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(30) Values for the oxidation potential of the methoxynaphthalenes were taken from the data of Zweig.[11] The oxidation potential for naphthalene was taken to be 1.65 V vs. SCE,[24] a value which agrees well with that determined by Loveland and Dimeler.[31] A value of 1.72 V vs. SCE in acetic acid solution was determined by Eberson and Nyberg,[32] and Yang reported a value of 1.54 V vs. SCE in acetonitrile solution.[33] This uncertainty in the oxidation potential of naphthalene does not qualitatively alter the conclusions of the present study.
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# Aromatic Protonation. 12. Solvent Isotope Effects in $H_2O$–$D_2O$ Mixtures on the Detritiation of Trimethoxybenzene[1,2]

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**Abstract:** The problem of kinetic solvent isotope effects in $H_2O$–$D_2O$ mixtures on systems for which proton transfer from $H_3O^+$ and some subsequent reaction step are each partly rate determining is considered, and an expression relating the isotope effect to the atom fraction of deuterium in the solvent is derived for a symmetrical isotope exchange process such as acid-catalyzed aromatic hydrogen exchange. This expression is then applied to data presented here for the detritiation of 1,3,5-trimethoxybenzene-*2-t* as well as to literature values for the same reaction and the detritiation of azulene-*1-t*. The analysis yields isotopic (Bronsted) exponents, $\alpha_i = 0.67$ for trimethoxybenzene and $\alpha_i = 0.57$ for azulene, which are not affected substantially by inclusion of corrections for nonadherence to the rule of the geometric mean and which are in good agreement with conventional Bronsted exponents as well as other measures of transition-state structure for these reactions.

Solvent isotope effects in mixtures of light and heavy water have excited the interest of chemists studying acid-base catalysis almost since the discovery of deuterium in 1932. This long history has produced a simple theory[6] which provides a good first approximation to complete quantitative interpretation of both kinetic and equilibrium phenomena in $H_2O$–$D_2O$ mixtures. Enough is understood, moreover, about some of the assumptions upon which this theory is based, such as neglect of medium effects or adherence to the rule of the geometric mean, to permit their removal, and thus to provide a second level of understanding, albeit at a considerable reduction in simplicity.[7]

This simple theory uses fractionation factors (D/H ratios at particular exchangeable sites relative to the D/H ratio of the solvent) to relate rate or equilibrium constants measured in $H_2O$–$D_2O$ mixtures to the deuterium content of the solvent. In favorable situations, these fractionation factors may be evaluated from the experimental data and, through them, information about reaction mechanism and/or transition state structure may be gained.

Application of the simple theory to equilibria is straightforward, as it is also to rates of even complex reactions, provided that a single step is wholly rate determining. When two or more steps are each partly rate determining, however, the analysis becomes considerably more difficult. Consider, for example, the reaction sequence shown in Scheme I. When the proton transfer step ($k_1$) is wholly rate determining, the dependence of rate upon isotopic content of the medium is given by

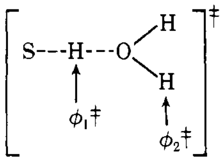
Scheme I

$$\mathrm{S} + \mathrm{H_3O^+} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{SH^+} + \mathrm{H_2O}$$

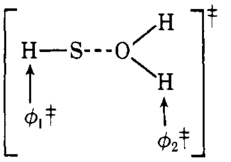
$$\mathrm{SH^+} + \mathrm{H_2O} \xrightarrow{k_2} \mathrm{H_2O\text{-}SH^+} \xrightarrow{\text{fast}} \text{products}$$

$$\frac{k_x}{k_{\mathrm{H}}} \frac{(1 - x + x\phi_1{}^{\ddagger})(1 - x + x\phi_2{}^{\ddagger})^2}{(1 - x + xl)^3} \tag{1}$$

where $k_{\mathrm{H}}$ and $k_x$ are rate constants for reactions in pure $H_2O$ and an $H_2O$–$D_2O$ mixture of atom fraction $x$, respectively, and $l$, $\phi_1{}^{\ddagger}$, are fractionation factors for the hydronium ion and the isotopically equilibrated positions of the proton transfer transition state **1**. The analysis is equally straightforward when



**1**



**2**

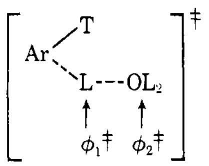
a later step is rate determining, and in the common case that attack of water, acting as a base or a nucleophile, upon $SH^+$ is the slow step ($k_2$), it is unchanged from eq 1 except that the values of the fractionation factors reflect a different structure for the transition state, i.e., **2**.

When proton transfer and a second step of the reaction occur at comparable rates, transition states for both steps must be considered. Normally, in such situations, the hydrogen transferred in the first step will not have reached isotopic equilibrium at the stage of the intermediate, and its isotopic composition therefore cannot be expressed by a fractionation factor independently of the isotopic composition of the medium; consequently, the expression for $k_x/k_H$ becomes more complicated.

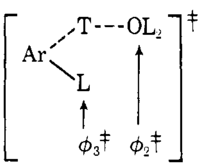
In certain cases, however, notably in two-step isotope exchange reactions such as the acid-catalyzed detritiation of aromatic substrates,[8,9] some simplification results. For this process, in fact, the relationship between $k_x/k_H$ and $x$ may still be represented by eq 1 provided that $\phi_1^\ddagger$ is replaced by what may be regarded as an effective fractionation factor $\phi_{eff}^\ddagger$:

$$\frac{k_x}{k_H} = \frac{(1 - x + x\phi_{eff}^\ddagger)(1 - x + x\phi_2^\ddagger)^2}{(1 - x + xl)^3} \qquad (2)$$

This effective fractionation factor is a function (eq 3) of $\phi_1^\ddagger$, the fractionation factor for the reacting hydrogen in the transition state for the first step of the process, **3**, and the molecular rate constants defined by Scheme II.

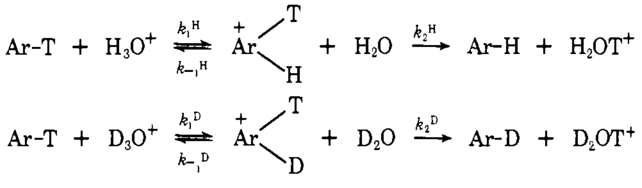


**3**



**4**

Scheme II



$$\phi_{eff}^\ddagger = \phi_1^\ddagger \left(\frac{1 + k_{-1}^H/k_2^H}{1 + k_{-1}^D/k_2^D}\right) \qquad (3)$$

(These expressions are derived in the Appendix.)

The properties of $\phi_{eff}^\ddagger$ give insight into its physical significance and into the course of the isotope exchange reaction. When $k_2 \gg k_{-1}$, and the first steps in Scheme II are fully rate determining, $\phi_{eff}^\ddagger$ reduces to $\phi_1^\ddagger$, the fractionation factor for the reacting hydrogen in the transition state for the first step. When $k_2 \ll k_{-1}$, on the other hand, $\phi_{eff}^\ddagger = \phi_1^\ddagger(k_{-1}^H k_2^D/k_{-1}^D k_2^H) = \phi_1^\ddagger(\phi_3^\ddagger/\phi_1^\ddagger) = \phi_3^\ddagger$, where $\phi_3^\ddagger$ is the fractionation factor for the same hydrogen in the transition state for the second step, **4**. In intermediate cases, $\phi_{eff}^\ddagger$ falls between $\phi_1^\ddagger$ and $\phi_3^\ddagger$ at a value determined by $k_{-1}/k_2$. Typically, since it refers to a hydrogen undergoing transfer, $\phi_1^\ddagger$ will be in the range 0.1–0.3, whereas $\phi_3^\ddagger$, which is for a hydrogen with a normal covalent band, should be close to 1.0.

Since structures **3** and **4**, the transition states for the two reactions of the phenonium ion intermediate, differ only isotopically, rate constants for reaction through them in a given direction can differ only isotopically as well. This is usually recognized in kinetic analyses of aromatic hydrogen exchange by using a single rate constant for $k_{-1}$ and $k_2$, with the isotopes written as superscripts "fore and aft", indicating the reacting and nonreacting hydrogens, respectively.[9] With this notation $\phi_{eff}^\ddagger$ becomes

$$\phi_{eff}^\ddagger = \phi_1^\ddagger \left\{\frac{1 + {}^Tk_2{}^H/{}^Hk_2{}^T}{1 + {}^Tk_2{}^D/{}^Dk_2{}^T}\right\}$$

and it is clear that the two rate constant ratios represent ratios of primary to secondary isotope effects: H–T in the numerator and D–T in the denominator. Since H–T isotope effects are much larger than D–T and, normally, primary isotope effects are much larger than secondary, $\phi_{eff}^\ddagger$ will typically be close to $\phi_3$, and thus much closer to 1.0, than is usual for the fractionation factor $\phi_1^\ddagger$ in a simple proton transfer.

A further useful formulation of $\phi_{eff}^\ddagger$ is wholly in terms of fractionation factors. Since ${}^Tk_2{}^H/{}^Hk_2{}^T$ and ${}^Tk_2{}^D/{}^Dk_2{}^T$ represent tritium and deuterium isotope effects, they may be expressed as deuterium effects alone by use of the Swain–Schaad relationship,[10] $k_H/k_T = (k_H/k_D)^{1.442}$, and $\phi_{eff}^\ddagger$ may be written

$$\phi_{eff}^\ddagger = \phi_1^\ddagger \left\{\frac{1 + ({}^Dk_2{}^H/{}^Hk_2{}^D)^{1.442}}{1 + ({}^Dk_2{}^H/{}^Hk_2{}^D)^{0.442}}\right\}$$

The deuterium effects may now be expressed in terms of fractionation factors, $\phi_1^\ddagger$ and $\phi_3^\ddagger$, and $\phi_{eff}^\ddagger$ becomes:

$$\phi_{eff}^\ddagger = \phi_1^\ddagger \left\{\frac{1 + (\phi_3^\ddagger/\phi_1^\ddagger)^{1.442}}{1 + (\phi_3^\ddagger/\phi_1^\ddagger)^{0.442}}\right\} \qquad (4)$$

An expression for $k_x/k_H$ for proton-transfer reactions in which the first and second steps occur at comparable rates and the reacting hydrogen is equilibrated at the stage of the intermediate has been obtained by Albery and Davies.[7a,11] Such behavior requires an independent mechanism for exchange of the intermediate, which does not exist in aromatic hydrogen exchange, and this equation therefore does not apply to this reaction.

Use of eq 2 is straightforward. It does not differ from that of eq 1 for a simple proton transfer, and values of $\phi_{eff}^\ddagger$ and $\phi_2^\ddagger$ are readily obtained. In this paper the equation is applied to measurement of tritium exchange in $H_2O$-$D_2O$ mixtures for the aromatic substrates trimethoxybenzene and azulene.

Our own measurements for trimethoxybenzene have already been briefly reported.[6] At that time, an attempt was made to correct $\phi_{eff}^\ddagger$ to $\phi_1^\ddagger$ using a method that we now recognize as being strictly accurate only in the case of pure isotopic solvents. Further measurements have since been reported by Batts and Kilford.[12] These were correctly analyzed using eq 1 but without recognizing that $\phi_1^\ddagger$ does not in this case represent a simple fractionation factor. Moreover, an attempt was made to determine not only $\phi_1^\ddagger$ and $\phi_2^\ddagger$ but also the fractionation factor for the hydronium ion ($l$), and this the data do not permit.[13] Measurements for azulene were reported in graphical form and discussed in qualitative terms by Schulze and Long.[14] Further details of these results have been kindly communicated by Professor Long.[15] Each set of data is now treated according to eq 2.

## Experimental Section

**Materials.** 1,3,5-Trimethoxybenzene-*2-t* was prepared from 2,4,6-trimethoxyphenyllithium and tritiated water as described previously.[16] Perchloric acid solutions were made from reagent grade 70% aqueous acid and deionized water, purified further by distillation from alkaline permanganate, or deuterium oxide (Bio-Rad Laboratories, 99.8 atom % D) as received.

**Table I.** Rates of Loss of Tritium from 1,3,5-Trimethoxybenzene-*2-t* to 0.0490 M Perchloric Acid in $H_2O$-$D_2O$ Mixtures at 24.6 °C

| $x^a$ | $10^4k$, $s^{-1}$ | $k_x/k_H{}^b$ |
|---|---|---|
| 0.000 | 2.92, 2.96, 3.01, 3.01, 3.06<br>3.08, 3.08, 3.11, 3.13 | 1.000 ± 0.008 |
| 0.045 | 3.10, 3.10, 3.11 | 1.021 ± 0.008 |
| 0.090 | 3.13, 3.13, 3.14, 3.22 | 1.037 ± 0.011 |
| 0.298 | 3.40, 3.46, 3.46, 3.47, 3.48 | 1.136 ± 0.010 |
| 0.497 | 3.82, 3.88, 3.90 | 1.272 ± 0.013 |
| 0.696 | 4.31, 4.31, 4.35 | 1.422 ± 0.012 |
| 0.995 | 5.12, 5.12, 5.14, 5.14, 5.15 | 1.688 ± 0.013 |

[a] $x$ = atom fraction of deuterium in the solvent. [b] Error estimates are standard deviations of the mean. Values of $k$, and not these ratios ($k_x/k_H$), were used in the calculations of $\phi_{\rm eff}^{\ddagger}$ and $\phi_2^{\ddagger}$.

**Kinetics.** Rates of detritiation were followed by radioactive assay (liquid scintillation counting) of trimethoxybenzene samples extracted from quenched aliquots of reaction mixtures into toluene as described before.[16] The reaction mixtures were prepared by combining appropriate volumes of stock $H_2O$ and $D_2O$ solutions of exactly the same acid concentration (0.0500 M). as determined by titration with standard alkali, allowing these to equilibrate with a constant temperature bath operating at 24.6 ± 0.02 °C, and then adding sufficient aqueous trimethoxybenzene solution (usually 1%) to give the desired initial counting rate (>10 000 cpm). The reactions were followed for at least 4–5, and sometimes as many as 10, exchange half-lives.

The results of these experiments are summarized in Table I; values of $x$ listed there are corrected for H introduced into the $D_2O$ stock solution by the 70% $HClO_4$.

**Data Analysis.** Albery and Campbell-Crawford have discussed in detail use of eq 1 in determining the fractionation factors $\phi_1^{\ddagger}$ and $\phi_2^{\ddagger}$ from measurements of $k_x/k_H$,[17] and we have followed their procedure with minor differences in using eq 2. The value of $\phi_2^{\ddagger}$ was iterated and a test value of $\phi_{\rm eff}^{\ddagger}$ calculated by least squares for each value until the variance of the measured rate constants

$$\sigma^2 = \Sigma\{[k_x(\text{obsd}) - k_x(\text{calcd})]^2/(N-3)\}$$

where $N$ is the number of measurements, was minimized; the value of $l$ was taken as 0.69. This gave $\phi_{\rm eff}^{\ddagger}$, $\phi_2^{\ddagger}$, and best values for $k_H$ and $k_D$, the rate constants in the pure isotopic solvents, but did not give errors. Standard deviations of the means were therefore determined by Albery and Campbell-Crawford's method in which eq 2 is written in the form

$$k_x(1 - x + xl)^3 + x^3\theta_1\theta_2{}^2k_H = k_H - k_H(2\theta_2 + \theta_1)x + k_H(2\theta_1\theta_2 + \theta_2{}^2)x^2 \quad (5)$$

where $\theta_1 = 1 - \phi_{\rm eff}^{\ddagger}$ and $\theta_2 = 1 - \phi_2^{\ddagger}$. The right-hand side of the equation is a quadratic which can be solved in the usual way for the coefficients and their errors. The left-hand side contains the cubic term from the expansion of the numerator in eq 2, $x^3\theta_1\theta_2{}^2k_H$, which is small and may be treated as a correction factor. In Albery's treatment this term was found by iteration but since we had already evaluated $\theta_1$, $\theta_2$, and $k_H$, we could calculate it directly. Also, whereas Albery treated $k_x(1 - x + xl)^3$ as an unweighted variable, we used weights of $1/(1 - x + xl)^3$ so that errors in the measured rate constants were weighted equally. In practice comparison of our results with values calculated by Albery's programs showed no appreciable differences.

Where deviations from the rule of the geometric mean were taken into account, the deviations were collected on the left-hand side of eq 5 so as to preserve its quadratic form.[17] The modified equation is

$$k_n\{(1-n)^3 + 3\lambda n(1-n)^2l + 3\lambda n^2(1-n)l^2 + n^3l^3\} + n^3\theta_1\theta_2{}^2k_H + 2n(1-n)(1-\gamma)(1-\theta_2)(1-n\theta_1) = k_H - k_H(2\theta_2 + \theta_1)n + k_H(\theta_2{}^2 + 2\theta_1\theta_2)n^2 \quad (6)$$

The additional symbols are defined in the discussion; $n$ is an analogue of $x$.

When the value of $\theta_1$ was independently determined, $k_H$ and $\theta_2$ were obtained by least-squares analysis of the expression

$$\{z + 2(1-\gamma)n\theta_2\}^{1/2} = k_H - k_H\theta_2 n$$

where $z$, which was also used as a weighting factor, is given by

$$z = \frac{k_x\{(1-n)^3 + 3n(1-n)^2l + 3n^2(1-n)l^2 + n^3l^3\}}{(1-n\theta)_1}$$

The form of the relation is readily recognizable when there are no corrections for deviations from the rule of the mean and $\gamma = \lambda = 1$ and $n = x$.

## Discussion

Values of the fractionation factors $\phi_2^{\ddagger}$ and $\phi_{\rm eff}^{\ddagger}$ found by fitting measurements of $k_x/k_H$ to eq 2 with $l = 0.69$ are listed for our own and for Batts and Kilford's data for trimethoxybenzene and for Schulze and Long's data for azulene in Table II. As expected, values of $\phi_{\rm eff}^{\ddagger}$ are closer to 1.0 than is normal for $\phi_1^{\ddagger}$ in simple proton-transfer reactions, while values of $\phi_2^{\ddagger}$ fall in the usual range for secondary O-H hydrogens in a transition state, 0.69–1.0.

The first point to consider is uncertainties in the results. It is apparent that fractionation factors from our own data and from Batts and Kilford's differ significantly despite the fact that $k_D/k_H = 1.7$ is the same in each case. Comparison with previous measurements[11] shows that the error bounds in $\phi_1^{\ddagger}$ and $\phi_2^{\ddagger}$ are unusually large for the variance of observed from calculated rate constants found. In fact, it was noted some years ago[6] that for values of $k_D/k_H$ close to those obtained here, eq 1 is quite insensitive to the separation of $\phi_1^{\ddagger}$ and $\phi_2^{\ddagger}$. This situation seems not to have been encountered hitherto because commonly occurring values of $\phi_1^{\ddagger}$ an $\phi_2^{\ddagger}$ lead to smaller or larger values of $k_D/k_H$. For aromatic hydrogen exchange, however, $\phi_1^{\ddagger}$ is replaced by an effective fractionation factor which is of quite different magnitude from normal values for $\phi_1^{\ddagger}$.

The behavior is usefully considered using an approach suggested by Albery and Davies.[11] Albery and Davies showed that within experimental error the dependence of $k_x/k_H$ upon the atom fraction $x$ in an $H_2O$-$D_2O$ mixture is quadratic. It follows that the dependence may be characterized by two parameters, most obviously $k_D/k_H$ and a constant reflecting the curvature of the plot. As a measure of the curvature, Albery and Davies suggested the deviation from linearity at $x = 0.5$ using $k_x/k_H$ corrected for contributions from known fractionation factors, most commonly those of the reactants. This function they denoted $y$, and in our case (cf. eq 2):

**Table II.** Fractionation Factors from Tritium Exchange in $H_2O$-$D_2O$ Mixtures[a]

| | $\phi_{\rm eff}^{\ddagger b}$ | $\phi_2^{\ddagger}$ | $k_H$ | $k_D/k_H$ | $10^3\ \sigma'^c$ |
|---|---|---|---|---|---|
| Trimethoxybenzene[d] | 0.626 ± 0.030 | 0.945 ± 0.023 | 3.033 ± 0.012 | 1.700 ± 0.010 | 2.6 |
| Trimethoxybenzene[e] | 0.729 ± 0.044 | 0.875 ± 0.026 | 3.346 ± 0.008 | 1.698 ± 0.006 | 1.1 |
| Azulene[f] | 0.582 ± 0.042 | 0.960 ± 0.037 | 0.1923 ± 0.0021 | 1.634 ± 0.021 | 4.5 |

[a] Errors are standard deviations of the means. [b] In order down the table covariances in $\phi_{\rm eff}^{\ddagger}$ and $\phi_2^{\ddagger}$, $10^3\sigma^2{}_{\phi_{\rm eff}^{\ddagger}\phi_2^{\ddagger}}$, are: −0.68, −1.14, and −1.54. [c] $\sigma'^2 = \Sigma_N\{k_x/k_H(\text{obsd}) - k_x/k_H(\text{calcd})\}/N(N-1)$. This parameter provides a measure of the quality of fit to the data that may be compared between different measurements; R. A. More O'Ferrall, G. W. Koeppl, and A. J. Kresge, *J. Am. Chem. Soc.*, **93,** 9 (1971). [d] Present work: $t$ = 24.6 °C. [e] B. D. Batts and J. Kilford, *J. Chem. Soc., Faraday Trans. 1*, **69,** 1033 (1973), $t$ = 25 °C. [f] J. Schulze and F. A. Long, *J. Am. Chem. Soc.* **86,** 331 (1964), $t$ = 25 °C.

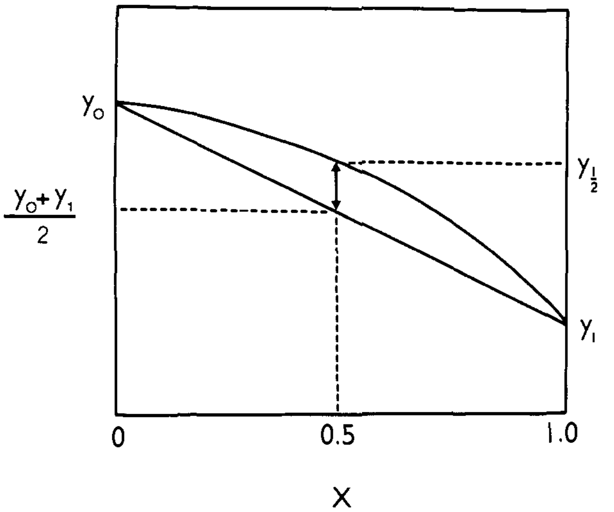


**Figure 1.** Curvature of a plot of $y$ vs. $x$.

$$y = (1 - x + xl)^3 k_x/k_H$$
$$= (1 - x + x\phi_2^{\ddagger})^2(1 - x + x\phi_{\text{eff}}^{\ddagger})$$

The curvature $c$ may then be expressed in terms of $y_0$ (= 1.0), $y_{1/2}$, and $y_1$, the values of $y$ at $x = 0, 0.5$, and 1.0, respectively, in the manner illustrated in Figure 1.

$$c = \frac{(1 + y_1)}{2} - y_{1/2}$$

Then, since

$$y_1 = \phi_{\text{eff}}^{\ddagger}\phi_2^{\ddagger 2}$$
$$c = \frac{(1 + \phi_{\text{eff}}^{\ddagger}\phi_2^{\ddagger 2})}{2} - \frac{(1 + \phi_2^{\ddagger})^2(1 + \phi_{\text{eff}}^{\ddagger})}{8}$$

$\phi_2^{\ddagger}$ and $\phi_{\text{eff}}^{\ddagger}$ may be obtained from measurements of $y_1$ (= $l^3k_D/k_H$) and $c$.

The advantage of this treatment is that the cumbersome rate dependence in $H_2O$-$D_2O$ mixtures is specified by a single parameter. Thus, the sensitivity of the measurements to separation of $\phi_{\text{eff}}^{\ddagger}$ and $\phi_2^{\ddagger}$ may be shown simply by plotting $c$ as a function of $\phi_{\text{eff}}^{\ddagger}$ or $\phi_2^{\ddagger}$ for different values of $k_D/k_H$.

This is done in Figure 2 with $c$ modified to a "percentage curvature"

$$\%c = 100c/[(1 + y_1)/2]$$

which expresses as a percentage the difference of the observed rate constant at $x = 0.5$ from that expected for a linear dependence of $y$ upon $x$. Values of $\phi_2^{\ddagger}$ cover the expected range 0.69–1.0 and for any value of $\phi_2^{\ddagger}$, $\phi_{\text{eff}}^{\ddagger} = y_1/\phi_2^{\ddagger 2}$. It is apparent that for large or small values of $k_D/k_H$ there is a substantial dependence of the curvature upon $\phi_2^{\ddagger}$; for $k_D/k_H$ = 0.3, for example, there is a variation of 20% between $\phi_2^{\ddagger}$ = 0.69 and 1.0. By contrast, for $k_D/k_H$ = 1.7, the value of $c$ changes by only 3% over the same range. Thus it is clear why the values of $\phi_{\text{eff}}^{\ddagger}$ and $\phi_2^{\ddagger}$ in Table II are relatively poorly defined.

In Figure 2, experimentally determined values of %$c$, for Batts and Kilford's data and for our own, are shown as straight lines. Although the values differ by only 1%, the corresponding values of $\phi_2^{\ddagger}$ read from the intersections with the curve for $k_D/k_H$ = 1.7 (common to both data sets) differ by 10%. In real terms, therefore, the agreement between the two sets of data is much better than Table II suggests. Indeed, in view of the sensitivity of the fractionation factors to changes in $c$, it is satisfactory that the simple analysis used yields reasonable values. In testing the effects of systematic errors, we found that small changes in $l$ mainly affect $\phi_{\text{eff}}^{\ddagger}$. Typically, an increase in $l$ from 0.69 to 0.71 increases $\phi_{\text{eff}}^{\ddagger}$ by 10%. In contrast $\phi_2^{\ddagger}$ is practically unaffected, and this behavior appears characteristic of reactions with $\phi_{\text{eff}}^{\ddagger}$ and $\phi_2^{\ddagger}$ nearly equal. As will be seen below, deviations from the rule of the mean affect both $\phi_{\text{eff}}^{\ddagger}$ and $\phi_2^{\ddagger}$.

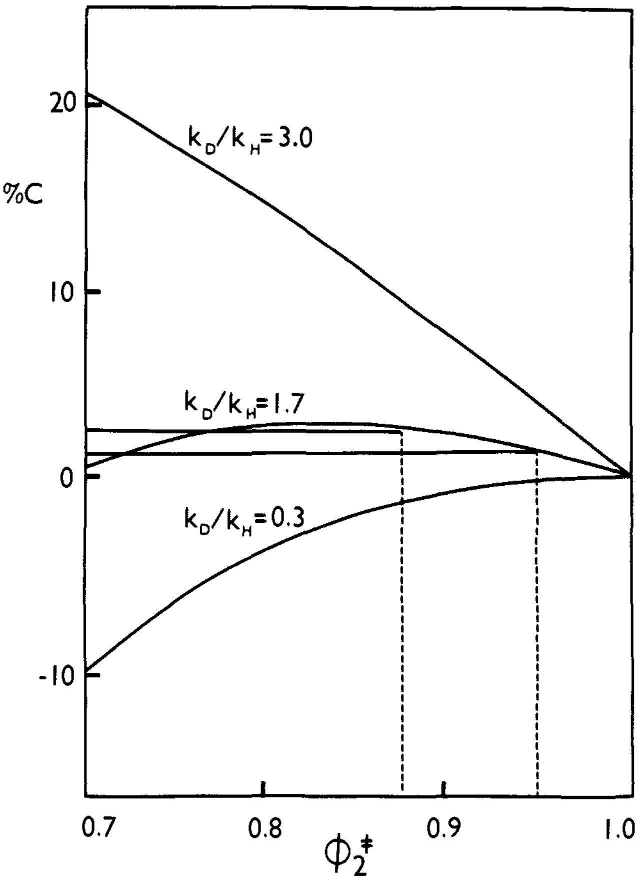


**Figure 2.** % curvature of $(1 - x + xl)^3k_x/k_H$ vs. $\phi_2^{\ddagger}$ for various $k_D/k_H$. Horizontal lines show values for exchange of trimethoxybenzene; upper line, present work; lower line, Batts and Kilford.

From their own analysis of the data for trimethoxybenzene, Batts and Kilford[12] obtained different values of $\phi_2^{\ddagger}$ and $\phi_{\text{eff}}^{\ddagger}$, but this was because they attempted to determine not only $\phi_{\text{eff}}^{\ddagger}$ and $\phi_2^{\ddagger}$ but also $l$. Because of the quadratic character of the variation of $k_x/k_H$ with $x$, the data do not allow determination of more than two fractionation factors. This has been commented on by Kresge and Albery,[13] and the point is emphasized by Figure 2 in which the difficulty of accurately separating $\phi_{\text{eff}}^{\ddagger}$ and $\phi_2^{\ddagger}$ demonstrates the impossibility of also determining $l$.

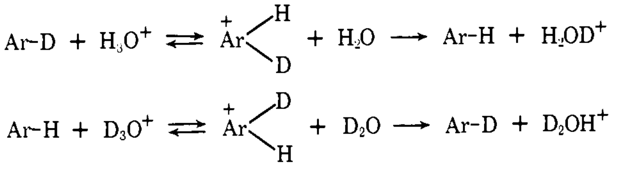
Figure 2 also shows that, for $k_D/k_H$ = 1.7, there are two possible solutions for fractionation factors in the range $\phi_2^{\ddagger}$ = 0.69–1.0. Both solutions were encountered in the least-squares analysis but the second solution was rejected as giving a value of $\phi_{\text{eff}}^{\ddagger} > 1.0$ and a value of $\phi_2^{\ddagger}$ inconsistent with independent measurements. More than one solution for solvent isotope measurements has previously been encountered in the analysis of fractionation of the hydroxide ion[18] and, indeed, for measurements in $H_2O$-$D_2O$ mixtures is a normal feature of the results.[7c] Usually, however, the alternative values are too unreasonable to merit consideration.

**Comparisons with Other Measurements.** Improved estimates of $\phi_{\text{eff}}^{\ddagger}$ and $\phi_2^{\ddagger}$ can be made with the use of further data. For trimethoxybenzene, measurements have been made of the exchange reactions of deuterated substrate with $H_2O$ and of the isotopically normal substrate with $D_2O$.[9]

**Table III.** Transition-State Fractionation Factors and Isotopic Bronsted Exponents for Hydrogen Exchange of Trimethoxybenzene

| Method | $\phi_2^{\ddagger}$ | $\alpha_i$ | Errors[a] $\phi_2^{\ddagger}$ | Errors[a] $\alpha_i$ |
|---|---|---|---|---|
| $k_x/k_H$[b] |  | 0.945 | 0.85 | 0.023 |
| 0.07 |  |  |  |  |
| $k_x/k_H$[c] | 0.875 | 0.64 | 0.026 | 0.08 |
| $k_x/k_H$[b,d] ($\phi_{eff}^{\ddagger} = 0.720$) | 0.880 | 0.66 | 0.006 | 0.02 |
| $k_x/k_H$[c,d] ($\phi_{eff}^{\ddagger} = 0.720$) | 0.880 | 0.66 | 0.004 | 0.01 |
| $k_D'/k_H'$ and $\phi_4$ | 0.881 | 0.66 | 0.003 | 0.01 |
| $k^{D_2O\text{-}T^+}/k^{H_2O\text{-}T^+}$[e] | 0.892 | 0.69 | 0.011 | 0.03 |

[a] Standard deviations of the mean. [b] Present work. [c] B. D. Batts and J. Kilford, *J. Chem. Soc., Faraday Trans. 1*, **69**, 1033 (1973). [d] With $\phi_{eff}^{\ddagger}$ assigned value shown. [e] A. J. Kresge, D. P. Onwood, and S. Slae, *J. Am. Chem. Soc.*, **90**, 6982 (1968); recalculation of errors in this paper leads to small changes in values.



$$\mathrm{Ar{-}D + H_3O^+ \rightleftarrows \overset{+}{Ar}(H)(D) + H_2O \longrightarrow Ar{-}H + H_2OD^+}$$

$$\mathrm{Ar{-}H + D_3O^+ \rightleftarrows \overset{+}{Ar}(D)(H) + D_2O \longrightarrow Ar{-}D + D_2OH^+}$$

If the measured rate constants are written $k_H'$ and $k_D'$, respectively (the primes distinguishing them from $k_H$ and $k_D$ for tritium exchange), then, with the notation for molecular rate constants and fractionation factors used already,

$$k_H' = \frac{{}^{D}k_1{}^{H}}{1 + {}^{D}k_2{}^{H}/{}^{H}k_2{}^{D}} = \frac{{}^{D}k_1{}^{H}}{1 + \phi_3^{\ddagger}/\phi_1^{\ddagger}}$$

$$k_D' = \frac{{}^{H}k_1{}^{D}}{1 + {}^{H}k_2{}^{D}/{}^{D}k_2{}^{H}} = \frac{{}^{H}k_1{}^{D}}{1 + \phi_1^{\ddagger}/\phi_3^{\ddagger}}$$

Denoting the fractionation factor for the substrate as $\phi_4$, we may write

$$\frac{k_D'}{k_H'} = \frac{\phi_4}{\phi_3^{\ddagger}} \frac{\phi_1^{\ddagger}\phi_2^{\ddagger}}{l^3} \frac{(1 + \phi_3^{\ddagger}/\phi_1^{\ddagger})}{(1 + \phi_1^{\ddagger}/\phi_3^{\ddagger})} = \frac{\phi_2^{\ddagger 2}\phi_4}{l^3}$$

and measurement of $k_D'/k_H'$ allows determination of $\phi_2^{\ddagger 2}/l^3$ if $\phi_4$ is known.

A value of $\phi_4$ for trimethoxybenzene has been obtained from analysis of isotopically equilibrated substrate in $H_2O$-$D_2O$ mixtures of varying deuterium content.[19] As a consequence of deviations from the rule of the geometric mean in the solvent, the fractionation factor shows a small but definite dependence on the isotopic composition of the solvent, and the value used here is $\phi_4 = \sqrt{\phi_4{}^{\circ}\phi_4{}^{\infty}}$ where $\phi_4{}^{\circ}$ and $\phi_4{}^{\infty}$ are the extrapolated values in pure $H_2O$ and pure $D_2O$, respectively. The reason for this choice is explained below.

From $\phi_4 = 0.854 \pm 0.003$ and $k_D'/k_H' = 2.016 \pm 0.014$

$$\frac{\phi_2^{\ddagger 2}}{l^3} = 2.361 \pm 0.018$$

and combining with

$$\frac{k_D}{k_H} = \frac{\phi_{eff}^{\ddagger}\phi_2^{\ddagger 2}}{l^3} = 1.70 \pm 0.01$$

gives $\phi_{eff}^{\ddagger} = 0.720 \pm 0.007$. If this value is inserted in eq 2 and a best fit of $k_x/k_H$ now used to determine $\phi_2^{\ddagger}$, both our own and Batts and Kilford's data yield $\phi_2^{\ddagger} = 0.88$. Not unexpectedly, these values differ from those of Table I but are in excellent agreement with each other. As they should, they also agree with values determined from $\phi_{eff}^{\ddagger}$ and $y_{1/2}$ directly (0.88 and 0.89).

In principle, having determined $\phi_{eff}^{\ddagger}$, we may now legitimately use $\phi_2^{\ddagger 2}/l^3$ and the curvature of the plot or, simply

$$(k_x/k_H)_{x=0.5} = \frac{(1 + \phi_{eff}^{\ddagger})(1 + \phi_2^{\ddagger})^2}{(1 + l)^3}$$

to evaluate not only $\phi_2^{\ddagger}$ but $l$. In practice, separation of $\phi_2^{\ddagger}$ and $l$, while not critically dependent upon the magnitude of $k_D/k_H$ in the manner illustrated in Figure 2 for $\phi_2^{\ddagger}$ and $\phi_{eff}^{\ddagger}$, is generally a rather insensitive function of the curvature of the plot. Considering the vulnerability of the treatment to systematic errors, such as neglect of small fractionation factors (solvation effects), the values obtained, $l = 0.687 \pm 0.01$ from Batts and Kilford's data and $0.729 \pm 0.014$ from our own, are in good agreement[20] with the accepted value of 0.69.

In practice it seems preferable to use the data to derive a second value of $\phi_2^{\ddagger}$, using the known value of $l$ in the usual way. From $\phi_2^{\ddagger 2}/l^3 = 2.361$ and $l = 0.69$, we obtain $\phi_2^{\ddagger} = 0.88$. The precise agreement with the previous values implies in effect that, when a common value of $\phi_{eff}^{\ddagger}$ is used, both parameters characterizing the $H_2O$-$D_2O$ data, i.e., $k_D/k_H$ and the curvature, yield a consistent value of $\phi_2^{\ddagger}$. The various values of $\phi_2^{\ddagger}$ for trimethoxybenzene are collected in Table III, together with an additional measurement based on the rates of tritium incorporation from $H_2TO^+$ and $D_2TO^+$ into unlabeled substrate,[21] giving $\phi_2^{\ddagger} = 0.892$, again in excellent agreement with the reliable values from the conventional exchange measurements.

The effective fractionation factor $\phi_{eff}^{\ddagger}$ contains two fractionation factors $\phi_1^{\ddagger}$ and $\phi_3^{\ddagger}$ (eq 4). A further relationship which combines $\phi_1^{\ddagger}$, $\phi_3^{\ddagger}$, and $\phi_4$ is provided by $k_H/k_H'$:

$$\frac{k_H}{k_H'} = \frac{{}^{T}k_1{}^{H}}{{}^{D}k_1{}^{H}} \frac{(1 + \phi_3^{\ddagger}/\phi_1^{\ddagger})}{\{1 + (\phi_3^{\ddagger}/\phi_1^{\ddagger})^{1.442}\}} = \frac{(\phi_3^{\ddagger}/\phi_4)^{1.442}}{(\phi_3^{\ddagger}\phi_4)} \frac{(1 + \phi_3^{\ddagger}/\phi_1^{\ddagger})}{\{1 + (\phi_3^{\ddagger}/\phi_1^{\ddagger})^{1.442}\}}$$

From the measured values, $\phi_{eff}^{\ddagger} = 0.720$, $\phi_4 = 0.854$, and $k_H/k_H' = 0.447 \pm 0.003$, $\phi_3^{\ddagger}$ and $\phi_1^{\ddagger}$ may be extracted by successive approximations[9] or by a graphical procedure similar to that illustrated in Figure 2. The values obtained are $\phi_3^{\ddagger} = 0.959 \pm 0.043$ and $\phi_1^{\ddagger} = 0.118 \pm 0.002$.

Thus all four fractionation factors $\phi_1^{\ddagger}$, $\phi_2^{\ddagger}$, $\phi_3^{\ddagger}$, and $\phi_4$ implicated in the exchange of trimethoxybenzene may be determined. In so far as the various isotope effects involved in the exchanges are related to these values the measurements provide an unusually detailed specification of the isotopic course of the reaction.

In the case of azulene, not quite such extensive measurements are available, but, in addition to $k_H$ and $k_D$ and tritium exchange in the $H_2O$-$D_2O$ mixtures, $k_H'$ has been determined,[22] and, if it is assumed that $\phi_3^{\ddagger}$ and $\phi_4$ are the same as for trimethoxybenzene, values of $\phi_{eff}^{\ddagger}$, $\phi_1^{\ddagger}$, and $\phi_2^{\ddagger}$ can be derived. The required assumption is not a critical one since the reactions are closely similar, and the magnitudes of $\phi_3^{\ddagger}$ and $\phi_4$, which must be close to 1.0, do not sensitively affect the results. From $k_H/k_H' = 0.403 \pm 0.009$, we obtain $\phi_1^{\ddagger} = 0.0945$ and $\phi_{eff}^{\ddagger} = 0.734$. This value of $\phi_{eff}^{\ddagger}$ may be used to derive values of $\phi_2^{\ddagger}$ both from $k_D/k_H$ and from the kinetic dependence in $H_2O$–$D_2O$ mixtures. As was the case with trimethoxybenzene, these two values are in close agreement.

$$\phi_2^{\ddagger} = 0.855 \text{ and } 0.853$$

Again $\phi_2^{\ddagger}$ and $\phi_{eff}^{\ddagger}$ so determined differ significantly from the (less reliable) values of Table II. However, the difference is not an unreasonable one, and the fact that it is in the same direction and similar in magnitude to that for our measurements is consistent with the expected influence of systematic errors; although, for trimethoxybenzene, Batts and Kilford's $H_2O$–$D_2O$ data yields values in notably good agreement with the independent measurements.

The fractionation factor $\phi_2^{\ddagger}$ for the secondary water hydrogens in the transition state is of special interest in providing an indication of transition-state structure.[6,7,23] A comparison of the kinetic and equilibrium acidities of the acids $H_2O$–$L^+$ and $D_2O$–$L^+$ within Bronsted's formalism[24] gives

$$\phi_2^{\ddagger} = l^{(1-\alpha_i)}$$

where $\alpha_i$ is the exponent of the Bronsted relationship and the subscript i emphasizes its derivation from secondary isotope effects. Values of $\alpha_i$ based on $\phi_2^{\ddagger}$ for trimethoxybenzene are listed in Table III; the average of these, excluding the first entry, is 0.67. This value and $\alpha_i = 0.57$ for azulene point to transition states that are close to symmetrical with respect to proton transfer. This is consistent with the relatively large primary isotope effects, $l/\phi_1^{\ddagger} = 5.9$ and 7.1 for trimethoxybenzene and azulene, respectively, and the fact that the larger of these is associated with the value of $\alpha_i$ closer to 0.5.

**Deviations from the Rule of the Mean.** In view of the very detailed analysis that is possible for isotope exchange of trimethoxybenzene, and also because the rate measurements in $H_2O$–$D_2O$ mixtures may be unusually sensitive to systematic errors, it is of interest to examine the effect on the results of taking account of deviations from the rule of the geometric mean (RGM).[7a,c,25]

The fractionation factors listed in Tables II and III were evaluated assuming that equilibration between equivalent exchangeable isotopic sites is statistically controlled and that in the case of water, for example, $K$ for the disproportionation of $H_2O$ and $D_2O$ into HDO is 4.0:

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

This assumption is not strictly correct. For liquid water the best value of $K$ determined experimentally[26] is 3.78. It has been argued,[17,23,27,28] and generally supposed, that the effect of deviations from statistical behavior is too small to be of significance for the kinds of conclusions that may be drawn from kinetic measurements. Exchange of trimethoxybenzene would appear to offer a good opportunity of putting this to the test.

First it is necessary to summarize a straightforward method for handling deviations from the rule of the mean. A fundamental difference from the simpler behavior considered so far is that fractionation factors, i.e., the D/H ratio at a particular isotopic site relative to that in the solvent, are no longer independent of isotopic composition. To preserve the simplicity of the statistical formalism, it is useful therefore to define constant "practical" fractionation factors and to make use of a slightly different measure of the solvent composition from the atom fraction of deuterium ($x$). Our approach complements and is consistent with the more empirical treatment developed by Albery and Davies.[28]

The practical fractionation factors are defined in terms of fully deuterated species; thus for the hydride $XH_n$

$$\phi = \frac{[\mathrm{XD}_n]^{1/n}[\mathrm{H_2O}]^{1/2}}{[\mathrm{XH}_n]^{1/n}[\mathrm{D_2O}]^{1/2}} = \frac{Q_{\mathrm{XD}_n}{}^{1/n}Q_{\mathrm{H_2O}}{}^{1/2}}{Q_{\mathrm{XH}_n}{}^{1/n}Q_{\mathrm{D_2O}}{}^{1/2}}$$

where the square brackets denote concentrations and the $Q$'s are partition functions. This definition has a number of advantages. All isotope effects involving pure isotopic solvents can be expressed in terms of such fractionation factors, so that deviations from the rule of the mean are confined to $H_2O$–$D_2O$ mixtures. Moreover, $\phi$ bears a simple relationship to the limiting values of the true fractionation factors in pure isotopic solvents, $\phi^{\circ}$ and $\phi^{\infty}$, i.e.

$$\phi = \sqrt{\phi^{\circ}\phi^{\infty}} \tag{7}$$

where the superscripts denote the D/H atom ratio in the solvents. This relationship is strictly true for fractionation at a single isotopic position X–H, for which[29]

$$\phi^{\circ} = \frac{2[\mathrm{X{-}D}][\mathrm{H_2O}]}{[\mathrm{X{-}H}][\mathrm{HDO}]}$$

$$\phi^{\infty} = \frac{[\mathrm{X{-}D}][\mathrm{HDO}]}{2[\mathrm{X{-}H}][\mathrm{D_2O}]}$$

and also for two equivalent positions, $XH_2$. For three or more positions it depends on the validity of Bernstein's rules,[30] that is on the identity of equilibrium constants for disproportionation of partially deuterated species of the type illustrated for $H_3O^+$:

$$\frac{[\mathrm{H_2DO^+}]}{[\mathrm{H_3O^+}]^{2/3}[\mathrm{D_3O^+}]^{1/3}} = \frac{[\mathrm{HD_2O^+}]}{[\mathrm{H_3O^+}]^{1/3}[\mathrm{D_3O^+}]^{2/3}} = K' \tag{8}$$

It seems certain that these rules hold within the limits of presently attainable experimental precision.[23]

Equation 7 is important in relating $\phi$ to conveniently measured[23,31] or calculated[32] quantities. It also shows that $\phi$ is the mean of extreme values for real fractionation factors. For this reason, and because measurements in the pure solvents are correctly expressed, use of $\phi$ minimizes error when RGM corrections are neglected. This is why $\sqrt{\phi_4{}^{\circ}\phi_4{}^{\infty}}$ was used for $\phi_4$, the composition dependent fractionation factor for trimethoxybenzene in the calculations above. It is also why, following Albery and Davies, the familiar symbol of $\phi$ for fractionation factors is retained. Other advantages of the present definition have been discussed from a somewhat different standpoint by Albery.[7a,28]

With $\phi$ defined in terms of fully deuterated species, rate dependences in $H_2O$–$D_2O$ mixtures are conveniently expressed not in terms of the deuterium atom fraction, $x$, but of $[D_2O]^{1/2}/([D_2O]^{1/2} + [H_2O]^{1/2})$ denoted[33] $n$. When RGM corrections are neglected, $x$ and $n$ are equal; when they are taken into account, $n$ is easily calculated, e.g., in four statements of a computer program. With this formulation the contribution to $k_n/k_H$ from a single fractionating site is $(1 - n + n\phi)$, which is precisely analogous to that in the absence of deviations.

For multiple fractionating sites, RGM deviations again have to be considered and contributions to $k_n/k_H$ are a little less straightforward. For $H_3O^+$, for example, the term $(1 - x - xl)^3$ is replaced by

$$\{(1 - n)^3 + 3\lambda n(1 - n)^2 l + 3\lambda n^2(1 - n)l^2 + n^3l^3\}$$

where $3\lambda$ is the disproportionation constant $K'$ of eq 8 and is written in this form because when there are no RGM corrections $\lambda = 1$ and it is apparent that, with $n = x$, the expression again reduces to its simpler counterpart. Contributions from any number of equivalent hydrogens can be expressed in an analogous manner.

For a proton-transfer transition state, the simplest treatment incorporating RGM corrections requires a further assumption. This is that there is no coupling between reacting and non-

**Table IV**. Fractionation Factors[a] from Tritium Exchange in $H_2O$-$D_2O$ Mixtures Corrected for Deviations from the Rule of the Mean

| | $\phi_{\text{eff}}^{\ddagger}$ | $\phi_2^{\ddagger}$ | $k_D/k_H$ | $10^3\sigma^2_{\phi_{\text{eff}}^{\ddagger}\phi_2^{\ddagger}}$ [b] | $10^3\sigma'$ [d] |
|---|---|---|---|---|---|
| Trimethoxybenzene[c] | 0.694 ± 0.047 | 0.897 ± 0.032 | 1.700 ± 0.006 | 1.5 | 2.6 |
| Azulene | 0.632 ± 0.055 | 0.921 ± 0.043 | 1.632 ± 0.022 | 2.3 | 4.5 |

[a] Errors are standard deviations of the means. [b] Covariance of $\phi_{\text{eff}}^{\ddagger}$ and $\phi_2^{\ddagger}$. [c] Present work. [d] See footnote *c* of Table II.

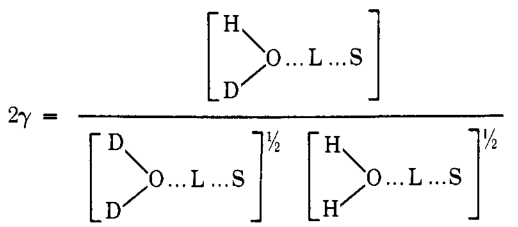
Table V. Isotopic Bronsted Exponents for the Exchange of Trimethoxybenzene Corrected for Deviations from the Rule of the Mean

| | | | Errors[a] | |
|---|---|---|---|---|
| Method | $\phi_2^{\ddagger}$ | $\alpha_i$ | $\phi_2^{\ddagger}$ | $\alpha_i$ |
| $k_x/k_H$ [b] | 0.897 | 0.71 | 0.032 | 0.10 |
| $k_x/k_H$ [b] ($\phi_{\text{eff}}^{\ddagger} = 0.720$) | 0.880[d] | 0.66 | 0.005[e] | 0.02 |
| $k_x/k_H$ [c] ($\phi_{\text{cff}}^{\ddagger} = 0.720$) | 0.878[d] | 0.65 | | |
| $k_D'/k_H'$ and $\phi_4$ | 0.881 | 0.66 | 0.003 | 0.01 |
| $k^{D_2O\text{-}T^+}/k^{H_2O\text{-}T^+}$ | 0.925 | 0.79 | 0.008 | 0.02 |

[a] Standard deviations of the mean. [b] Present work. [c] B. D. Batts and J. Kilford, *J. Chem. Soc., Faraday Trans. 1*, **69**, 1033 (1973). [d] With $\phi_{\text{cff}}^{\ddagger}$ assigned the value shown. [e] From errors in $y_1$, $y_{1/2}$, and $\phi^{\ddagger}$ (not calculable for Batts and Kilford's data).

reacting hydrogens, i.e., that isotopic substitution at one position is independent of that at the other. Calculations suggest that this is likely to be true when proton transfer has progressed to a reasonable degree in the transition state[23] (cf. also ref 17 and 28), as must be the case in the reactions considered here. In practical terms this is also the most sensible assumption in the absence of direct evidence to the contrary, and, in so far as deviations from non-RGM corrected behavior are maximized, it should fairly represent the limit of their influence.

With this assumption the transition-state contributions to $k_n/k_H$ are, for the reacting hydrogen, $(1 - n + n\phi_1^{\ddagger})$, and, for the nonreacting hydrogens, $\{(1 - n)^2 + 2\gamma n(1 - n)\phi_2^{\ddagger} + n^2\phi_2^{\ddagger 2}\}$, where $2\gamma$ is the equilibrium constant for the hypothetical isotopic disproportionation:[34]



$$2\gamma = \frac{\left[\mathrm{HDO}\ldots\mathrm{L}\ldots\mathrm{S}\right]}{\left[\mathrm{D_2O}\ldots\mathrm{L}\ldots\mathrm{S}\right]^{1/2}\left[\mathrm{H_2O}\ldots\mathrm{L}\ldots\mathrm{S}\right]^{1/2}}$$

For a simple proton transfer, therefore, the expression for the rate dependence in $H_2O$–$D_2O$ mixtures is

$$\frac{k_n}{k_H} = \frac{(1 - n + n\phi_1^{\ddagger})\{(1 - n)^2 + 2\gamma n(1 - n)\phi_2^{\ddagger} + n^2\phi_2^{\ddagger 2}\}}{\{(1 - n)^3 + 3\lambda n(1 - n)^2 l + 3\lambda n^2(1 - n)l^2 + n^3 l^3\}} \tag{9}$$

For trimethoxybenzene and azulene a factor that potentially modifies this behavior is the presence of a further isotopically substituted hydrogen at the carbon to which proton transfer occurs. However, for the reasonably symmetrical transition states involved in these exchange reactions, the coupling of this hydrogen with the reacting hydrogen is likely to be weak; it is therefore assumed to be absent. This is a critical assumption because it implies that there is no coupling in the transition state between either the reacting or nonreacting carbon-bound hydrogen and other hydrogens of the system. Since these are the sites at which tritium is substituted, the presence of tritium does not lead to additional deviations from the rule of the mean, and the only modification required of eq 9 is the replacement of $\phi_1^{\ddagger}$ by $\phi_{\text{eff}}^{\ddagger}$. Were this not the case, simple analogues of eq 2 and 3 would not exist (cf. Appendix).

Solution of eq 9 requires assignment of the values of $\lambda$ and $\gamma$ for the hydronium ion and the transition state. No measurements of these quantities have been made but it is reasonable to use for $\lambda$ the value of 0.97 determined for $NH_3$[23,35] and for $\gamma$ the value of $K^{1/2}/2 = 0.972$ which applies to water. The choice for $\gamma$ is again consistent with the application of a maximum RGM correction. The data analysis with eq 9 is similar to that with eq 2 save that, in the use of eq 6 to calculate errors in $\phi_2^{\ddagger}$ and $\phi_{\text{eff}}^{\ddagger}$, deviations from the rule of the mean are accumulated on the left-hand side of the equation to maintain a quadratic dependence upon $n$.

Values of $\phi_2^{\ddagger}$ and $\phi_{\text{eff}}^{\ddagger}$ for trimethoxybenzene and azulene are listed in Table IV and may be compared with their counterparts lacking RGM corrections in Table II. The results obtained from our measurements for trimethoxybenzene, shown in the first rows of the tables, change by 5%, while derived values of $\alpha_i$, which are shown in Tables III and V, change from 0.85 to 0.71, about 20%; similar differences are seen for azulene. Considering the unusual sensitivity of the measurements to systematic errors, the differences are hardly large enough to suggest serious shortcoming in the neglect of deviations from the RGM.

The sensitivity of the measurements to the corrections is underlined by the fact that application of eq 9 to Batts and Kilford's data for trimethoxybenzene leads to no solution. The curvature of the $k_n/k_H$ plot falls outside the range of the values of $\phi_2^{\ddagger}$ and $\phi_{\text{eff}}^{\ddagger}$ consistent with $k_D/k_H$ and, in a plot similar to that of Figure 2, the experimental curvature falls above the maximum in the %c vs. $\phi_2^{\ddagger}$ curve. This behavior may indicate that the RGM corrections applied, which are the maximum possible, are too large. On the other hand, for our own data and Long's data for azulene, the corrections clearly lead to improved values of $\phi_2^{\ddagger}$ and $\phi_{\text{eff}}^{\ddagger}$.

Corrected values of $\phi_2^{\ddagger}$ and $\alpha_i$ determined by other methods are shown in Table V and may be compared with the corresponding values in Table III. There is no change where the measurements involve pure isotopic solvents, nor where tritium is present as a label in the aromatic substrate, in which case it can be assumed to be uncoupled with other hydrogens either in the reactants or in the transition state. The value of $\phi_4$, the fractionation factor for trimethoxybenzene, varies with isotopic composition,[19] but, since it enters both calculations in the form $\phi_4 = \sqrt{\phi_4{}^{\circ}\phi_4{}^{\infty}}$, this also leads to no change.

Thus the values of $\phi_2^{\ddagger}$ and $\phi_{\text{eff}}^{\ddagger}$ found from the measurements of $\phi_4$, $k_D/k_H$, and $k_D'/k_H'$ are still 0.88 and 0.720, respectively. Differences can be detected when $\phi_2^{\ddagger}$ is determined from the curvature of the $H_2O$-$D_2O$ plots with $\phi_{eff}^{\ddagger}$ taken as 0.720, but only just barely; e.g., for Batt's and Kilford's data $\phi_2^{\ddagger} = 0.878$ compared with 0.880. Although not shown, the results for azulene behaved similarly.

On the other hand, real differences again occur when $\phi_2^{\ddagger}$ is determined from tritium incorporation into trimethoxybenzene from $H_2TO^+$ and $D_2TO^+$. Here deviations arise from coupling of tritium with other isotopic hydrogens in the hydronium ion of the reactants. What is determined in these measurements is the initial rates, $V_{H_2O}$ and $V_{D_2O}$, of incorporation of radioactivity into trimethoxybenzene from $H_2O$ and $D_2O$ under catalysis by $H^+$. Dividing $V_{H_2O}$ and $V_{D_2O}$ by $[L_3O^+]$ and the radioactivity of trimethoxybenzene at equilibrium $[Ar{-}T]_e$ gives two rate ratios $R_{H_2O}$ and $R_{D_2O}$ which may be expressed in terms of isotopic rate constants as follows:

$$R_{H_2O} = \frac{V_{H_2O}}{[H_3O^+][Ar{-}T]_e} = \frac{k_1^{T\text{-}OH_2}}{1 + k_2^T/k_2^H}\,\frac{[Ar{-}H]}{[Ar{-}T]_e}\,\frac{[H_2TO^+]}{[H_3O^+]}$$

$$R_{D_2O} = \frac{V_{D_2O}}{[D_3O^+][Ar{-}T]_e} = \frac{k_1^{T\text{-}OD_2}}{1 + k_2^T/k_2^H}\,\frac{[Ar{-}H]_o}{[Ar{-}T]_e}\,\frac{[D_2TO^+]}{[D_3O^+]}$$

where for $R_{D_2O}$ it should be noted that, since the concentrations of H and T in the system are small relative to D, $[Ar{-}H]_o$, the amount of trimethoxybenzene originally present is equal to $[Ar{-}D]$ at equilibrium. Also determined were the ratio of equilibrium constants $K_H/K_D$ for the isotopic equilibria:

$$Ar{-}H + HTO \underset{}{\overset{K_H}{\rightleftharpoons}} Ar{-}T + H_2O$$

$$Ar{-}D + DTO \underset{}{\overset{K_D}{\rightleftharpoons}} Ar{-}T + D_2O$$

With the assumption that there is no coupling between reacting and nonreacting hydrogens in the transition state, $k_1^{T\text{-}OD_2}/k_1^{T\text{-}OH_2}$ may be expressed as

$$\frac{k_1^{T\text{-}OD_2}}{k_1^{T\text{-}OH_2}} = \phi_2^{\ddagger 2}\,\frac{[H_2TO^+][D_2O]}{[D_2TO^+][H_2O]}$$

and it then follows that

$$\frac{R_{D_2O}K_D}{R_{H_2O}K_H} = \frac{\phi_2^{\ddagger 2}}{l^3}\,\frac{[HTO][D_2O]^{1/2}}{[DTO][H_2O]^{1/2}} \qquad (10)$$

When no correction for deviations from the RGM is applied, this reduces to $\phi_2^{\ddagger 2}/l^3$ and for $l = 0.69$ yields the values of $\phi_2^{\ddagger}$ and $\alpha_i$ shown in Table III. When corrections are applied, the term $[HTO][D_2O]^{1/2}/[DTO][H_2O]^{1/2}$ corresponds to $(K_{HT}/K_{DT})^{1/2}$ where $K_{HT}$ and $K_{DT}$ are the equilibrium constants for disproportionation of HTO and DTO.

$$K_{HT} = \frac{[HTO]^2}{[H_2O][T_2O]} \qquad K_{DT} = \frac{[DTO]^2}{[D_2O][T_2O]}$$

In fact $(K_{HT}/K_{DT})^{1/2}$ is readily determined from $K_D/K_H$, since

$$\frac{K_D}{K_H} = \frac{1}{\phi_4}\left(\frac{K_{HT}}{K_{DT}}\right)^{1/2}$$

where $\phi_4$ is the fractionation factor for trimethoxybenzene. From $K_D/K_H = 1.09$ and $\phi_4 = 0.854$, $(K_{HT}/K_{DT})^{1/2} = 0.93$ which agrees well with the value of 0.94 extrapolated from the measured value of $K_{HD}$ using harmonic calculations as a guide.[23]

In practice use of $K_H/K_D$ twice in the calculation implies that its presence is not essential when $\phi_4$ is known. Indeed, using eq 10 and remembering that the initial concentration $[Ar{-}H]_o$ for tritium uptake in $D_2O$ is equal to the concentration of Ar-D in equilibrium with Ar-T when exchange is complete, it can be seen that:

$$\frac{R_{D_2O}}{R_{H_2O}} = \frac{\phi_2^{\ddagger 2}\phi_4}{l^3}$$

With $R_{H_2O}/R_{D_2O} = 0.450$, this gives $\phi_2^{\ddagger} = 0.925$, which is listed in Table V together with the derived value of $\alpha_i = 0.79$.

Comparison of this result with the corresponding value $\alpha_i = 0.70$ from Table III shows that here again deviations from the RGM have a substantial effect. In fact, fractionation of tritium provides another source of unusually large RGM corrections. Corrections arising from coupling of D and T are small but from H and T are large; where the two are compared, care must be taken. Sometimes the need for corrections may be obviated by appropriately combining measurements. Thus, in the present case, had $\phi_2^{\ddagger}$ been determined originally using $\phi_4$ instead of $K_H/K_D$, the same value would have been obtained with and without corrections. On the other hand, it should be recognized that the values of $\phi_2^{\ddagger}$ and $\alpha_i$ in Table V are based on the assumption that coupling of hydrogens in the transition state is absent. Where there is important coupling, for example, in a sufficiently reactant-like transition state, $\phi_2^{\ddagger}$ of Table III would be more appropriate.

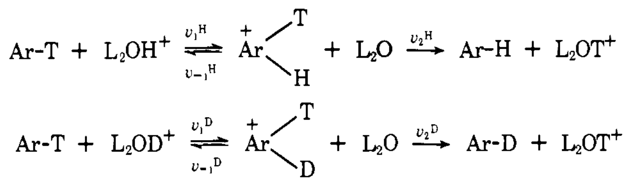
The corrected values of $\phi_2^{\ddagger}$ and $\alpha_i$ from tritium uptake are in poorer agreement with independent measurements than the uncorrected values. The difference is not excessive; again it is 5% in $\phi_2^{\ddagger}$ and 20% in $\alpha_i$, which probably represents a reasonable discrepancy between measurements made by quite different methods. However, it is larger than the change produced by the corrections themselves and emphasizes that even where these are unusually large they are probably no greater than the intrinsic uncertainties in the measurements.[36] It may be significant that, of the four instances in which RGM corrections affect the results, in two cases, our $H_2O/D_2O$ data for trimethoxybenzene and Long's for azulene, agreement with independent measurements is improved, while in the other two cases, Batts and Kilford's $H_2O$-$D_2O$ measurements and the tritium incorporation from $H_2O$-$T^+$ and $D_2O$-$T^+$ into trimethoxybenzene, it is made worse.

**Comparisons with Other Determinations of Bronsted Exponents.** Inspection of Tables III and V shows that nine of the eleven values of $\alpha_i$ for trimethoxybenzene listed fall in the range 0.64-0.71. The mean of these is 0.67 and of all eleven, 0.69 with standard deviations of 0.01 and 0.02, respectively. The value of $\alpha_i$ is thus unusually well established, and it is of interest to compare it with Bronsted exponents for the same substrate determined from catalysis of exchange by weak acids[37] and from correlations of rate and equilibrium acidity dependences in concentrated solutions of strong acids.[38,39]

Catalysis of tritium exchange has been studied for a variety of weak acids, and the value of $\alpha$ depends in some degree upon the acids chosen. For carboxylic acids, however, it is 0.59, and it is perhaps surprising that this is significantly smaller than $\alpha_i$ which refers to proton transfer from $H_3O^+$: for the stronger acid one might have expected $\alpha$ to be smaller. The discrepancy may stem from the two exponents measuring different properties of the transition state, but it is also true that $\alpha$ for the acid catalysis pertains to $k_H = {}^Tk_1^H/(1 + {}^Tk_2^H/{}^Hk_2^T)$ whereas $\alpha_i$ is based directly on $k_1$. In fact, ${}^Tk_2^H/{}^Hk_2^T$ varies with the catalyzing acid and allowance for this corrects $\alpha$ upward to $0.68 \pm 0.06$, very close to the value for $\alpha_i$.

A value of $\alpha_A$, derived from a plot of kinetic vs. the extrapolated equilibrium acidity dependence in the range 0.8-2.8 M perchloric acid, is 0.55, in good agreement with the value of 0.56 derived from a plot of $d\Delta G^{\ddagger}/d\Delta G^{\circ}$ based upon extrapolated rate constants and $pK_a$'s for protonation of a series of aromatic substrates in aqueous perchloric acid.[38] Here the lower value may be consistent with a greater acidity of $H_3O^+$ in fairly strongly acidic than in dilute solution, but the probability of systematic differences between the two types of

Scheme III



measurement makes the discrepancy hardly significant. The principal conclusion, indeed, is that the different measures of transition-state structure yield remarkably consistent values. This is corroborated by similar behavior of azulene; compared with $\alpha_i = 0.57$, $\alpha$ for catalysis by carboxylic acids[40] is 0.61 ± 0.07 (uncorrected for isotope effects) and from acidity dependence in moderately concentrated perchloric acid[41] $\alpha_A = 0.55 \pm 0.01$.

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## Appendix. Origin of the Effective Fractionation Factor $\phi_{\mathrm{eff}}^{\ddagger}$

For proton-transfer reactions in which two steps are rate determining and the intermediate is not at isotopic equilibrium with the solvent, the rate expression in $H_2O$-$D_2O$ mixtures is obtained by summing contributions from reactions via protonated and deuterated intermediates. For $H_3O^+$ catalyzed tritium exchange from an aromatic substrate, the reactions are shown in Scheme III. The symbol L denotes H or D at a position in isotopic equilibrium with the solvent, and reaction velocities $v$ rather than rate constants are written because each reaction step includes contributions from various H and D species. Application of the steady-state approximations to the two reactions gives the net rate of tritium loss from the substrate:

$$\frac{-\mathrm{d}[\mathrm{Ar\text{-}T}]}{\mathrm{d}t} = \frac{v_1^{\mathrm{H}}}{1 + v_{-1}^{\mathrm{H}}/v_2^{\mathrm{H}}} + \frac{v_1^{\mathrm{D}}}{1 + v_{-1}^{\mathrm{D}}/v_2^{\mathrm{D}}} \quad (11)$$

The first step of the reaction is a simple proton transfer and the sum of the rates, $v_1^{\mathrm{H}} + v_1^{\mathrm{D}}$, is given by

$$v_1^{\mathrm{H}} + v_1^{\mathrm{D}} = \frac{(1 - x + x\phi_1^{\ddagger})(1 - x + x\phi_2^{\ddagger})^2}{(1 - x + xl)^3} \times [\mathrm{Ar\text{-}T}][\mathrm{L_3O^+}]k_1^{\mathrm{H}} \quad (12)$$

where $[L_3O^+]$ is the total acid concentration and $\phi_1^{\ddagger}$ and $\phi_2^{\ddagger}$ have the same significance as in transition state (**1**). The ratio of rates $v_1^{\mathrm{D}}/v_1^{\mathrm{H}}$ reflects the relative concentrations of transition states in which H and D are undergoing transfer and is related in the usual way to the isotopic composition of the medium and the fractional factor for the transferred hydrogen, i.e.

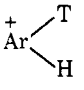
$$\frac{v_1^{\mathrm{H}}}{v_1^{\mathrm{D}}} = \frac{[\mathrm{L_2O{-}{-}D{-}{-}Ar\text{-}T}]}{[\mathrm{L_2O{-}{-}H{-}{-}Ar\text{-}T}]} = \frac{x\phi_1^{\ddagger}}{(1 - x)}$$

[For reactions in which proton transfer is rate determining ($v_2 \gg v_{-1}$), this relationship is used to determine $\phi_1^{\ddagger}$ from the isotopic composition of the product.[7c,42]] Here, combination with $v_1^{\mathrm{H}} + v_1^{\mathrm{D}}$ from eq 11 permits separation of $v_1^{\mathrm{H}}$ and $v_1^{\mathrm{D}}$.

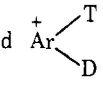
$$v_1^{\mathrm{H}} = \frac{(1 - x)(1 - x + x\phi_2^{\ddagger})^2}{(1 - x + xl)^3}[\mathrm{Ar\text{-}T}][\mathrm{L_3O^+}]k_1^{\mathrm{H}}$$

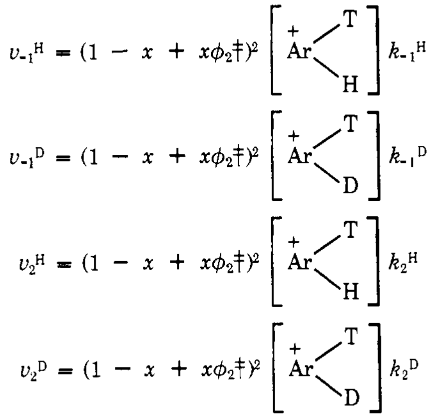
$$v_1^{\mathrm{D}} = \frac{x\phi_1^{\ddagger}(1 - x + x\phi_2^{\ddagger})^2}{(1 - x + xl)^3}[\mathrm{Ar\text{-}T}][\mathrm{L_3O^+}]k_1^{\mathrm{H}}$$

Expressions for $v_{-1}$ and $v_2$, the rates of the forward and back reactions from the intermediates i and ii can be written at once.


i

and


ii



$$v_{-1}^{\mathrm{H}} = (1 - x + x\phi_2^{\ddagger})^2 \left[\overset{+}{\mathrm{Ar}}{<}^{\mathrm{T}}_{\mathrm{H}}\right] k_{-1}^{\mathrm{H}}$$

$$v_{-1}^{\mathrm{D}} = (1 - x + x\phi_2^{\ddagger})^2 \left[\overset{+}{\mathrm{Ar}}{<}^{\mathrm{T}}_{\mathrm{D}}\right] k_{-1}^{\mathrm{D}}$$

$$v_2^{\mathrm{H}} = (1 - x + x\phi_2^{\ddagger})^2 \left[\overset{+}{\mathrm{Ar}}{<}^{\mathrm{T}}_{\mathrm{H}}\right] k_2^{\mathrm{H}}$$

$$v_2^{\mathrm{D}} = (1 - x + x\phi_2^{\ddagger})^2 \left[\overset{+}{\mathrm{Ar}}{<}^{\mathrm{T}}_{\mathrm{D}}\right] k_2^{\mathrm{D}}$$

Since the overall reaction is isotopic exchange, the transition states for these two steps differ only isotopically and the fractionation factor $\phi_2^{\ddagger}$ is the same in each case.[8,9] This makes the ratios of reaction velocities $v_{-1}/v_2$ independent of the isotopic composition of the solvent.

$$\frac{v_{-1}^{\mathrm{H}}}{v_2^{\mathrm{H}}} = \frac{k_{-1}^{\mathrm{H}}}{k_2^{\mathrm{H}}} \qquad \frac{v_{-1}^{\mathrm{D}}}{v_2^{\mathrm{D}}} = \frac{k_{-1}^{\mathrm{D}}}{k_2^{\mathrm{D}}}$$

Substitution of the values for $v_1$ and $v_{-1}/v_2$ into eq 11 gives as the net rate of tritium loss:

$$\frac{-\mathrm{d}[\mathrm{Ar\text{-}T}]}{\mathrm{d}t} = k_1^{\mathrm{H}}\left\{\frac{(1 - x)}{1 + k_{-1}^{\mathrm{H}}/k_2^{\mathrm{H}}} + \frac{x\phi_1^{\ddagger}}{1 + k_{-1}^{\mathrm{D}}/k_2^{\mathrm{D}}}\right\}\frac{(1 - x + x\phi_2^{\ddagger})^2}{(1 - x + xl)^3}[\mathrm{Ar\text{-}T}][\mathrm{L_3O^+}]$$

and this may be expressed in the more usual form for the dependence on isotopic composition, $k_x/k_{\mathrm{H}}$. At the composition $x$

$$k_x = \frac{-\mathrm{d}[\mathrm{Ar\text{-}T}]}{\mathrm{d}t}\Big/[\mathrm{Ar\text{-}T}][\mathrm{L_3O^+}]$$

and in pure $H_2O$

$$k_{\mathrm{H}} = \frac{k_1^{\mathrm{H}}}{1 + k_{-1}^{\mathrm{H}}/k_2^{\mathrm{H}}}$$

whence

$$\frac{k_x}{k_{\mathrm{H}}} = \left\{1 - x + x\phi_1^{\ddagger}\left(\frac{1 + k_{-1}^{\mathrm{H}}/k_2^{\mathrm{H}}}{1 + k_{-1}^{\mathrm{D}}/k_2^{\mathrm{D}}}\right)\right\} \times \frac{(1 - x + x\phi_2^{\ddagger})^2}{(1 - x + xl)^3} \quad (13)$$

and this is equivalent to eq 2 with $\phi_{\mathrm{eff}}^{\ddagger}$ given by eq 3.

It is apparent that the simple form of $k_x/k_{\mathrm{H}}$ given in this instance arises from the independence of isotopic composition of values of $v_{-1}/v_2$. This applies only for tritium exchange reactions, and in other cases the behavior is complex, although where fractionation factors for the nonreacting hydrogens in the two transition states are similar, the approximation to eq 13 may be quite close. It should also be clear that, while deviations from the rule of the mean arising from coupling between hydrogen of the $H_2O$ group in the transition state can be introduced in the normal way, isotope dependent coupling of these, or indeed of the hydrogen bound to carbon, with the reacting hydrogen would destroy the constancy of $v_{-1}/v_2$.

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(33) A minority of authors use *n* for *x*. The present use can hardly cause confusion and takes advantage of the affinity of *n* and *x*.

(34) Without the assumption of no coupling between reacting and nonreacting hydrogens, the contribution to $k_n/k_H$ from all three hydrogens is $\{(1-n)^3 + (\phi_1{}^{\ddagger}\gamma_2{}^2 + 2\phi_2{}^{\ddagger}\gamma_1\gamma_2)n(1-n)^2 + (\phi_2{}^{\ddagger 2}\gamma_2{}^2 + 2\phi_1{}^{\ddagger}\phi_2{}^{\ddagger}\gamma_1\gamma_2)n^2(1-n) + n^3\phi_1{}^{\ddagger}\phi_2{}^{\ddagger 2}\}$ where $\gamma$ is now $\gamma_1$ and $\gamma_2 = [D_2O\text{--}H\text{--}S]^{1/2}[H_2O\text{--}D\text{--}S]^{1/2}/[D_2O\text{--}D\text{--}S]^{1/2}[H_2O\text{--}H\text{--}S]^{1/2}$.

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# A Generalized Gauche NMR Effect in $^{13}C$, $^{19}F$, and $^{31}P$ Chemical Shifts and Directly Bonded Coupling Constants. Torsional Angle and Bond Angle Effects

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**Abstract:** The $^{31}P$, $^{13}C$, or $^{19}F$ chemical shifts of atoms arranged in a gauche conformation are upfield from the shifts of atoms in a trans conformation. In contrast to earlier explanations for the $\gamma$ effect, these shifts are attributed to bond angle changes which arise from a coupling of bond angles to torsional angles. Conformationally dependent, directly bonded coupling constants are also attributed to the bond angle deformation resulting from torsional bond angle changes.

The steric theory of Grant and Cheney[2a] has been widely accepted[2b,c] as a basis for understanding the $\gamma$ shift (the upfield $^{13}C$ shift of a $\gamma$ carbon resulting from substitution on the $\gamma$ carbon of a hydrocarbon chain). Thus, the $^{13}C$ chemical shifts of the $\gamma$-methylene carbon and the methyl carbon in axially substituted methylcyclohexane are shifted 3-5 ppm upfield relative to the signals in equatorially substituted methylcyclohexane.[3] These shifts are proposed to result from polarization of the electrons due to steric interactions. In the case of the axial methylcyclohexane, the methyl hydrogens and the axial $\gamma$-methylene hydrogens sterically interact, leading to an increase in the electron density on carbon.

We wish to argue against this explanation of the $\gamma$ effect and to propose that the $\gamma$ effect follows, at least in part, from a generalized "gauche" NMR effect applicable to $^{13}C$ as well as $^{19}F$, $^{31}P$, and other heavy-atom chemical shifts. In addition we wish to point out that the conformational sensitivity of heavy-atom chemical shifts and directed bonded coupling constants are related and originate from a bond angle distortion dependent upon the torsional conformation.

## Results and Discussion

We have recently shown that $^{31}P$ chemical shifts of phosphate esters are primarily determined by the RO-P-OR bond angle[4] and the RO-P-OR torsional angles.[5] Thus, a decrease in the RO-P-OR bond angle leads to a downfield shift in the $^{31}P$ signal. In addition, the $^{31}P$ chemical shift of an ester in a gauche, gauche (g,g) conformation is upfield from the chemical shift of an ester in a non-g,g conformation, such as gauche, trans (g,t).

We have also observed that ester torsional angles and bond angles are strongly "coupled".[6] Thus, rotation about the O-P bond from a gauche to a trans conformation results in ca. a ~5° reduction in the RO-P-OR bond angle. As a result of this coupling, $^{31}P$ shifts in acyclic phosphate esters are largely determined by the torsional conformation, with bond angle