

# SOLVENT ISOTOPE EFFECT IN H<sub>2</sub>O-D<sub>2</sub>O MIXTURES

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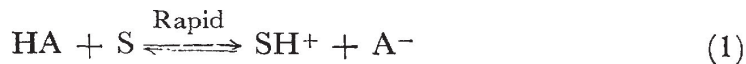
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## INTRODUCTION

It is well known that the isotope effect on proton transfer reactions in mixtures of light and heavy water is seldom a linear function of solvent deuterium content. Rates of acid-catalysed reactions usually change less rapidly with increasing solvent deuterium content when the fraction of deuterium in the solvent is low than when this fraction is high. The same is true of acid association constants for weak acids. This behaviour results in curved plots of isotope effect *versus* solvent deuterium content which have a characteristic sag towards an isotope effect of unity.

This phenomenon was discovered nearly thirty years ago by LaMer who measured the dissociation constant of acetic acid in H<sub>2</sub>O-D<sub>2</sub>O mixtures<sup>1</sup>. Shortly after, a number of additional examples were provided by Gross<sup>2</sup> and by Butler<sup>3</sup>. With these added examples, Gross and Butler offered a quantitative explanation of the phenomenon which accounted quite well for most of the observed cases. This explanation has, therefore, come to be known as the Gross-Butler theory, and the equation expressing it, the Gross-Butler equation.

It was noticed quite early in the development of the Gross-Butler theory that, whereas all isotope effects on acid ionization equilibria conformed to the Gross-Butler equation, only some of the isotope effects on reaction rates did. The reactions whose kinetic isotope effects could be accounted for by the theory were all reactions for which a pre-equilibrium mechanism of acid catalysis could be justified:

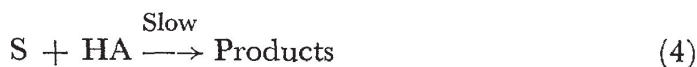


The effect of acid on the rate of such a reaction is due to its influence on the concentration of the intermediate SH<sup>+</sup>, and this intermediate is provided by a reaction which is formally similar to an acid association equilibrium:



Since the reactions of equations (1) and (3) are similar, the effects of substituting deuterium for hydrogen in the solvent of each should be alike. In this way, the similarity of solvent isotope effects in H<sub>2</sub>O-D<sub>2</sub>O mixtures on equilibria and some reaction rates was rationalized.

Of the reactions whose solvent isotope effects did not conform to the Gross-Butler theory, the worst deviant was the mutarotation of glucose<sup>4</sup>. The isotope effect on this reaction showed a linear dependence on solvent deuterium content. Since general acid catalysis had been observed for this reaction, and since its rate was slower in D<sub>2</sub>O than in H<sub>2</sub>O, the reaction was assigned a rate-determining proton transfer mechanism:



Thus, the isotope effect on the mutarotation of glucose was thought to be on a rate, whereas the isotope effects on reactions which did conform to the Gross-Butler equation were on an equilibrium. Isotope effects on rates and equilibria could not be expected to be the same, and the deviant behaviour was reconciled.

In an extension of this reasoning, the form of the dependence of isotope effect on solvent deuterium content was proposed as a criterion of reaction mechanism. If a reaction showed a solvent isotope effect which conformed to Gross-Butler predictions, it could be assigned a pre-equilibrium proton transfer mechanism. If its isotope effect deviated from the Gross-Butler equation, and especially if it showed a linear dependence on solvent deuterium content, it could be assigned a rate-determining proton transfer mechanism.

This situation remained unchanged for nearly two decades. A very recent revival of interest in the Gross-Butler phenomenon, however, has altered matters considerably. This new work began with Purlee's re-examination of the Gross-Butler theory<sup>5</sup>. Purlee revised the parameters in the Gross-Butler equation, evaluated some of the assumptions on which the theory was based, and concluded that the Gross-Butler equation was still a valid criterion for distinguishing pre-equilibrium and rate-determining proton transfer reactions. Shortly after, an equation relating isotope effect to solvent deuterium content for rate-determining proton transfer was derived for the first time by Gold<sup>6</sup>. This work showed that, for a limiting isotope effect in pure D<sub>2</sub>O of 2.00 ( $k_D/k_H$ ), the difference in predicted behaviour for pre-equilibrium proton transfer and rate-determining proton transfer was very small. Gold concluded, therefore, that the Gross-Butler phenomenon was of little value as a criterion of mechanism. Gold also suggested further that agreement between experimental isotope effects and values predicted by the Gross-Butler equation, which has a cubic form, was evidence that the proton exists in aqueous solution principally as the monohydrate, H<sub>3</sub>O<sup>+</sup>. Halevi, Long and Paul<sup>7</sup> took exception to this: they claimed that a linear form of the equation based on a model in which the solvation of the proton is not specified fitted some of the data better than the original cubic form. These investigators also treated the phenomenon purely as a medium effect and showed that some of the data conformed well to this interpretation. Shortly afterwards, Swain<sup>8</sup> proposed a further series of equations which related isotope effect to solvent deuterium content. These were based on a monohydrated proton model and rather detailed structures for transition states. They fit some of the data well, and they predicted easily measurable differences between isotope effects on pre-equilibrium and rate-determining proton transfer reactions.

The situation today, then, is one of renewed activity and considerable confusion. In this paper we shall attempt to remove some of the confusion by showing how the previous treatments of the Gross-Butler phenomenon are related to one another and under what conditions the conclusions drawn from them are valid.

### DERIVATION OF A GENERAL EQUATION

Consider a system in which an acid with  $i$  equivalent hydrogens reacts with water to give an anion with  $i - 1$  equivalent hydrogens plus a proton solvated by  $n$  molecules of water:



In a mixture of light and heavy water an analogous reaction will occur. The situation here, however, is complicated by the fact that each of the solute species is present in a number of isotopically different forms: all combinations of hydrogen and deuterium are possible. But the notation at least can be simplified by using the symbol L to designate either hydrogen or deuterium. Thus, in an H<sub>2</sub>O-D<sub>2</sub>O mixture:



The ionization constant of this acid in H<sub>2</sub>O can be expressed in the usual way in terms of activities of the various species:

$$K_H = \frac{(H_{i-1}A^-)(H_qO^+)}{(H_iA)(H_2O)^n} \quad (7)$$

$$q = 2n + 1$$

In an H<sub>2</sub>O-D<sub>2</sub>O mixture of deuterium atom fraction  $x$ , the operationally significant equilibrium constant has a similar form:

$$K_x = \frac{(L_{i-1}A^-)(L_qO^+)}{(L_iA)(L_2O)^n} \quad (8)$$

$$x = \left( \frac{D}{D + H} \right)_{L_2O}$$

$$\begin{aligned} (L_{i-1}A^-) &= (H_{i-1}A^-) + (H_{i-2}DA^-) + \dots + (D_{i-1}A^-) \\ (L_qO^+) &= (H_qO^+) + (H_{q-1}DO^+) + \dots + (D_qO^+) \\ (L_iA) &= (H_iA) + (H_{i-1}DA) + \dots + (D_iA) \\ (L_2O) &= (H_2O) + (HDO) + (D_2O) \end{aligned}$$

The manner in which  $K_x$  changes with  $x$  can now be determined by expressing the activities of equation (8) in terms of  $x$ . This can be done by using probability. Let  $H_1$ ,  $H_2$ , and  $H_3$  be the probabilities of finding hydrogen and  $D_1$ ,  $D_2$ , and  $D_3$ , the probabilities of finding deuterium in  $L_iA$ ,  $L_{i-1}A^-$ , and  $L_qO^+$  respectively. Then the concentration of any isotopic form of a given solute species will be equal to the total concentration of the species times the probability of finding that particular isotopic form. For example,



$$[H_iA] = (H_1)^i [L_iA]$$

$$[H_{i-2}D_2A] = \frac{i(i-1)}{2} (H_1)^{i-2} (D_1)^2 [L_iA]$$

The factor  $i(i-1)/2$  in the second case above is the number of ways  $i-2$  hydrogens and 2 deuteriums can be distributed among  $i$  equivalent sites. In this manner, ratios of concentrations of isotopically different forms of a solute species can be written<sup>†</sup>:

$$\frac{[H_iA]}{[H_{i-2}D_2A]} = \frac{2}{i(i-1)} (H_1/D_1)^2 \quad (9)$$

Using this method, the concentrations of all isotopically different forms of a given solute species can be written in terms of the form containing only hydrogen:

$$\begin{aligned} [H_iA] &= [H_iA] \\ [H_{i-1}DA] &= i(D_1/H_1)[H_iA] \\ [H_{i-2}D_2A] &= \frac{i(i-1)}{2} (D_1/H_1)^2 [H_iA] \\ &\vdots \\ [D_iA] &= (D_1/H_1)^i [H_iA] \end{aligned} \quad (10)$$

The coefficients of  $[H_iA]$  in equations (10) are the terms of the binomial expansion of  $[1 + (D_1/H_1)]^i$ . Thus, the sum of equations (11) is:

$$\sum_{j=i}^{j=0} [H_{i-j}D_jA] = [L_iA] = [1 + (D_1/H_1)]^i [H_iA] \quad (11)$$

The ratio  $(D_1/H_1)$  is related to the deuterium content of the solvent through the fractionation factor,  $\phi_1$ , for the species  $L_iA$ :

$$\begin{aligned} \phi_1 &= \frac{(D_1/H_1)}{(D/H)_{\text{solvent}}} = \frac{(D_1/H_1)}{x/(1-x)} \\ (D_1/H_1) &= \phi_1 x / (1-x) \end{aligned}$$

Substitution of this result into equation (11) gives

$$[L_iA] = [1 + \phi_1 x / (1-x)]^i [H_iA] \quad (12)$$

Expressions similar to equation (12) for the other solute species can be obtained in the same way:

$$\begin{aligned} [L_{i-1}A^-] &= [1 + \phi_2 x / (1-x)]^{i-1} [H_{i-1}A^-] \\ [L_qO^+] &= [1 + \phi_3 x / (1-x)]^q [H_qO^+] \\ [L_2O] &= [1 + x / (1-x)]^2 [H_2O] \end{aligned} \quad (13)$$

<sup>†</sup> This is equivalent to applying the rule of the geometric mean<sup>9</sup>. In the example of equation (9) the factor  $2/i(i-1)$  is the ratio of symmetry numbers of  $H_{i-2}D_2A$  and  $H_iA$ , and  $(H_1/D_1)^2$  is the factor by which the partition functions of  $H_{i-2}D_2A$  and  $H_iA$  differ.



The fractionation factor for the solvent is unity by definition. Substituting the values stated in equations (12) and (13) into equation (8) gives:

$$K_x = \frac{(L_{i-1}A^-)(L_qO^+)}{(L_iA)(L_2O)^n} = \frac{f_{L_{i-1}A^-} f_{L_qO^+}}{f_{L_iA} f^n_{L_2O}} \times \frac{[L_{i-1}A^-][L_qO^+]}{[L_iA][L_2O]^n} \quad (8)$$

$$K_x = \frac{f_{L_{i-1}A^-} f_{L_qO^+}}{f_{L_iA} f^n_{L_2O}} \times \frac{[1 + \phi_2x/(1-x)]^{i-1} [1 + \phi_3x/(1-x)]^q}{[1 + \phi_1x/(1-x)]^i [1 + x/(1-x)]^{2n}} \times \frac{[H_{i-1}A^-][H_qO^+]}{[H_iA][H_2O]^n} \quad (14)$$

Since  $q = 2n + 1$ , the second factor on the right of equation (14) can be simplified:

$$K_x = \frac{f_{L_{i-1}A^-} f_{L_qO^+}}{f_{L_iA} f^n_{L_2O}} \times \frac{(1-x+\phi_2x)^{i-1} (1-x+\phi_3x)^q}{(1-x+\phi_1x)^i} \times \frac{[H_{i-1}A^-][H_qO^+]}{[H_iA][H_2O]^n} \quad (15)$$

The last factor in equation (15) is related to equation (7), the expression for the equilibrium constant of this reaction in pure H<sub>2</sub>O:

$$K_H = \frac{f_{H_{i-1}A^-} f_{H_qO^+}}{f_{H_iA} f^n_{H_2O}} \times \frac{[H_{i-1}A^-][H_qO^+]}{[H_iA][H_2O]^n} \quad (7)$$

Therefore:

$$\frac{K_x}{K_H} = \frac{f_{L_{i-1}A^-} f_{L_qO^+}}{f_{L_iA} f^n_{L_2O}} \times \frac{f_{H_iA} f^n_{H_2O}}{f_{H_{i-1}A^-} f_{H_qO^+}} \times \frac{(1-x+\phi_2x)^{i-1} (1-x+\phi_3x)^q}{(1-x+\phi_1x)^i} \quad (16)$$

This expression is valid within the limits of reliability of equations of the type of equation (9). These should be the same as the limits of reliability of the rule of the geometric mean<sup>9</sup>. An approximate expression may be obtained by assuming that the activity coefficients in equation (16) cancel individually†:

$$\frac{K_x}{K_H} = \frac{(1-x+\phi_2x)^{i-1} (1-x+\phi_3x)^q}{(1-x+\phi_1x)^i} \quad (17)$$

Equation (17) consists of factors of the form  $(1-x+\phi x)$ . The factors which refer to the products of the related chemical reaction (equation 6) appear in the numerator, and the factors which refer to the reactants appear in the denominator. Each factor is raised to a power which corresponds to the number of equivalent hydrogens or deuteriums in the relevant solute species. Equations of this form can be derived for protolytic equilibria in H<sub>2</sub>O-D<sub>2</sub>O mixtures involving any number of solute species. Thus for the general case

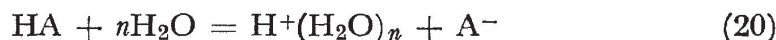
† Though this assumption is usually made in treatments of phenomena in H<sub>2</sub>O-D<sub>2</sub>O mixtures, it is difficult to assess its validity<sup>7, 8</sup>.



$$\frac{K_x}{K_H} = \frac{(1 - x + \phi_Y x)^r (1 - x + \phi_Z x)^s \dots}{(1 - x + \phi_A x)^i (1 - x + \phi_B x)^j \dots} \quad (19)$$

### APPLICATION TO EQUILIBRIA

The ionization of a monobasic acid in water to give a proton solvated by any number of water molecules



is a special case of equation (18). Therefore, the isotope effect on this reaction can be written as

$$\frac{K_x}{K_H} = \frac{(1 - x + \phi_2 x)^{2n+1}}{(1 - x + \phi_1 x)} \quad (21)$$

It is common practice to give  $\phi_2$ , the fractionation factor for the solvated proton, the symbol  $l$  when the proton is monosolvated; *i.e.*,  $l = \phi_2$  for  $\text{H}_3\text{O}^+$ . Then, for the general case of  $\text{H}^+(\text{H}_2\text{O})_n$ ,  $\phi_2 = \lambda$ . The remaining fractionation factor,  $\phi_1$ , can be evaluated by taking the limit of equation (21),  $x = 1$ :

$$\begin{aligned} \left(\frac{K_x}{K_H}\right)_{x=1} &= \frac{K_D}{K_H} = \frac{\lambda^{2n+1}}{\phi_1} \\ \phi_1 &= \lambda^{2n+1} K_H / K_D \\ \frac{K_x}{K_H} &= \frac{(1 - x + \lambda x)^{2n+1}}{1 - x + x \lambda^{2n+1} K_H / K_D} \end{aligned} \quad (22)$$

When  $n = 1$ , equation (20) becomes



and equation (22) is the usual Gross-Butler equation:

$$\frac{K_H}{K_x} = \frac{1 - x + x l^3 K_H / K_D}{(1 - x + x l)^3} \quad (23)$$

When  $n = 0$ , equation (20) represents the ionization of a monobasic acid to give a proton with unspecified solvation:



and equation (22) now takes the form

$$\frac{K_H}{K_x} = \frac{1 - x + x l' K_H / K_D}{1 - x + x l'} \quad (24)$$

which is identical with the expression derived by Gold<sup>6</sup> and by Halevi, Long, and Paul<sup>7</sup> for this case<sup>†</sup>.

<sup>†</sup> The fractionation factor  $l'$  in equation (24) is different from  $l$  in equation (23); though both measure the D:H ratio in the solvated proton, they do so for solvated protons of different structure.

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Similar treatments can be applied to polybasic acids. For example, in the case of a dibasic acid ionizing to give a monohydrated proton:



$$\phi_1 = \frac{(\text{D}/\text{H})_{\text{L}_2\text{A}}}{(\text{D}/\text{H})_{\text{L}_2\text{O}}}$$

$$l = \frac{(\text{D}/\text{H})_{\text{L}_3\text{O}^+}}{(\text{D}/\text{H})_{\text{L}_2\text{O}}}$$

$$\phi_2 = \frac{(\text{D}/\text{H})_{\text{LA}^-}}{(\text{D}/\text{H})_{\text{L}_2\text{O}}}$$

$$\frac{K_{\text{H}}}{K_x} = \frac{1 - x + x l^{3/2} \phi_2^{1/2} (K_{\text{H}}/K_{\text{D}})^{1/2}}{(1 - x + x l)^3 (1 - x + x \phi_2)}$$

This is a special case of an equation recently derived for polybasic acids by Long<sup>10</sup>. Here, only one of the two fractionation factors,  $\phi_1$  and  $\phi_2$ , is defined by the limiting value of  $K_{\text{H}}/K_x$  in pure D<sub>2</sub>O, but the other can be determined by measuring the solvent isotope effect on the second ionization of H<sub>2</sub>A.

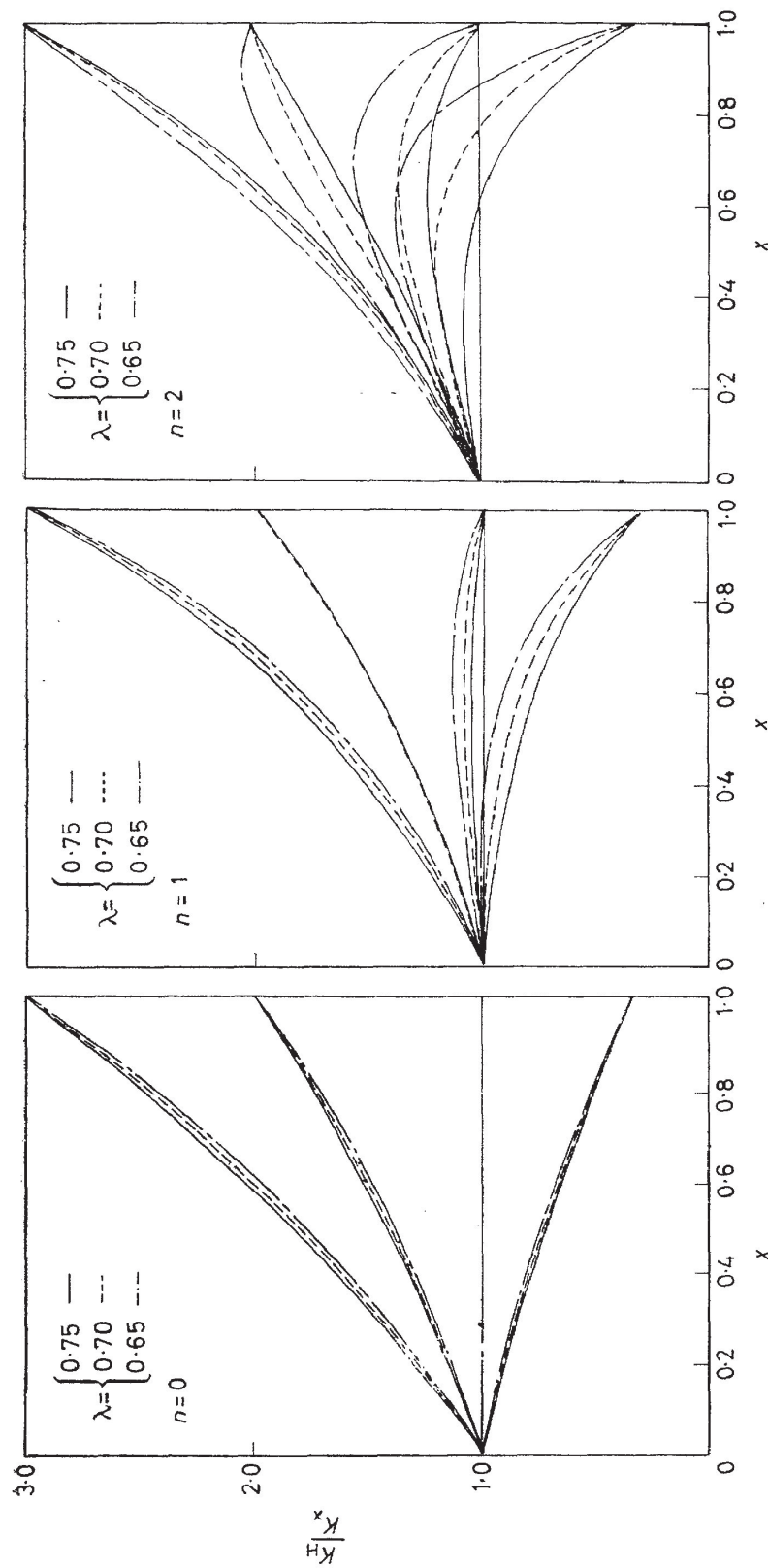
Equation (22) shows that the solvent isotope effect on the ionization of a monobasic acid depends on two parameters,  $\lambda$  and  $n$ , in addition to  $x$ , the deuterium atom fraction of the solvent, and  $K_{\text{H}}/K_{\text{D}}$ , the limiting isotope effect in pure D<sub>2</sub>O. In *Figures 1* and *2*, equation (22) is plotted for representative values of  $\lambda$  and  $n$ . It can be seen that both of these parameters are important in fixing the shape of these curves. For small values of  $n$  and values of  $\lambda$  close to unity, equation (22) is nearly linear in  $x$ . As  $n$  increases and  $\lambda$  decreases, curvature develops. For the values of  $K_{\text{H}}/K_{\text{D}}$  represented in *Figures 1* and *2*, increases in  $n$  and decreases in  $\lambda$  seem to affect the shape of the plots in much the same way. These changes in  $n$  and  $\lambda$  generally have the most pronounced effect at low values of  $K_{\text{H}}/K_{\text{D}}$ ; they have a minimum effect when  $K_{\text{H}}/K_{\text{D}}$  is 2 or 3.

These trends in the values of  $K_{\text{H}}/K_x$  with  $n$  and  $\lambda$  make it unlikely that definitive information concerning the extent of solvation of the proton in aqueous solution will be obtained from measurement of acid dissociation constants in H<sub>2</sub>O-D<sub>2</sub>O mixtures. The fit between experimental data and calculated isotope effects is not uniquely determined by  $n$  unless  $\lambda$  is fixed. Unfortunately, changes in  $n$  and  $\lambda$  affect the fit in nearly the same way and one parameter cannot be fixed independently of the other.

## APPLICATION TO KINETICS

The transition state theory of reaction rates states that transition states are in equilibrium with reactants and the rate of formation of products from transition states is the same for all reactions. The rate of any reaction, therefore, is controlled solely by the equilibrium between reactants and transition state, and a ratio of two rate constants is equal to a ratio of two equilibrium constants. The kinetic problem thus becomes an equilibrium one, and the general equation derived on pp. 245-248 for the solvent isotope effect on equilibria can be applied to solvent isotope effects on rates of reaction.

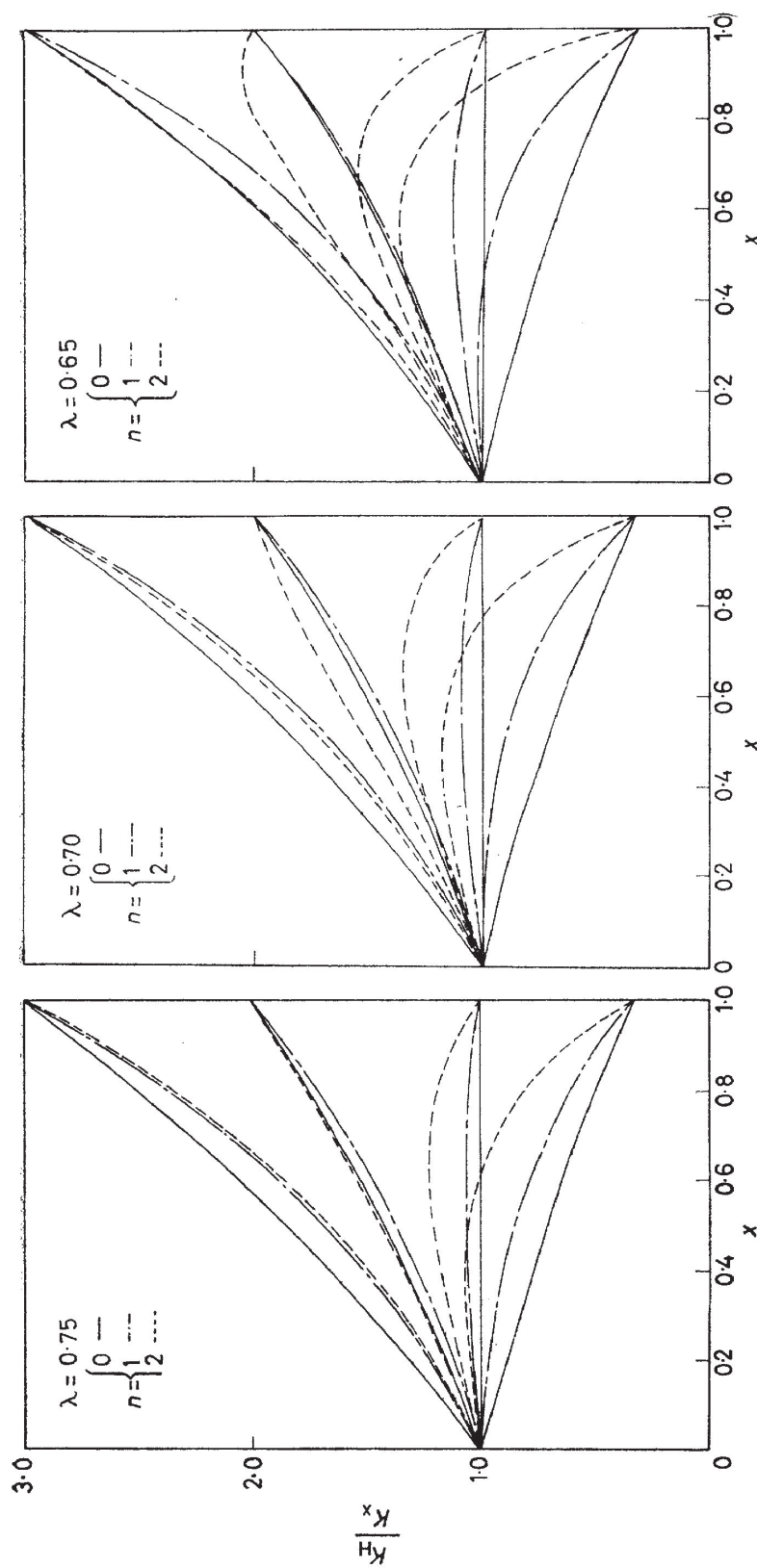




$$\frac{K_H}{K_x} = \frac{1 - x + x\lambda^{(2n+1)} K_H/K_D}{(1 + x + x\lambda)(2n+1)}$$

Figure 1. Solutions of equation (22) showing the dependence of the relationship between  $K_H/K_x$  and  $x$  on  $\lambda$  and  $n$  for representative values of  $K_H/K_D$

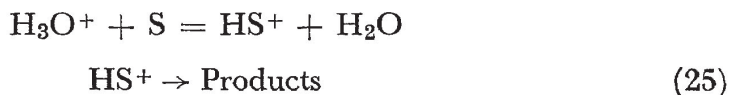
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$$\frac{K_H}{K_x} = \frac{1-x+x\lambda(2n+1)}{(1+x+x\lambda)(2n+1)} \frac{K_H}{K_D}$$

Figure 2. As for Figure 1

For example, in an acid-catalysed reaction with a pre-equilibrium proton transfer to substrate followed by unimolecular decomposition of the substrate conjugate acid (*A*-1 mechanism):



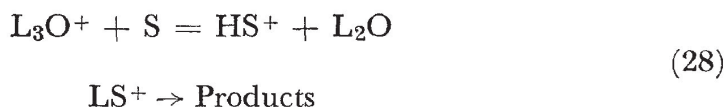
the equilibrium between reactants and transition state may be written as:



The equilibrium constant for this reaction is

$$K_{\text{H}}^\ddagger = \frac{(\text{HS}^+)^\ddagger (\text{H}_2\text{O})}{(\text{H}_3\text{O}^+) (\text{S})} \quad (27)$$

In an  $\text{H}_2\text{O}$ - $\text{D}_2\text{O}$  mixture, a similar reaction occurs:



which can also be formulated as an equilibrium:



$$K_x^\ddagger = \frac{(\text{LS}^+)^\ddagger (\text{L}_2\text{O})}{(\text{L}_3\text{O}^+) (\text{S})} \quad (30)$$

The specific rate constants for reactions (25) and (28) are†:

$$\begin{aligned} k_{\text{H}} &= K_{\text{H}} \frac{kT}{h} K_{\text{H}}^\ddagger \\ k_x &= K_x \frac{kT}{h} K_x^\ddagger \end{aligned}$$

and their ratio is

$$\frac{k_x}{k_{\text{H}}} = \frac{K_x^\ddagger}{K_{\text{H}}^\ddagger}$$

The ratio  $K_x^\ddagger/K_{\text{H}}^\ddagger$  can be evaluated by the method developed in pp. 245–248. For the case of equation (28):

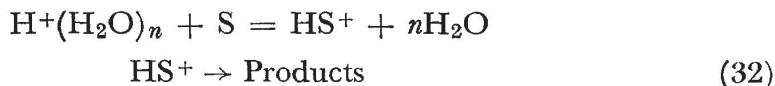
$$\begin{aligned} \frac{K_x^\ddagger}{K_{\text{H}}^\ddagger} &= \frac{k_x}{k_{\text{H}}} = \frac{(1 - x + \phi x)}{(1 - x + xl)^3} \\ \left( \frac{k_x}{k_{\text{H}}} \right)_{x=1} &= \frac{k_{\text{D}}}{k_{\text{H}}} = \frac{\phi}{l_3} \\ \frac{k_x}{k_{\text{H}}} &= \frac{1 - x + xl^3 k_{\text{D}}/k_{\text{H}}}{(1 - x + xl)^3} \end{aligned} \quad (31)$$

† The symbols have their usual meaning:  $k$  is Boltzman's constant,  $T$  is absolute temperature,  $h$  is Planck's constant, and  $K$  is the transmission coefficient. The isotope effect on the latter is generally assumed to be unity.



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This is the usual Gross-Butler equation for an *A*-1 reaction. It is a special case of the more general equation which applies to an *A*-1 reaction in which the catalysing proton is solvated by any number of water molecules:



$$\frac{k_x}{k_H} = \frac{1 - x + x\lambda^{2n+1}k_D/k_H}{(1 - x + x\lambda)^{2n+1}} \quad (33)$$

When  $n = 0$ , solvation of the catalysing proton is unspecified, and equation (33) becomes:

$$\frac{k_x}{k_H} = \frac{1 - x + x\lambda'k_D/k_H}{1 - x + x\lambda'} \quad (34)$$

This is similar to equation (29) derived above for acid ionization equilibria with unspecified solvation of the proton. It is identical with equations derived by Gold<sup>6</sup> and by Halevi, Long and Paul<sup>7</sup> for this case.

Acid-catalysed reactions in which proton transfer is rate-determining (*A*-S<sub>E</sub>2 mechanism)



can be treated in a similar way. Here the transition state



has two different kinds of hydrogen, one which is in transit and  $2m$  which are in the process of becoming hydrogens of the solvent water. The structure of the water-like portion of this transition state will be intermediate between the structures of the solvated proton and the solvent. In H<sub>2</sub>O-D<sub>2</sub>O mixtures, therefore, the D:H ratio of this part of the transition state will lie between those of its two limiting forms. If the parameter  $\alpha$  is defined as the degree to which the water-like portion of the transition state resembles the solvent, the fractionation factor for the hydrogens in this part of the transition state will be  $\lambda^{1-\alpha}$ . With  $\phi$  as the fractionation factor for the hydrogen in transit, the isotope effect on this reaction can be written:

$$\begin{aligned} \frac{k_x}{K_H} &= \frac{(1 - x + x\lambda^{1-\alpha})^{2m}(1 - x + x\phi)}{(1 - x + x\lambda)^{2n+1}} \\ \left(\frac{k_x}{K_H}\right)_{x=1} &= \frac{k_D}{k_H} = \frac{\lambda^{2m(1-\alpha)}\phi}{\lambda^{2n+1}} \\ \phi &= \lambda^{2[n-m(1-\alpha)]+1}k_D/k_H \\ \frac{k_x}{k_H} &= \frac{(1 - x + x\lambda^{1-\alpha})^{2m}(1 - x + x\lambda^{2[n-m(1-\alpha)]+1}k_D/k_H)}{(1 - x + x\lambda)^{2n+1}} \end{aligned} \quad (36)$$

When  $\alpha = 1$ , this equation reduces to:

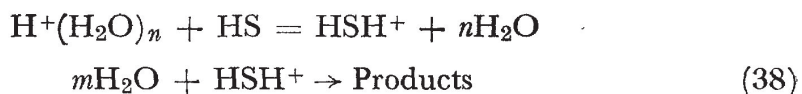
$$\frac{k_x}{k_H} = \frac{(1 - x + x\lambda^{2n+1}k_D/k_H)}{(1 - x + x\lambda)^{2n+1}}$$

Which is the same as the expression (equation 33) for an  $A-1$  reaction. When  $n = m = 1$ , equation (36) becomes:

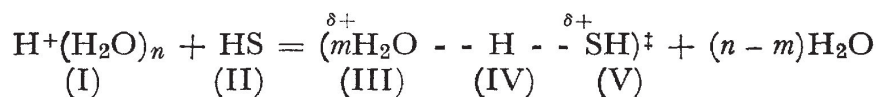
$$\frac{k_x}{k_H} = \frac{(1 - x + x\lambda^{1-\alpha})^2(1 - x + x\lambda^{2\alpha+1}k_D/k_H)}{(1 - x + x\lambda)^3} \quad (37)$$

This is equivalent to the expressions derived by Gold<sup>6</sup> and by Swain<sup>8</sup> for an  $A-S_E2$  reaction with a monosolvated proton.

The method illustrated above for the  $A-1$  and  $A-S_E2$  reactions can be used to predict the solvent isotope effect in  $H_2O-D_2O$  mixtures on the rate of any proton transfer reaction. For example, the  $A-2$  mechanism of acid catalysis



has a transition state in which water is acting on the substrate conjugate acid to remove a proton which is different from the one added in the pre-equilibrium step. This reaction can be formulated as the equilibrium:



The fractionation factors  $\lambda$ ,  $\phi_1$ ,  $\lambda^{1-\alpha}$ ,  $\phi_2$ , and  $\phi_3$  can be assigned to the hydrogens designated (I), (II), (III), (IV), and (V) respectively. Then

$$\frac{k_x}{k_H} = \frac{(1 - x + x\lambda^{1-\alpha})^{2m}(1 - x + x\phi_2)(1 - x + x\phi_3)}{(1 - x + x\lambda)^{2n+1}(1 - x + x\phi_1)} \quad (39)$$

$$\left(\frac{k_x}{k_H}\right)_{x=1} = \frac{k_D}{k_H} = \frac{\lambda^{2m(1-\alpha)}\phi_2\phi_3}{\lambda^{2n+1}\phi_1}$$

$$\phi_2 = \lambda^{2[n-m(1-\alpha)]+1}\phi_1\phi_3^{-1}k_D/k_H$$

$$\frac{k_x}{k_H} = \frac{(1 - x + x\lambda^{1-\alpha})^{2m}(1 - x + x\lambda^{2[n-m(1-\alpha)]+1}\phi_1\phi_3^{-1}k_D/k_H)}{(1 - x + x\lambda)^{2n+1}(1 - x + x\phi_1)} \quad (40)$$

When  $\phi_1$  and  $\phi_3$  are equal to unity, that is when the hydrogens (II) and (V) have the same isotopic content as the solvent, this expression becomes equivalent to equation (36) for the  $A-S_E2$  reaction.

Swain has formulated an expression for the solvent isotope effect in  $H_2O-D_2O$  mixtures on the  $A-2$  reaction with the limiting condition of the second proton transfer being complete at the transition state; this equation predicts a linear dependence of  $k_x/k_H$  on  $x$ . Swain's limiting conditions can be imposed on equation (39):  $\alpha = 0$ ,  $\phi_2 = \lambda$ , and  $m = n$ . Then

$$\frac{k_x}{k_H} = \frac{1 - x + x\phi_1k_D/k_H}{1 - x + x\phi_1} \quad (41)$$

Equation (41) is linear in  $x$  only if  $\phi_1 = 1$ . This is an assumption which was implicit in Swain's treatment.

Another common reaction mechanism for acid catalysis is one in which water acting as a nucleophile attacks the conjugate acid of the substrate:

SOLVENT ISOTOPE EFFECT IN H<sub>2</sub>O-D<sub>2</sub>O MIXTURES



This reaction can be formulated as an equilibrium:



and the fractionation factors  $\phi_1$  and  $\phi_2$  can be assigned to the hydrogens of the attacking water and the hydrogen transferred in the equilibrium step respectively. The solvent isotope effect in H<sub>2</sub>O-D<sub>2</sub>O mixtures can then be written as:

$$\frac{k_x}{k_H} = \frac{(1-x+x\phi_1)^{2m}(1-x+x\phi_2)}{(1-x+x\lambda)^{2n+1}}$$

$$\phi_2 = \lambda^{2n+1}\phi^{-2m}k_D/k_H$$

$$\frac{k_x}{k_H} = \frac{(1-x+x\phi_1)^{2m}(1-x+x\lambda^{2n+1}\phi_1^{-2m}k_D/k_H)}{(1-x+x\lambda)^{2n+1}} \quad (42)$$

In this mechanism, the attacking water is very often taking on positive charge. The fractional amount of this positive charge can be designated as  $\beta$ , and  $\phi_1$  can be expressed in terms of  $\lambda$ :

$$\phi_1 = \lambda^\beta$$

In this situation, equation (42) becomes:

$$\frac{k_x}{k_H} = \frac{(1-x+x\lambda^\beta)^{2m}(1-x+x\lambda^{2(n-m\beta)+1}k_D/k_H)}{(1-x+x\lambda)^{2n+1}} \quad (43)$$

If  $1-x$  is substituted for  $\beta$  in this equation, the expression becomes identical with equation (40) for the A-2 reaction. When  $n = m = 1$ ; i.e., when the proton is monohydrated and only one molecule of water reacts in the slow step:

$$\frac{k_x}{k_H} = \frac{(1-x+x\lambda^\beta)^2(1-x+x\lambda^{3-2\beta}k_D/k_H)}{(1-x+x\lambda)^3} \quad (44)$$

The limiting case for  $\beta = 1$  gives:

$$\frac{k_x}{k_H} = \frac{1-x+x\lambda k_D/k_H}{1-x+x\lambda} \quad (45)$$

This is similar to equation (34) for an A-1 reaction with unspecified solvation of the catalysing proton.

In this method of formulating the solvent isotope effect on reaction rates in H<sub>2</sub>O-D<sub>2</sub>O mixtures, only reactants and transition states are considered. The result, therefore, does not depend upon the path which the system has taken to reach the transition state, and the variation of isotope effect with solvent deuterium content cannot in itself give information about intermediates along the reaction path. Since the form of the relationship between  $k_x/k_H$  and  $x$  does depend on the magnitude of fractionation factors, these may sometimes be deduced from a comparison of experimental data with



predicted values. These fractionation factors may, in turn, reveal a reaction mechanism. This process, though difficult, could conceivably yield more information than examination of the magnitude of the limiting solvent isotope effect in pure D<sub>2</sub>O alone.

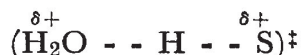
The difficulty of deducing a reaction mechanism from the dependence of isotope effect on solvent deuterium content can be appreciated by comparing forms of the relationship between  $k_x/k_H$  and  $x$  for several different mechanisms. There is a good deal of similarity in the expressions for the four general mechanisms considered above (equations 33, 36, 40 and 42). Three of these equations contain parameters which may vary from case to case of the general mechanism, and, in fact, limiting cases often degenerate into expressions which are identical with those for special cases of another mechanism.

The Gross-Butler phenomenon, therefore, would seem to have little value as a mechanistic tool. It might, however, be capable of providing further information about a reaction whose mechanism is already known. In this case, the primary choice of a general relationship between  $k_x/k_H$  and  $x$  is already made and attention can be concentrated on evaluating the still disposable parameters of that relationship. A case in point is equation (36) for the  $A-S_E2$  reaction:

$$\frac{k_x}{k_H} = \frac{(1 - x + x\lambda^{1-\alpha})^{2n}(1 - x + x\lambda^{2[n-m(1-\alpha)]+1}k_D/k_H)}{(1 - x + x\lambda)^{2n+1}} \quad (36)$$

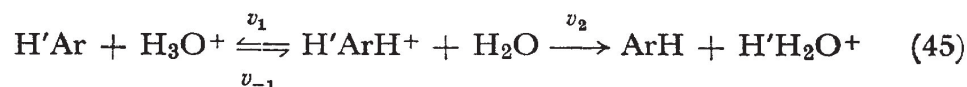
Of the parameters in this expression,  $n$  and  $\lambda$  have recently been measured by independent methods<sup>11, 12</sup>. This work indicates that reasonable values are  $n = 1$  and  $\lambda = l = 0.7$ . This also fixes  $m$  at 1. Two parameters remain, and of these  $k_D/k_H$  can be determined by measuring the limiting isotope effect in D<sub>2</sub>O. Provided, therefore, that  $k_x/k_H$  is a sufficiently sensitive function of  $\alpha$ ,  $\alpha$  may be determined from a fit of experimental data for an  $A-S_E2$  reaction to equation (36). Figure 3 shows that with  $n = m = 1$  and  $l = 0.7$ ,  $k_x/k_H$  is not very sensitive to changes in  $\alpha$  when  $k_D/k_H$  is between 1.0 and 2.0, but the sensitivity increases outside this range. Fortunately,  $A-S_E2$  reactions can have limiting solvent isotope effects less than 1.0, and there is some hope of determining  $\alpha$  for suitable examples of this reaction.

The parameter  $\alpha$  was defined above as the degree to which the water-like portion of the  $A-S_E2$  transition state



resembles solvent water. It is a measure of the extent to which the O-H bond is broken and H-S bond is formed. This parameter, therefore, indicates the degree of proton transfer at the transition state.

We have applied such a treatment to rates of aromatic hydrogen exchange for 1,3,5-trimethoxybenzene in H<sub>2</sub>O-D<sub>2</sub>O mixtures. The mechanism of this reaction is known to consist of two consecutive proton transfers<sup>13</sup>:



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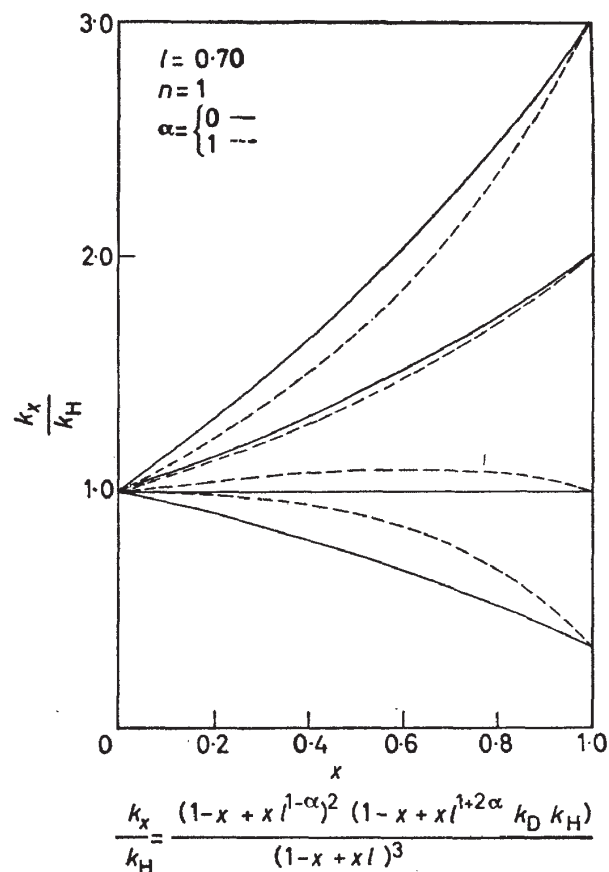


Figure 3. Solutions of equation (36) showing the sensitivity of the relationship between  $k_x/k_H$  and  $x$  to changes in  $\alpha$  for representative values of  $k_D/k_H$

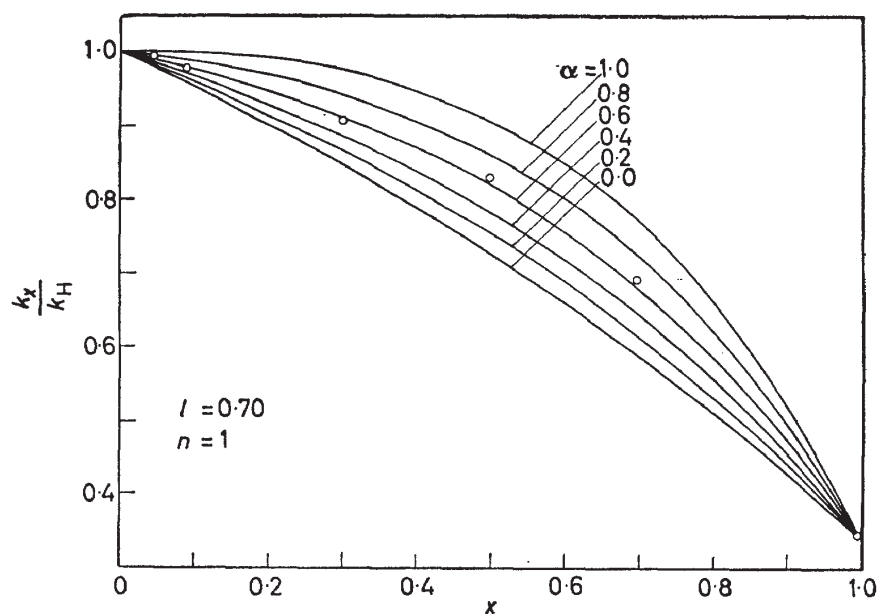


Figure 4. Comparison of predicted and experimentally observed solvent isotope effects on aromatic hydrogen exchange in 1,3,5-trimethoxybenzene

Only one of these,  $v_1$ , is an  $A-S_E2$  reaction, but the rate constant for  $v_1$  can be obtained from observed rates if both deuterium and tritium exchanges are done<sup>14</sup>. In this way, the isotope effect on  $v_1$ ,  $(k_D/k_H)_1$ , can be shown to be 0.34. This is a value which makes equation (36) fairly sensitive to changes in  $\alpha$ . Consequently, rates of tritium loss from 1,3,5-trimethoxybenzene to 0.05 M  $\text{HClO}_4$  in  $\text{H}_2\text{O}-\text{D}_2\text{O}$  mixtures were measured at 25°<sup>15</sup>, and these rates,  $(k_x/k_H)_{\text{obs.}}$ , were transformed into rate constants,  $(k_x/k_H)_1$ , for the first forward step of reaction (44) in a manner similar to that used to obtain  $(k_D/k_H)_1$ . Figure 4 shows that the results agree quite well with values predicted by equation (36) when  $\alpha = 0.6$ . The curves presented in this figure were calculated with  $l = 0.70$ . Though the calculated values are fairly sensitive to the choice of  $l$ , this parameter also enters into the transformation of  $(k_x/k_H)_{\text{obs.}}$  to  $(k_x/k_H)_1$  in a way which compensates for part of the variation in the predicted values of  $k_x/k_H$ . The net result is little change in the best value of  $\alpha$  obtained from a comparison of experimental data with calculated values.

This treatment indicates that in the transition state for aromatic hydrogen exchange of 1,3,5-trimethoxybenzene in dilute perchloric acid, the catalysing proton is 0.6 transferred from solvating water to the aromatic substrate. This value is in good agreement with that required to justify the magnitude of the primary isotope effect for this step of the reaction, and it is consistent with the value of the Brönsted  $\alpha$  observed in general acid catalysis for this substance.

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