156) have drawn attention to the general tendency for the Brönsted coefficient α to increase with decreasing strength of the nucleophile, i.e. 'for catalysis to be most evident where it is most needed'. These observations are accounted for by an equation such as (43.a), and, as expected from the present model, the values of α found for a range of different nucleophiles and substrates correlate better with estimates of the ease of addition than with those of nucleophilicity alone. The increase in the ρ^+ value from 0.77 to 0.94 found by Cordes and Jencks (163) in the acid-catalysed addition of semicarbazide to a number of substituted benzaldehydes as the catalyst was changed from monochloroacetic acid to water is similarly explained by equation (46) in terms of an increase in d. Isotope effect studies on other types of carbonyl addition reactions might be expected to provide a further test of these ideas.

The present model would be expected to be particularly suitable for predicting transition-state configurations in reactions which consist solely of concerted proton transfers. Experimental data are rather sparse, but an important example is provided by the work of Grunwald and Meiboom (154), who found evidence for the following two mechanisms for proton exchange in methanolic solutions of substituted benzoic acid buffers.

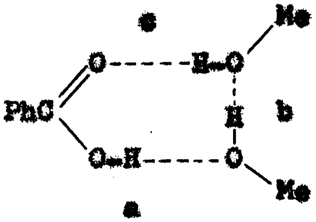
I



$$\underset{a}{\mathrm{A{-}H}}\text{------}\underset{b}{\overset{\mathrm{Me}}{\overset{|}{\mathrm{O}}}\mathrm{{-}H}}\text{------}\bar{\mathrm{A}}$$

$\alpha = 0.26$

II



$\alpha = 0.53$

Since reaction I is an example of the simple proton transfer system discussed in section (1), it should be possible to use this to explain the observed Brönsted coefficient of 0.26. From equation (42),

$$\alpha = \frac{\delta E_{ts}}{\delta pK_a} = \frac{E_B - E_A}{E_1} = a - b \quad ,$$

from which, by the use of data from Table 55 and taking the mean pK_a

of the substituted acids to be ~ 4,

$$a = 0.62, \quad b = 0.38, \quad \text{and} \quad \alpha = 0.24.$$

For reaction II Grunwald and Meiboom argue that the true Brönsted α for proton transfer through the hydrogen bonded system should be higher than the experimental value because of the expected increased solvation of the carbonyl group with increasing pK_a. Application of the model according to the usual principles gives

$$a = 1.00, \quad b = 0.38, \quad c = 0.00, \quad \text{and} \quad \alpha = 1.00,$$

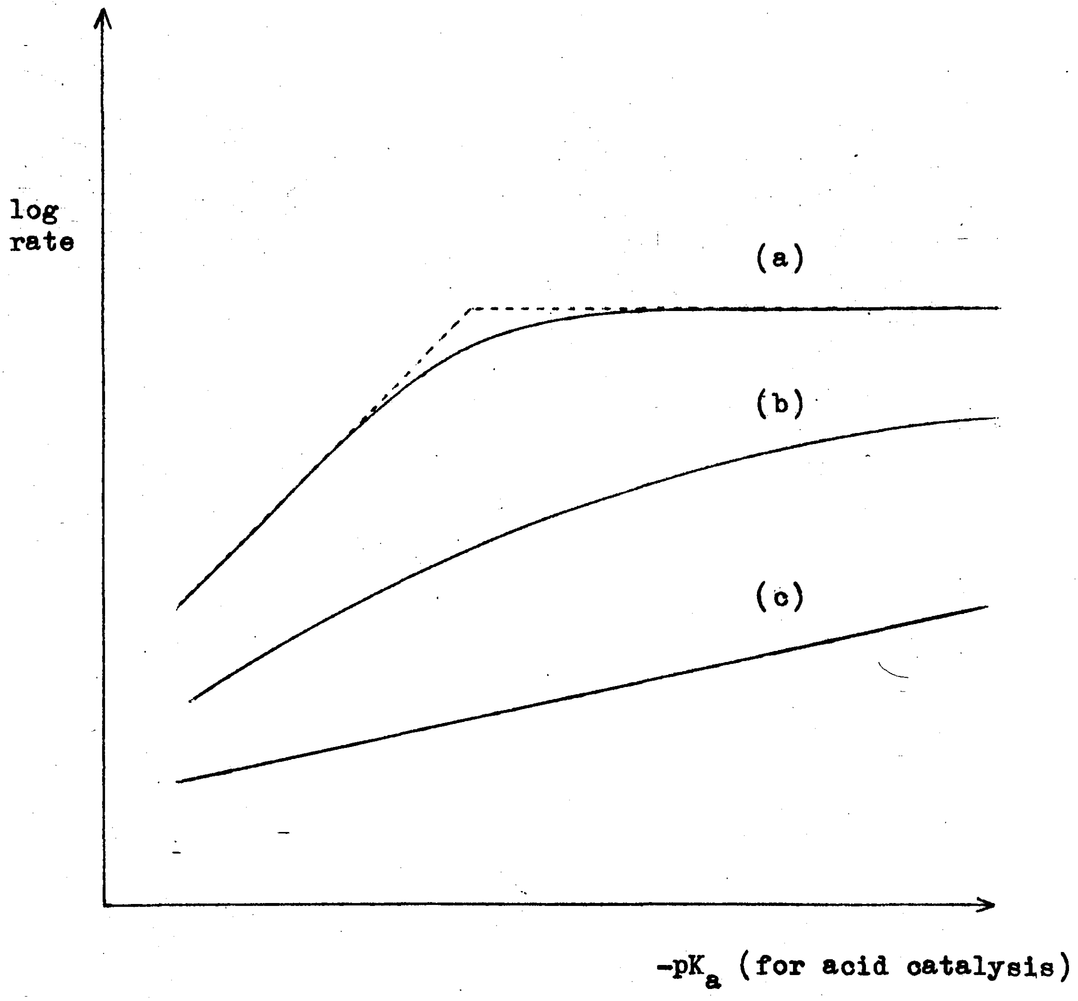
where the coordinates are as indicated. It is therefore possible to give a reasonable account of the experimental data, and to substantiate the authors' conclusion that mechanism I is synchronous while mechanism II proceeds in a step-wise fashion. More data of this type and the development of methods for measuring the isotope effect would be very welcome.

Finally, a few qualitative applications of the model may be mentioned to show how the conclusions of Thornton (152) and More O'Ferrall (148) can be arrived at in a simple way from estimates of the effect of substitution on the energy required to effect the individual processes. For example, the base-catalysed cyclisation of ω-haloalcohols to cyclic ethers allows the possibility that proton abstraction may be concerted with the process of carbon-oxygen bond formation and displacement of the chloride ion, but, whereas 4-chlorobutanol gives a good linear Brönsted plot with $\beta = 0.25$, the reaction for 2-chloroethanol is subject to apparent specific base catalysis (149). This may be explained by the large internal strain in the latter ring formation process, which accordingly requires virtually complete proton transfer in the transition-state, leading to the masking of any general base catalysis by that of the hydroxide ion. The model makes predictions for S_N2 reactions which are very similar to those made by Thornton (152), and supported by solvent and leaving-group isotope effect data. Bimolecular (E2) eliminations from carbon, another classic group of concerted reactions, present more problems than the analogous dehydration of carbonyl hydrates, since as pointed out by More O'Ferrall (148) a change of base normally involves also a change of solvent; however, the increase of the Hammett ρ parameter with decreasing leaving group ability, shown by the data collected by Bunnett (164) receives a simple interpretation in terms of the present model.

The ideas presented in this chapter may be added to those of Eigen (34) to give a general account of the relation between the rate of an acid or base catalysed reaction and the pK_a of the catalyst. The experimental Brönsted plots are shown diagrammatically in Figure (21). The scales on the two axes are the same, but no values have been inserted as it is not intended to compare the rates of different reactions. Curve (a) represents simple proton transfers between oxygen atoms, which exhibit fractional Brönsted coefficients only over a very small range near $\Delta pK_a = 0$; the reactions are not concerted, and activation is required merely to break and form an oxygen-hydrogen linkage. Curve (c) represents the opposite extreme found for reactions in which proton transfer occurs synchronously with some other process, and in which the activation energy arises from the combination of an 'uphill' and 'downhill' process, as described by the model developed above. (In contrast to the idea put forward by Albery (42), the present treatment shows that linear Brönsted plots do not require simultaneous acid and base catalysis). The middle curve (b), found for proton transfers from carbon acids, shows intermediate behaviour, and it is suggested that in this case the activation energy arises from a combination of both effects. It would be predicted that E2 eliminations would resemble curve (b) if the appropriate data could be obtained in a single solvent. Hydrogen isotope effects in reactions of type (a) should vary rapidly with pK_a and rise to a fairly high maximum, while those in reactions of type (c) vary much

FIGURE 21

The Brönsted relation in different types of acid-base catalysed reactions.



more slowly and are never large. The behaviour of the isotope effect in intermediate types is the most difficult to account for since neither of the simple models appropriate for the two extremes is very satisfactory.

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