

Solvent Deuterium Isotope Effects on Acid-Base Reactions

Part III. Relative Acidity Constants of Inorganic Oxyacids in Light and Heavy Water. Kinetic Applications

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The relative acidity constants in light and heavy water have been measured for a large number of inorganic oxyacids at 25°C. It is found that the values of $\Delta pK = pK(D_2O) - pK(H_2O)$ vary very irregularly showing no simple relation to the acid strengths, in contrast to some earlier observations made on other acids. It is proposed that the anomalous behavior is primarily due to two factors: first, the values of ΔpK are not directly comparable for mono- and polybasic acids since they are composed of different numbers of isotope exchange equilibrium constants and, second, the values of ΔpK include free energies of transfer from light to heavy water which exhibit individual variations.

An assumption is made that a linear free energy correlation exists between the equilibrium of proton transfer from the OH-bond and the isotope exchange equilibrium involving the same bond. It is shown that this assumption merely requires that, for "idealized" pK values, *i.e.*, for pK values from which the influence of change in the solvent from H_2O to D_2O has been eliminated, the pK values in light water are in linear relation to those in heavy water. This assumption leads to an empirical equation which describes the dependence of the isotopic fractionation factor on the acid strength of the OH-proton. The equation finds some support, apart from the theoretical arguments, from the following sources of experimental evidence. First, in cases in which directly measured fractionation factors are available these are in agreement with those calculated from the equation. Second, when application is made to the kinetics of hydronium ion-catalyzed reactions in which the acidity constant for the transition state can be evaluated, the equation permits a calculation of the relative reaction rates in light and heavy water. The values derived in this way agree excellently with those measured experimentally for reactions the mechanisms of which are firmly established.

Further applications to acid-catalyzed reactions of unknown mechanisms are discussed.

It is well known that the acidity constants of protoacids in light water (I) are generally higher than those of the corresponding deuterioacids in heavy water (II), and that the value of K_H/K_D usually increases with decreasing acid strength.¹



One argument for the latter feature is that, with decreasing acid strength, the proton in AH becomes more firmly bound and the zero-point energy of this bond becomes higher;¹ in the deuterated system the corresponding variation of the zero-point energy with the firmness of the A—D bond is smoother, because the zero-point energies themselves are lower, which increases the values of K_H/K_D with decreasing acidity. In fact, Bell¹ noted that the empirical eqn. (1) was reasonably well obeyed by a number of acids. Exceptions to this equation, in particular those which can be attributed to intramolecular hydrogen bond formation, have been discussed by McDougall and Long.²

$$\Delta pK = pK_D - pK_H = 0.41 + 0.02 pK_H \quad (\text{1})$$

In the preceding papers^{3,4} it was emphasized that in general the values of ΔpK are composed of two kinds of factors, that is, those relating to the isotope exchange equilibria involved, and those brought about by changes in the thermodynamic quantities when the participants of acid-base reactions are transferred from light to heavy water. The primary aim of the present study was to obtain additional information about these factors and, if possible, to investigate methods by which their relative influence on the ΔpK values could be estimated separately. A further interest was in applications to the kinetics of hydronium ion-catalyzed reactions.

EXPERIMENTAL

Reagent grade chemicals were used throughout. Deuterium oxide was supplied by Norsk Hydro-Elektrisk Kvaestofaktieselskab, Norway. For acids with pK_H values higher than about 2, the acidity constants were measured by the glass electrode method as described earlier.⁴⁻⁶ In order to eliminate the influence of random errors on the values of $\Delta pK = pK_D - pK_H$, measurements were made, in addition to those in the pure waters, in 7 to 9 solvents in which the deuterium atom fraction n varied from 0.1 to 0.9. The method of least squares was then applied to the measured pK values employing quadratic polynomials, from which the best values were calculated for ΔpK . Thus, for example, the following equation was obtained for the acidity constant of arsenious acid as the function of n at 25°C:

$$pK_n = 9.279 + 0.397 n + 0.125 n^2$$

from which $\Delta pK = 0.522$. For the dissociation of boric acid the corresponding least-squares equation was:

$$pK_n = 9.227 + 0.384 n + 0.134 n^2$$

giving $\Delta pK = 0.518$. The latter reaction has been also studied recently by Gold and Lowe,⁷ allowing a direct comparison to be made. It is found that their value for ΔpK , 0.516, and that given above are in excellent agreement, the relative pK values in mixtures of light and heavy water being also the same within a few thousandths.

For acids of moderately high acid strength, *e.g.*, for the hydrogen sulfate ion, a kinetic method was used to determine the relative acidity constants in light and heavy

water (and in their mixtures). First, rate coefficients were measured for the hydronium ion-catalyzed hydrolysis of a standard substance (propyl acetate) using a strong acid (perchloric acid) as the catalyst. Then, rate coefficients were determined for the same compound and in the same solvents using as catalyst the acid under study (*e.g.*, bisulfate ion, in concentrations 0.02 to 0.06 M). By combining the values from the both sets of measurements the degree of dissociation of the acid under study could be calculated in each case, and a value derived for the dissociation constant. The values of the latter were then extrapolated to zero electrolyte concentration by the Debye-Hückel approximation.⁶ In the case of the bisulfate ion, in which other experimental values were available for comparison, the results were in good agreement with each other (see below).

RESULTS AND DISCUSSION

Relative acid strengths in light and heavy water. Table 1 summarizes the values of ΔpK for twelve inorganic oxyacids studied in the present work, along with some earlier values. It is seen that, in the two cases in which comparable data exist, the present values are in good agreement with the earlier ones. From the methods of determination of the pK values (see the experimental part) it follows that fairly accurate values can be obtained for the pK differences in heavy and light water, ΔpK , whereas those for the pK 's themselves are less precise. However, the latter circumstance is less important in the present context as the influence of acid strength on the ΔpK values is generally rather small (*cf.*, *e.g.*, eqn. 1). In the table, the acids are classified as monobasic, polybasic and as those displaying anomalous acid-base reac-

Table 1. The values of $\Delta pK = pK_D - pK_H$ for inorganic oxyacids at 25°C. The acids are classified as follows: *M*, monobasic; *P*, polybasic; *A*, acids displaying anomalous dissociation reactions. σ_{HA} and σ_{A^-} are the symmetry numbers of the parent acids and their corresponding bases, respectively, and $pK_H(\text{chem.})$ stands for symmetry-corrected pK value in protium oxide.

Acid	Class	ΔpK	Ref.	pK_H	σ_{HA}/σ_{A^-}	$pK_H(\text{chem.})$
Iodic, $\text{IO}_2(\text{OH})$	<i>M</i>	0.303	2	0.85	0.333	0.37
Hypophosphorous, $\text{H}_2\text{PO}(\text{OH})$	<i>M</i>	0.313	This work	1.31	0.5	1.01
Phosphorous (1st), $\text{HPO}(\text{OH})_2$	<i>P</i>	0.143	»	1.43	1	1.43
Periodic (1st), $\text{IO}(\text{OH})_5$	<i>A</i>	0.079	6	1.61	0.25	1.01
Sulfuric (2nd), $\text{SO}_3(\text{OH})^-$	<i>M</i>	0.350	This work	1.84	0.25	1.24
»	»	0.355	8	1.99	»	1.39
Phosphoric (1st), $\text{PO}(\text{OH})_3$	<i>P</i>	0.205	5	2.15	1.5	2.33
Arsenic (1st), $\text{AsO}(\text{OH})_3$	<i>P</i>	0.295	»	2.30	»	2.48
Selenious (1st), $\text{SeO}(\text{OH})_2$	<i>P</i>	0.332	This work	2.62	1	2.62
Phosphorous (2nd), $\text{HPO}_2(\text{OH})^-$	<i>M</i>	0.553	»	6.54	0.333	6.06
Phosphoric (2nd), $\text{PO}_2(\text{OH})_2^-$	<i>P</i>	0.644	»	7.05	0.667	6.87
Sulfurous (2nd), $\text{SO}_2(\text{OH})^-$	<i>M</i>	0.619	4	7.44	0.333	6.96
Periodic (2nd), IO_4^-	<i>A</i>	0.657	6	8.25	6	9.03
Selenious (2nd), $\text{SeO}_2(\text{OH})^-$	<i>M</i>	0.538	This work	8.25	0.333	7.77
Boric, $\text{B}(\text{OH})_3?$	<i>A</i>	0.518	»	9.23	0.25?	8.63?
»	»	0.516	7	»	»	»
Arsenious (1st), $\text{As}(\text{OH})_3?$	<i>P</i> or <i>A</i>	0.522	This work	9.28	3?	9.76?
Carbonic (2nd), $\text{CO}_2(\text{OH})^-$	<i>M</i>	0.617	»	10.35	0.333	9.87
Phosphoric (3rd), $\text{PO}_3(\text{OH})^{2-}$	<i>M</i>	0.665	»	12.15	0.25	11.55

tions in water. This classification is made in accordance with the generally accepted dissociation schemes of the acids in question, although there are cases in which the actual dissociation schemes are still uncertain.

In spite of the observation that the values of ΔpK generally tend to increase with decreasing acid strength, that is, with increasing pK values, no simple relation seems to exist between these two quantities in the case of inorganic oxyacids. This becomes evident from Fig. 1, in which the values

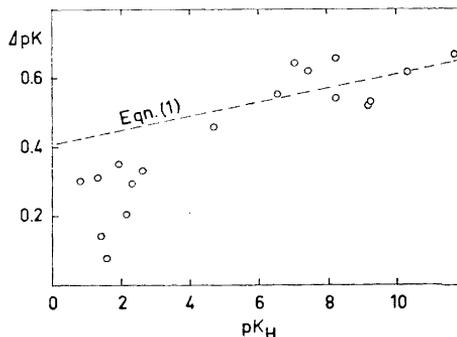


Fig. 1. Plot of $\Delta pK = pK_D - pK_H$ against pK_H for inorganic oxyacids at 25°C. The line drawn in the figure is for eqn. (1).

of ΔpK are plotted against pK_H . The plot will not become more regular, if one replaces the pK values by their statistically corrected, or "chemical" values, in which corrections are made using the symmetry numbers of the components. The values for the latter, also given in Table 1, have been calculated according to Benson.⁹

If one adopts the view, supported by considerations of the zero-point energies (see above), that for similar acids ΔpK should normally increase with the value of pK_H , the irregularities encountered here must be due to two kinds of factors. First, the values of ΔpK for the acids of Table 1 are not always comparable, because fundamentally different dissociation and isotope exchange schemes are involved. Depending on the nature of the acid-base reaction in question, the value of ΔpK includes one or several isotopic fractionation factors, in addition to that of the hydronium ion.³ Second, the values of ΔpK also contain contributions from the change in the solvent when one replaces light water by heavy water,^{3,4} and the magnitudes of these contributions may vary in an individual way. These factors are discussed below.

A more detailed analysis of ΔpK values. Let us first consider the case of a simple monobasic acid of any charge type, which in water dissociates according to the normal proton transfer scheme (I), and which contains no isotopically exchangeable hydrogens except the acidic one. As discussed earlier,³ the value of ΔpK can be represented in this case as

$$\Delta pK(\text{monobasic}) = -3 \log l + \log \varphi + \log F \quad (2)$$

$$F = (f_{H_2O} f_A / f_{HA} f_{H_2O})_{D_2O} / (f_{H_2O} f_A / f_{HA} f_{H_2O})_{H_2O} \quad (3)$$

Here the fractionation factors l and φ refer to the hydronium ion and to the acid HA, respectively, and the last term of eqn. (2) includes the solvent effect

when the light isotope components and the anion A^- which participate in equilibrium (I) are transferred from light to heavy water. Combining the terms that are general in the sense that they do not relate to any particular acid HA one obtains from eqn. (2)

$$\Delta pK(\text{monobasic}) = \text{const.} + \log \varphi + \log\{(f_{A^-}/f_{HA})_{D_2O}/(f_{A^-}/f_{HA})_{H_2O}\} \quad (2')$$

where the value of the constant is the same for all acids. It must be emphasized here that an equation of the form (2') is thermodynamically exact and does not necessitate any of the assumptions inherent in the theory of solvent deuterium isotope effects.³ Thus the proper formulations for the hydronium ion and water in their isotope exchange equilibria and in the acid-base reaction itself are immaterial, except for calculation of the correct value for the constant in eqn. (2'). One does not either have to assume the constancy of the isotope fractionation factor φ throughout the H_2O-D_2O system³ when the value of this quantity is chosen for pure deuterium oxide as the solvent. One thus finds that, in addition to a constant of general nature, the values of ΔpK for monobasic acids can be represented in terms of isotope exchange equilibrium constants, φ , and of the solvent effects associated with transfer of the protoacid and its conjugate base from light to heavy water.

It follows from the above discussion that, if a linear free energy correlation like that given by eqn. (1) holds for monobasic acids, it is actually composed of two such correlations, one of which relates to the isotope exchange equilibria and the other to the solvent effects involved. Considering the former of these, one might well infer that the equilibrium constant φ for the isotope exchange equilibrium (III) will increase when the proton in HA



becomes more tightly bound, *i.e.*, when the acid strength of HA decreases, since the loss in the zero-point energy when going from HA to DA will then become more marked. As the variations in the values of φ in isotope exchange equilibria are always comparatively small, unlike other types of equilibria, a linear free energy correlation

$$\log \varphi = a pK_H + b \quad (a > 0) \quad (4)$$

is expected to hold fairly well, at least for such acids in which the acidic hydrogens are attached to similar atoms, like the oxygen atoms. A somewhat more sophisticated argumentation, which leads to the same expectation, is to consider "idealized" values of ΔpK . Let us assume that it were possible to determine such values for pK in heavy water (denoted by $pK_D^{\text{id.}}$) from which the effect of the change in solvent from light to heavy water had been eliminated. For such pK values (light water having been chosen as the reference solvent) one obtains from eqn. (2')

$$\Delta pK^{\text{id.}}(\text{monobasic}) = pK_D^{\text{id.}} - pK_H = \text{const.} + \log \varphi \quad (2'')$$

As the processes of dissociation, after elimination of the solvent effects, are quite similar for the corresponding proto- and deuterioacids, their standard free energies and hence the values of $pK_D^{\text{id.}}$ and pK_H are expected to exhibit an approximately linear correlation. It is seen from eqn. (2'') that such a relation, in turn, leads directly to eqn. (4).

Considering the possible effect of acid strength on the activity coefficient quotients in eqns. (2) and (2'), it is to be noted that these quotients refer only to protoacids in the two different solvents, H₂O and D₂O. For a great number of similar protoacids studied in two different solvents it has been found experimentally that the p*K* differences in the two solvents are approximately constant and independent of the acids in question.¹⁰ This, if applicable to the present case, would mean that the last terms in eqns. (2) and (2') had the same constant values for all acids. However, the monobasic acids studied here differ by their charges and it is thus very questionable to make such a generalization. An essentially less stringent tentative assumption would be that the values of log *F* were not just constant, but varied with the acid strength according to eqn. (5).

$$\log F = A \text{ p}K_{\text{H}} + B \quad (5)$$

An equation of this type might be plausible in the present case, because acids of similar charges usually fall into the same p*K* range, and the values of log *F* are expected to increase with ionic charges.⁴ However, owing to the complicated nature of ion-solvent interactions in water solutions,¹¹ individual variations in the last terms of eqns. (2) and (2') may be encountered. Eqn. (5) is therefore much less supported by theoretical arguments than eqn. (4), which relates to the isotope exchange equilibria.

An indirect test of eqns. (4) and (5) can be made when one considers monobasic acids alone. According to these equations and eqn. (2) (or eqn. 2', correspondingly)

$$\Delta \text{p}K(\text{monobasic}) = (a + A) \text{p}K_{\text{H}} + (b + B - 3 \log l) \quad (6)$$

In Fig. 2 the values of Δ*pK* are plotted against their corresponding p*K*_H's for the monobasic acids studied. In making the plot, the use of symmetry-

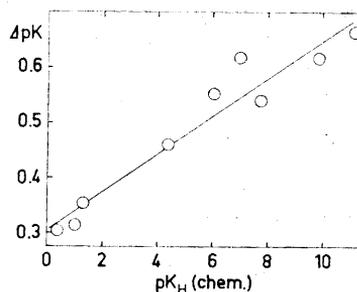


Fig. 2. Plot of Δ*pK* against p*K*_H(chem.) for monobasic inorganic oxyacids at 25°C. The radius of the circles corresponds to 0.01 unit in the values of Δ*pK*.

corrected "chemical" p*K* values was preferred (the values of Δ*pK* and Δ*pK*(chem.) being naturally the same). The equation of the straight line drawn in the figure is

$$\Delta \text{p}K(\text{monobasic}) = 0.0343 \text{ p}K_{\text{H}}(\text{chem.}) + 0.304 \quad (6')$$

It was computed from the experimental values by the method of least squares. The average deviation in Δ*pK* is 0.03 unit, and the maximum deviation

(sulfurous acid, 2nd diss.) is almost 0.08 unit. It is thus seen that eqn. (6) holds but approximately. As discussed above, this is probably mainly due to the approximate character of eqn. (5) rather than to substantial deviations from eqn. (4). Evidence for this conclusion comes also from the preceding study,⁴ in which it was shown that the activity coefficient of the sulfite ion increases much more materially than that of the carbonate ion when going from light to heavy water. As the parent acids are of similar charges, and the acid strength of the bisulfite ion is even higher than that of the bicarbonate ion, eqn. (5) can be but very approximate. In fact, the bisulfite ion shows the largest deviation from eqn. (6') and this deviation is in the positive direction, as expected by the relatively high increase in the activity coefficient of the sulfite ion.

A further point of interest becomes evident when a comparison is made between eqns. (1) and (6'). The former equation, derived by Bell from data consisting mainly of organic oxyacids, shows a much smaller slope for the plot of ΔpK against pK_H than does eqn. (6'). This, in turn, confirms the above conclusion about the importance of the activity coefficient quotients in eqns. (2) and (2'), which vary differently depending on the acids considered. It is thus very probable that the value of a in eqn. (4) is even essentially smaller than either of the slopes obtained from the ΔpK plots, *i.e.*, smaller than 0.02 (see below).

For polybasic acids with normal proton transfer schemes the composition of the ΔpK values is complicated by the presence of an additional fractionation factor.³ If H_iA denotes an i -basic acid of any charge type and with i equivalent acidic hydrogens, one obtains

$$\Delta pK(i\text{-basic}) = -3 \log l + i \log \varphi - (i-1) \log \varphi' + \log F \quad (7)$$

in which F has a similar meaning as above, and the fractionation factors φ and φ' relate to the acid and its conjugate base, respectively. From the nature of the ΔpK values in this case it follows that they cannot bear any simple relation on the acid strength, though relations (4) and (5) were applicable. This is seen when the values of $\log \varphi$ and $\log F$ from the latter equations are substituted in eqn. (7):

$$\Delta pK(i\text{-basic}) = a[i pK_H^I - (i-1) pK_H^{II}] + A pK_H^I + (b+B-3 \log l) \quad (8)$$

Here pK_H^I and pK_H^{II} refer to the first and second dissociations of the acid in question, irrespective of its charge type. As the fractionation factors φ for polybasic acids are statistically corrected to correspond to isotope exchange reaction *per* one hydrogen atom of the acid,^{3,5} it follows that eqn. (4) should hold for these acids as well as for the monobasic ones, *i.e.*, the values of the parameters a and b should be the same for the both types of oxyacids. It is much less certain, whether similar generalization can be made about the coefficients A and B in eqn. (5).

Although the assumptions concerning the parameters of eqn. (8) may be but approximate, an idea about the magnitude of a in eqn. (4) may be gained when one uses eqns. (6) and (6') for the unknown parameter values. With $(a+A)=0.0343$, and $(b+B-3 \log l)=0.304$, eqn. (8) can be reduced to the form

$$\Delta pK(i\text{-basic}) = a(i-1)(pK_{\text{H}^{\text{I}}} - pK_{\text{H}^{\text{II}}}) + 0.0343 pK_{\text{H}^{\text{I}}} + 0.304 \quad (8')$$

from which the value of a can be estimated using the values of Table 1 for polybasic acids with normal dissociation schemes. The weighted average and its standard error obtained in this way is $a = 0.0135 \pm 0.0058$. In the calculations, "chemical" pK values were used and the values of $(i-1)(pK_{\text{H}^{\text{I}}} - pK_{\text{H}^{\text{II}}})$ were chosen as the weights in averaging.

The value estimated for a is seen to be significantly smaller than the slope obtained from the plot in Fig. 2, 0.0343. From this it can be inferred that a very substantial contribution to the values of ΔpK measured here must come from the solvent effects. This is in full agreement with the conclusions drawn from the preceding studies.^{3,4}

Dependence of isotopic fractionation factors of oxyacids on their acid strengths. As discussed above, there are fairly reasonable arguments for an approximately linear free energy correlation associated with isotope exchange equilibria (eqn. 4), if one is confined to acids in which the acidic hydrogens are attached to the same kind of atoms. Until more decisive and direct experimental information becomes available, one might tentatively suggest that eqn. (4) should hold for the solvent water and the hydronium ion themselves, as well as for other oxyacids dissolved in water. The fractionation factors for the former two acids are well known, *viz.*, unity for water by definition, and 0.69 for the hydronium ion.^{3,4} An apparent difficulty in such a treatment is in assigning proper values for the acidity constants of the hydronium ion and water, as their naïve pK values, -1.74 and 15.74 , contain the doubtful figure 55.5 as the concentration of water molecules in pure water.¹² In fact, pK_{H} values from -2.35 to -3.43 have been reported for the hydronium ion from more direct acidity measurements.^{13,14} However, as shown below, this circumstance has but a minor influence on the results.

Let us first assign the values -1.74 and 15.74 for the uncorrected pK 's of the hydronium ion and water, respectively. If one prefers to use their symmetry-corrected values,⁹ -1.56 and 16.04 , and substitutes the known values of the respective fractionation factors in eqn. (4), one obtains

$$\log \varphi_{\text{OH}} = 0.0092 pK_{\text{H}}(\text{chem.}) - 0.147 \quad (4')$$

On the other hand, as the extreme case, one might choose a pK_{H} value of -3.43 for the hydronium ion, the equation corresponding to eqn. (4') becoming now

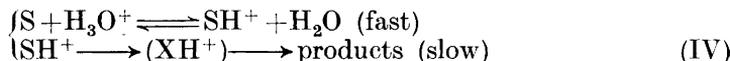
$$\log \varphi_{\text{OH}} = 0.0084 pK_{\text{H}}(\text{chem.}) - 0.134 \quad (4'')$$

Although the values of the parameters in eqns. (4') and (4'') are different, their differences do not materially affect the values estimated for the fractionation factors. The maximum differences in the values of $\log \varphi$ calculated from eqns. (4') and (4'') are 0.01 unit within the whole acidity range from the hydronium ion to water, which correspond to differences of 2% or less in the fractionation factors themselves. The same, of course, also applies to the pK value chosen for water.

The approximate validity of eqn. (4') (or eqn. 4'', correspondingly) finds support from several independent sources. First, Bell¹ has carried out some

crude quantum-mechanical calculations on the dependence of ΔpK on pK_H , arriving at values 0.011 to 0.014 for the slope in the plot of ΔpK against pK_H . Since these calculations did not account for the solvent effects associated with transfer of the components from light to heavy water, the values derived had actually the same meaning as that of the parameter a in eqn. (4) (*cf.* eqn. 2''). This shows that the values obtained here for a are of acceptable magnitudes. Also the value estimated above from eqn. (8'), 0.0135 ± 0.0058 , is of similar magnitude. In addition, Kreevoy¹⁵ has recently measured directly the value 0.83 ± 0.02 for the fractionation factor of the dihydrogen phosphate ion, which coincides with that calculated from eqn. (4'), 0.83 (eqn. 4'' giving the same result). Further, kinetic applications of eqn. (4') lead to results that are consistent with directly measured rate constants (see below).

Applications to reaction kinetics. Let us first consider an $A-1$ reaction, the mechanism of which can be represented as



Here the transition state has been denoted by XH^+ . The solvent deuterium isotope effect is given by³

$$\log(k_D/k_H) = -3 \log l + \log \varphi + \frac{1}{2.303RT} \Delta(\Delta G^\circ) \quad (9)$$

where the fractionation factor φ relates to the transition state, and $\Delta(\Delta G^\circ)$ is the standard free energy of transferring XH^+ and H_2O from light to heavy water minus that of transferring S and H_3O^+ the same way. There are strong arguments to believe that for most reactions taking place according to (IV) the last term in eqn. (9) is of negligible magnitude, unlike for ordinary acid-base dissociation equilibria.³ This is due to the circumstance that the components which are transferred, $(\text{S} + \text{H}_3\text{O}^+)$ and $(\text{XH}^+ + \text{H}_2\text{O})$, are of similar charges and are composed of similar molecular constituents, so that their influences are largely cancelled out. Moreover, the values of ΔG° themselves for uncharged organic substrates undergoing hydrolytic reactions are expected to be relatively small.³ In fact, solubility measurements on a number of organic oxygen bases have confirmed this conclusion.¹⁶ Thus, for example, the relative molar solubilities of propyl and *tert.*-butyl acetates in light and heavy water at 25°C are 1.015 and 1.018, respectively, corresponding to values of +9 and +11 cal/mole for ΔG° . The influence of free energies of this magnitude on the transfer free energy terms, like that in eqn. (9), is less than 0.01 unit.

Eqns. (4') and (9) can be used for the calculation of the values of k_D/k_H in cases in which the acid strengths of the transition states are known. The latter can be evaluated for a number of reactions by a method devised by Kurz.¹⁷ If the substrate S is also hydrolyzed by an uncatalyzed mechanism which is similar to (IV) except that the transition state does not now contain a proton,



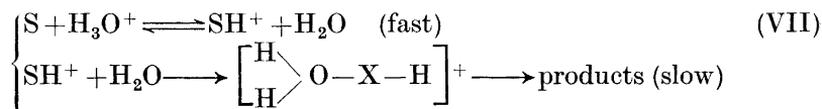
then the ratio of the rate coefficients of reactions (V) and (IV), $k(\text{uncat.})/k(\text{cat.})$, is the equilibrium constant of the hypothetical reaction:



This equilibrium constant is, of course, the acidity constant of XH^+ .

When one is confined to transition states XH^+ which are oxyacids, for which eqn. (4') is expected to hold, there are at present only two sets of relevant data for reactions the mechanisms of which are firmly established as (IV) and (V). In one of these, the hydrolysis of methoxymethyl acetate,¹⁸ the value determined for $K_H^\ddagger = k(\text{uncat.})/k(\text{cat.})$ was 2.0×10^{-3} moles per liter at 25°C. Eqns. (4') and (9) give thus a value of 2.30 for k_D/k_H when the transfer free energy term is assumed to be negligible. The value determined experimentally, 2.23, agrees excellently with this calculated value. The second example is furnished by the data given by Fife,¹⁹ who studied the uncatalyzed (S_N1) and hydronium ion-catalyzed ($A-1$) hydrolysis of γ -ethoxy- γ -butyrolactone. The ratio of his values for the two rate coefficients, 3.8×10^{-4} moles per liter, gives, respectively, a value of 2.39 for k_D/k_H ; the experimental value measured by Fife was 2.37. Put another way, the agreement between the calculated and experimental k_D/k_H values can be also considered as confirmatory evidence for the mechanistic conclusions drawn from these studies.

Application to an $A-2$ reaction (VII) is less amenable, because here



the transition state contains three isotopically exchangeable hydrogens of which only two are equivalent. For this case³

$$\log(k_D/k_H) = -3 \log l + \log \varphi + 2 \log \varphi' + \frac{1}{2.303RT} \Delta(\Delta G^\circ) \quad (10)$$

where the fractionation factors φ and φ' refer to the two types of hydrogens present in the transition state. As the values of $\log \varphi$ are relatively insensitive to the acid strengths, except when the pK values differ grossly, one can first make the approximation: $\varphi = \varphi'$ (cf. also Ref. 5). An application of the Kurz method¹⁷ to the calculation of K_H^\ddagger now requires that the transition state of the uncatalyzed reaction also contains a water molecule, *i.e.*, that the mechanism of the uncatalyzed reaction is bimolecular. Such a situation prevails in the normal case of hydrolysis of carboxylic esters. Thus, in the case of the hydrolysis reactions of vinyl acetate, the values determined for the hydronium ion-catalyzed hydrolysis²⁰ and for the uncatalyzed hydrolysis²¹ give $K_H^\ddagger = 7.8 \times 10^{-4}$ moles per liter, from which one obtains with the above approximation the value 1.35 for k_D/k_H . The experimental value for the latter quantity, determined by Yrjänä,²⁰ is 1.33. Similar calculations on ethyl acetate, using the rate coefficients for the uncatalyzed²¹ and hydronium ion-catalyzed²² reactions, predict a value of 1.58 for k_D/k_H . Unfortunately, no experimental k_D/k_H values for this compound are available, but it can be seen that the experimental value for methyl acetate,⁵ 1.68, is very close to that calculated for ethyl acetate.

The agreement between the calculated and experimental k_D/k_H values for ester hydrolysis is somewhat better than could be expected in view of

the approximation made when the two fractionation factors were equalized. One might therefore ask, whether reactions of the *A*-2 type could be found in which the two fractionation factors differed grossly enough to invalidate this approximation. A case in point is the hydrolysis of 2,5,5-trimethyl-dioxolone-(4),²³ which compound is both an ester and an acetal. The hydrolysis mechanism was assumed to be neither of the *A*-1 type of acetal hydrolysis nor of the *A*-2 type of the common ester hydrolysis. Stereochemical arguments suggested a mechanism of an *A*-2 type in which the role of the water molecule in the transition state was to release the steric strain involved. In fact, if one makes calculations on the magnitudes of the isotope effects expected by the ordinary mechanisms of acetal and ester hydrolysis, one obtains from the experimental values: $K_H^\ddagger = 1.41 \times 10^{-1}$ moles per liter, $k_D/k_H = 2.21$ (*A*-1 mechanism), and $k_D/k_H = 1.17$ (normal mechanism of ester hydrolysis), respectively. The experimental value for k_D/k_H was 1.68, which does not agree with either of the calculated values. The inference that can be drawn from these calculations, *viz.*, that the actual mechanism is neither of those two mentioned above, is in good harmony with the previous conclusions.

Further refinements of the theory and its applications will be dealt with in forthcoming publications.

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