2-isopropyl-2-trimethylsilyl-1,3-dithiane: bp 121–123° (2.35 torr); nmr spectrum (CCl_4 with CH_2Cl_2 as internal standard) τ 7.05 and 7.51, dithiane ring proton multiplets; 8.02, methine proton septet, J = 7 Hz; 8.79, $CH(CH_3)_2$ doublet, J = 7 Hz; 9.78, $Si(CH_3)_3$ singlet; ratios, 2:4:1:6:9.

Anal. Calcd for $C_{10}H_{22}S_2Si$: C, 51.22; H, 9.46; S, 27.35. Found: C, 51.15; H, 9.54; S, 27.50.

Acetyltrimethylsilane (1) was prepared in 64% yield using the procedure outlined by Brook.[11]

Isobutyryltrimethylsilane (2). The hydrolysis of 2-isopropyl-2-trimethylsilyl-1,3-dithiane was effected using the method outlined by Brook[11] with the following modifications. When the evolution of gas from the hydrolysis had ceased the reaction mixture was filtered. The filtrate was extracted with five 25-ml portions of ether. The combined ether extracts were washed with three 50-ml portions of water and dried over anhydrous sodium sulfate. The ether solution was filtered and distilled to give 1.43 g (58.2%) of impure isobutyryltrimethylsilane, bp 120–130°. The pure compound was obtained by preparative gas chromatography using a 25 ft × $^3/_8$ in. aluminum column, packed with 25% SE-30 on 40–60 mesh Chromosorb P, operating at 155° with a carrier gas flow of 200 cc of He/min. Under these conditions its retention time is 5 min; infrared spectrum 2965 (s), 2930 (m), 2900 (m), 2870 (m), 1640 (s) (C=O), 1465 (m), 1409 (w), 1377 (m), 1360 (w), 1325 (w), 1250 (s), 1170 (w), 1110 (w), 1065 (m), 990 (m), 860 (s), 830 (s), 750 (m), 695 (m), 620 (m), 365 (m), and 280 cm^{-1} (s); n^{24}D 1.4198; nmr spectrum (CCl_4 with CH_2Cl_2 as an internal standard) τ 7.56, methine septet, J = 6 Hz; 8.05, $-CH(CH_3)_2$ doublet, J = 6 Hz; 9.05, $-Si(CH_3)_3$ singlet; ratios 1:6:9; ultraviolet spectrum (isooctane) λ_{max} 371 mμ (ϵ 119), with shoulders at 343, 357, and 386 mμ and λ_{max} <200 mμ (ϵ >3000).

Anal. Calcd for $C_7H_{16}OSi$: C, 58.27; H, 11.18; Si, 19.46. Found: C, 58.52; H, 11.30; Si, 19.11.

Pinacolone was obtained from the Aldrich Chemical Co., Inc., Milwaukee, Wis., and was used without further purification.

Pentamethylacetone was obtained from Columbia Organic Chemicals Co., Inc., Columbia, S. C. Its purity was verified by gas chromatography prior to use; ultraviolet spectrum (isooctane) λ_{max} 293 (19) and <200 mμ (ϵ>600).

Ketone Radical Anions. The solvents were prepared for use by distillation under a nitrogen atmosphere from lithium aluminum hydride or sodium into a receiver containing anthracene. Sodium–potassium alloy was added to the receivers which were then attached to a vacuum line and degassed until the deep blue color of anthracene radical anion appeared in the solvent. When a sample was being prepared, the appropriate amounts of the solvents to give the indicated *volume* composition were transferred by appropriate high vacuum techniques to a calibrated trap. The solvent mixture was then transferred to a trap containing a mirror of sodium–potassium alloy and used from this reservoir in the preparation of samples.

The samples themselves were prepared in 4-mm quartz sample tubes which were sealed to an 8-mm tube having a side arm and an "O" ring fitting for attaching the sample preparation tube to the vacuum line. The desired reducing metal was placed in the side arm, about 0.01 cc of the desired ketone was placed in the sample tube, and the entire apparatus was attached to the vacuum line. The sample was degassed and sufficient solvent mixture was transferred from the reservoir to fill the sample tube to a height of 40–70 mm. The reducing metal was then distilled from the side arm into the upper portion of the quartz sample tube, and the tube was sealed off. The samples were kept frozen in liquid nitrogen until use. To develop the radical anion, the contents of the sample tube were allowed to warm to slightly above the melting point, the tube was inverted to bring the sample into contact with the mirror, and the sample tube immediately was inserted into the variable-temperature probe of the spectrometer which was cooled to about −120°. As soon as sufficient radical anions had been produced, spectra were recorded at various temperatures up to about −50°. The solutions of all the ketyls were colorless to pale yellow in this temperature range.

Above −40° the solution of the silylketyls became an intense red color as the species giving the secondary spectra slowly developed. This change was not reversible on cooling.

The esr spectra were determined on a Varian Model V4502-13 spectrometer equipped with 100-kc field modulation, dual cavity, and a standard Varian variable-temperature accessory. All of the g values and coupling constants were measured using Fremy's salt (a = 13.00 G, g = 2.00550 ± 0.00005) as a standard in the reference cavity. The values reported in Table I represent averages of at least three separate measurements.

Aromatic Protonation. V. Secondary Hydrogen Isotope Effects on Hydrogen Ion Transfer from the Hydronium Ion[1]

A. J. Kresge, D. P. Onwood, and S. Slae[2]

Contribution from the Department of Chemistry, Illinois Institute of Technology, Chicago, Illinois 60616. Received June 19, 1968

Abstract: The effect of deuterium substitution in the nonreacting bonds of the hydronium ion on the rate of hydrogen ion transfer from this acid to an aromatic substrate was determined using a method which eliminates primary isotope effects. Measurements were carried out on two substrates, 1,3-dimethoxybenzene and 1,3,5-trimethoxybenzene, and, despite the fact that these substances react at rates which differ by 10^3, identical secondary isotope effects were found: $(k_H/k_D)_{sec}$ = 0.59 ± 0.01 at 25°. This result implies that the magnitude of this isotope effect is not sensitive to changes in transition-state structure, at least over the range investigated here. Possible reasons for this behavior are discussed.

Most of the common acids have protons which exchange rapidly with aqueous solvents, and isotope effects on hydrogen ion transfer from these species are therefore usually measured by comparing rates of reaction in light and heavy water In this kind of experiment, the primary isotope effect is necessarily accompanied by a solvent isotope effect, but the latter is likely to be comparatively small.[3] The hydronium ion, however, presents a somewhat special case, for this acid has three readily exchangeable hydrogen atoms. This will introduce a secondary isotope effect into the quantity measured, and this secondary effect, moreover, is likely to be sizeable, for the additional isotopic substitution occurs in "nonreacting" bonds which are very near the reaction site. This expectation is sup-

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(1) (a) This research was supported by the Atomic Energy Commission under USAEC Contract No. AT(11-1)-1025 to the Illinois Institute of Technology. (b) Part IV: A. J. Kresge, Y. Chiang, and Y. Sato, *J. Amer. Chem. Soc.*, **89**, 4418 (1967).

(2) National Institutes of Health, Predoctoral Fellow.

(3) R. E. Robertson, *Progr. Phys. Org. Chem.*, **4**, 251 (1967).

ported by theoretical considerations,[4] which lead to the further prediction that this secondary isotope effect will be inverse ($k_H/k_D < 1$). This is, of course, consistent with the fact that the maximum over-all isotope effect observed by comparing rates of hydrogen ion transfer from the hydronium ion in H_2O and in D_2O is only about half the value expected for simple oxygen–hydrogen bond breaking.[5] This lowering is of obvious importance to mechanistic conclusions drawn from the magnitude of observed isotope effects.

It is difficult to measure this secondary isotope effect directly, for the equivalence of all hydrogens in H_3O^+ and their very rapid exchange with water preclude the experimental use of individual isotopically mixed species. It is possible, however, to estimate separately primary and secondary isotope effects on hydrogen ion transfer from the hydronium ion using data obtained from kinetic experiments on H_2O–D_2O mixtures.[6] Since the various isotopically mixed hydronium ions occur in these solvents in proportions dependent on the total deuterium content of the medium, primary and secondary isotope effects can be made to contribute to the over-all rate in different combinations. A suitable analysis of the data will yield both isotope effects. The analysis,[7] however, is based on certain assumptions of unknown validity concerning the separability of primary and secondary isotope effects and the applicability of the rule of the geometric mean.[8]

Another means to the same end combines kinetic with extra-kinetic information.[9] A product isotope effect is obtained by comparing the deuterium content of the solvent with that of the product of a reaction performed in an H_2O–D_2O mixture. This product isotope effect is the primary isotope effect on hydrogen ion transfer from a water molecule; it can be converted, through application of the known[10] H–D fractionation factor for hydronium ion and water species, to the primary isotope effect on hydrogen ion transfer from the hydronium ion. Combination of the latter with the over-all isotope effect measured in isotopically homogeneous H_2O and D_2O then yields the secondary isotope effect. This method, however, relies on essentially the same assumptions as that employing kinetic data obtained from H_2O–D_2O mixtures.

It is possible to attack the problem of measuring this secondary isotope effect more directly by eliminating the primary isotope effect entirely. This may be done by using the third isotope of hydrogen, tritium, in addition to protium and deuterium. Rates of incorporation of tritium into a suitable substrate are measured in acidified solutions of H_2O and in acidified solutions of D_2O, each containing tracer amounts of tritium. As long as tritiation is the only reaction under observation, and provided that the tritium level is low enough to prevent double labeling, then the operationally effective hydronium ion species in one solvent will be H_2TO^+ and in the other solvent, D_2TO^+. The same kind of bond, oxygen–tritium, will be broken in each case (see eq 1 and 2), and there will be no primary isotope effect.

$$H_2O\text{-}T^+ + S \xrightarrow{k_H} H_2O + TS^+ \tag{1}$$

$$D_2O\text{-}T^+ + S \xrightarrow{k_D} D_2O + TS^+ \tag{2}$$

Thus, the ratio of the two rate constants k_H and k_D (eq 1 and 2) is in fact the secondary isotope effect. In practice, this method still relies on use of the rule of the geometric mean, but, since no primary isotope effect is present, it does not depend on the separability of primary and secondary effects.

This more direct method of measuring the secondary isotope effect on hydrogen ion transfer from the hydronium ion can be applied particularly well to acid-catalyzed aromatic hydrogen exchange, for here tritium incorporation into the aromatic substrate can easily be measured in isolation from any other reaction. We have already reported[11] the preliminary results of such an investigation in which 1,3-dimethoxybenzene was the aromatic substrate. In this paper, we describe that work in detail and present also the results of a companion study performed for the purpose of determining the sensitivity of this secondary isotope effect to changes in substrate reactivity.

Results

Rates of tritiation were measured by monitoring the incorporation of radioactivity into aromatic substrates dissolved in dilute aqueous perchloric acid solutions containing tracer amounts of tritium. These substrates were isotopically normal initially, *i.e.*, they contained no deuterium or tritium over natural abundance, but, in D_2O solution, they were gradually deuterated by a process analogous to acid-catalyzed tritiation. In order to avoid the complications which this systematic change in substrate identity would produce, kinetic measurements were generally confined to times corresponding to no more than 2% reaction. An analysis employing the known isotope effects on this reaction[12] shows that the amount of deuteration produced in these times was insufficient to alter measured rate constants significantly.

Acid-catalyzed aromatic hydrogen exchange is a reversible reaction, but, under the conditions of the initial rate measurements performed here, the reverse process, detritiation, could not have occurred to any appreciable extent. The process studied, therefore, can be considered to be nonreversible, and kinetic analysis may be based on the abbreviated form of the rate expression for aromatic hydrogen exchange.[13] Thus, eq 4 gives the rate law for the reaction in H_2O (eq 3), and eq 6 gives the corresponding expression for the reaction in D_2O (eq 5). The same intramolecular isotope effect, k_2^T/k_2^H, appears in the denominators of both rate expressions; these, therefore, will cancel in

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[4] (a) C. A. Bunton and V. J. Shiner, Jr., *J. Amer. Chem. Soc.*, **83**, 3214 (1961); (b) C. G. Swain and E. R. Thornton, *ibid.*, **83**, 3884 (1961).

[5] (a) A. J. Kresge and Y. Chiang, *ibid.*, **84**, 3976 (1962); (b) A. J. Kresge, D. S. Sagatys, and H. L. Chen, *ibid.*, **90**, 4174 (1968).

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[11] A. J. Kresge and D. P. Onwood, *J. Amer. Chem. Soc.*, **86**, 5014 (1964).

[12] A. J. Kresge and Y. Chiang, *ibid.*, **89**, 4411 (1967).

[13] A. J. Kresge and Y. Chiang, *ibid.*, **83**, 2877 (1961).

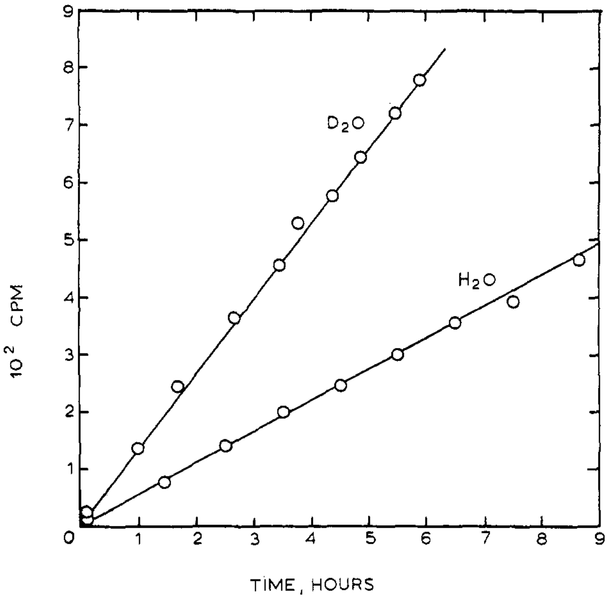

Figure 1. Zero-order rate plots for the perchloric acid catalyzed tritiation of 1,3-dimethoxybenzene at 25°.

the ratio of the two rates, v_{H_2O}/v_{D_2O}. Provided, then, that rates in the two solvents are compared at equivalent aromatic substrate and tritiated hydronium ion concentrations, the ratio v_{H_2O}/v_{D_2O} will give the secondary isotope effect on hydrogen ion transfer from the hydronium ion, $(k_H/k_D)_{sec}$, directly.

$$\mathrm{HAr} + \mathrm{H_2TO^+} \underset{k_2^{\mathrm{T}}}{\overset{k_1^{\mathrm{T-OH_2}}}{\rightleftharpoons}} \mathrm{HArT^+} + \mathrm{H_2O} \xrightarrow{k_2^{\mathrm{H}}} \mathrm{TAr} + \mathrm{H_3O^+} \quad (3)$$

$$v_{H_2O} = \frac{d(\mathrm{ArT})}{dt} = \frac{k_1^{\mathrm{T-OH_2}}}{1 + k_2^{\mathrm{T}}/k_2^{\mathrm{H}}}(\mathrm{HAr})(\mathrm{H_2TO^+}) \quad (4)$$

$$\mathrm{HAr} + \mathrm{D_2TO^+} \underset{k_2^{\mathrm{T}}}{\overset{k_1^{\mathrm{T-OD_2}}}{\rightleftharpoons}} \mathrm{HArT^+} + \mathrm{D_2O} \xrightarrow{k_2^{\mathrm{H}}} \mathrm{TAr} + \mathrm{D_3O^+} \quad (5)$$

$$v_{D_2O} = \frac{d(\mathrm{ArT})}{dt} = \frac{k_1^{\mathrm{T-OD_2}}}{1 + k_2^{\mathrm{T}}/k_2^{\mathrm{H}}}(\mathrm{HAr})(\mathrm{D_2TO^+}) \quad (6)$$

For both of the aromatic substrates studied, 1,3-dimethoxybenzene and 1,3,5-trimethoxybenzene, the quantities v_{H_2O} and v_{D_2O} were determined by least-squares analysis of plots (Figure 1 shows a typical example) of aromatic radioactivity (measured by counting toluene extracts of quenched aliquots of reaction mixtures) *vs.* time. These zero-order rates were then reduced to equivalent substrate and tritiated hydronium ion concentrations by methods which differed somewhat for the two aromatic substrates.

1,3-Dimethoxybenzene. Concentrations of this aromatic substrate in the reaction solutions were determined directly by a bromination method: 1,3-dimethoxybenzene reacts rapidly and quantitatively with bromine to give 1,3-dimethoxy-4,6-dibromobenzene. The very rapid exchange of tritium between the solvent and the hydronium ions H_2TO^+ and D_2TO^+, however, prevented direct measurement of the concentrations of these species. Relative values of these concentration variables were supplied instead, and this was done using a method which required knowledge of the total acidity and the total radioactivity of each reaction solution. Total acidities were determined by standard titrimetric assay; these, of course, were equivalent to the concentration of H_3O^+ for runs performed in H_2O solution and to the concentration of D_3O^+ for runs in D_2O solution: since tritium is present only as a tracer, the concentrations of the other hydronium ion species present, H_2TO^+ and D_2TO^+, each contribute negligibly to total acidities. Total radioactivities were measured by counting aliquots of spent reaction solution. Here again, because the concentrations of the other tritiated substances, aromatic substrate and hydronium ions, were low (*ca.* 10^{-2} *M*) compared to water concentrations (55 *M*), these total radioactivities were essentially proportional to the concentrations of the water species HTO and DTO. Since, moreover, the molar volumes of H_2O and D_2O are very nearly equal,[14] the total radioactivities of H_2O and D_2O reaction mixtures were proportional to the concentration ratios $(\mathrm{HTO})/(\mathrm{H_2O})$ and $(\mathrm{DTO})/(\mathrm{D_2O})$, respectively.

Division of zero-order rates of reaction by each of these measured quantities produced bimolecular rate constants (eq 7 and 8) whose ratio differed from the desired secondary isotope effect only by a collection of hydronium ion and water concentration terms (eq 9).

$$\frac{v_{H_2O}}{(\mathrm{HAr})(\mathrm{H_3O^+})(\mathrm{HTO})/(\mathrm{H_2O})} = \left(\frac{k_1^{\mathrm{T-OH_2}}}{1 + k_2^{\mathrm{T}}/k_2^{\mathrm{H}}}\right)\left(\frac{(\mathrm{HAr})(\mathrm{H_2TO^+})}{(\mathrm{HAr})(\mathrm{H_3O^+})(\mathrm{HTO})/(\mathrm{H_2O})}\right) = \left(\frac{k_1^{\mathrm{T-OH_2}}}{1 + k_2^{\mathrm{T}}/k_2^{\mathrm{H}}}\right)\left(\frac{(\mathrm{H_2TO^+})(\mathrm{H_2O})}{(\mathrm{H_3O^+})(\mathrm{HTO})}\right) = R_{H_2O} \quad (7)$$

$$\frac{v_{D_2O}}{(\mathrm{HAr})(\mathrm{D_3O^+})(\mathrm{DTO})/(\mathrm{D_2O})} = \left(\frac{k_1^{\mathrm{T-OD_2}}}{1 + k_2^{\mathrm{T}}/k_2^{\mathrm{H}}}\right)\left(\frac{(\mathrm{HAr})(\mathrm{D_2TO^+})}{(\mathrm{HAr})(\mathrm{D_3O^+})(\mathrm{DTO})/(\mathrm{D_2O})}\right) = \left(\frac{k_1^{\mathrm{T-OD_2}}}{1 + k_2^{\mathrm{T}}/k_2^{\mathrm{H}}}\right)\left(\frac{(\mathrm{D_2TO^+})(\mathrm{D_2O})}{(\mathrm{D_3O^+})(\mathrm{DTO})}\right) = R_{D_2O} \quad (8)$$

$$\frac{R_{H_2O}}{R_{D_2O}} = \left(\frac{k_1^{\mathrm{T-OH_2}}}{k_1^{\mathrm{T-OD_2}}}\right)\left(\frac{(\mathrm{H_2TO^+})(\mathrm{H_2O})}{(\mathrm{H_3O^+})(\mathrm{HTO})}\right)\Bigg/\frac{(\mathrm{D_2TO^+})(\mathrm{D_2O})}{(\mathrm{D_3O^+})(\mathrm{DTO})} \quad (9)$$

These hydronium ion and water species can be related to one another through two isotope exchange reactions (eq 10 and 11), and the concentration terms may therefore be replaced by the isotope exchange equilibrium constants K_{10} and K_{11}. Neither of these constants

$$\mathrm{H_3O^+} + \mathrm{HTO} \rightleftharpoons \mathrm{H_2TO^+} + \mathrm{H_2O} \quad (10)$$

$$\mathrm{D_3O^+} + \mathrm{DTO} \rightleftharpoons \mathrm{D_2TO^+} + \mathrm{D_2O} \quad (11)$$

$$K_{10} = \frac{(\mathrm{H_2TO^+})(\mathrm{H_2O})}{(\mathrm{H_3O^+})(\mathrm{HTO})} \qquad K_{11} = \frac{(\mathrm{D_2TO^+})(\mathrm{D_2O})}{(\mathrm{D_3O^+})(\mathrm{DTO})} \quad (12)$$

has been measured directly, but their ratio can be reduced to a quantity whose value is known. The constants may be expressed in terms of partition functions, and the rule of the geometric mean[8] can be used to replace the partition functions of mixed species with partition functions of isotopically homogeneous substances (eq 13 and 14). In the ratio K_{10}/K_{11}, partition functions of tritium-containing species cancel, and the remaining function is exactly equal to *l*, the known[10]

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[14] I. Kirshenbaum, "Physical Properties and Analysis of Heavy Water," McGraw-Hill Book Co., Inc., New York, N. Y., 1951, Chapter 1.

$$K_{10} = \frac{Q_{\mathrm{H_2TO}}Q_{\mathrm{H_2O}}}{Q_{\mathrm{H_3O}}Q_{\mathrm{HTO}}} = \frac{3(Q_{\mathrm{H_3O}})^{2/3}(Q_{\mathrm{T_3O}})^{1/3}Q_{\mathrm{H_2O}}}{2Q_{\mathrm{H_3O}}(Q_{\mathrm{H_2O}})^{1/2}(Q_{\mathrm{T_2O}})^{1/2}} = \frac{3(Q_{\mathrm{T_3O}})^{1/3}(Q_{\mathrm{H_2O}})^{1/2}}{2(Q_{\mathrm{H_3O}})^{1/3}(Q_{\mathrm{T_2O}})^{1/2}} \quad (13)$$

$$K_{11} = \frac{Q_{\mathrm{D_2TO}}Q_{\mathrm{D_2O}}}{Q_{\mathrm{D_3O}}Q_{\mathrm{DTO}}} = \frac{3(Q_{\mathrm{D_3O}})^{2/3}(Q_{\mathrm{T_3O}})^{1/3}Q_{\mathrm{D_2O}}}{2Q_{\mathrm{D_3O}}(Q_{\mathrm{D_2O}})^{1/2}(Q_{\mathrm{T_2O}})^{1/2}} = \frac{3(Q_{\mathrm{T_3O}})^{1/3}(Q_{\mathrm{D_2O}})^{1/2}}{2(Q_{\mathrm{D_3O}})^{1/3}(Q_{\mathrm{T_2O}})^{1/2}} \quad (14)$$

H–D fractionation factor for hydronium ion and water species (eq 15). Combination of eq 9, 12, and 15 then

$$\frac{K_{10}}{K_{11}} = \frac{(Q_{\mathrm{D_3O}})^{1/3}(Q_{\mathrm{H_2O}})^{1/2}}{(Q_{\mathrm{H_3O}})^{1/3}(Q_{\mathrm{D_2O}})^{1/2}} = l \quad (15)$$

leads to eq 16 from which the desired secondary isotope effect, $(k_{\mathrm{H}}/k_{\mathrm{D}})_{\mathrm{sec}} = k_1^{\mathrm{T-OH_2}}/k_1^{\mathrm{T-OD_2}}$, can be calculated.

$$R_{\mathrm{H_2O}}/R_{\mathrm{D_2O}} = l(k_{\mathrm{H}}/k_{\mathrm{D}})_{\mathrm{sec}} \quad (16)$$

Table I summarizes the results of these experiments. In both solvents, first-order rate constants (zero-order rates divided by substrate concentrations and total radioactivities) were linear functions of total acidity with zero intercepts (Figure 2). This shows that acid-catalyzed tritiation was the only reaction which the aromatic substrate was undergoing and that, in spite of the high levels of radioactivity which had to be used to obtain significant results (*ca.* 1 Ci of tritium/l. of reaction mixture), radiation decomposition did not contribute to the formation of toluene-soluble radioactivity.

Table I. Rates of Incorporation of Tritium into 1,3-Dimethoxybenzene Catalyzed by Dilute Perchloric Acid at 25°

Solvent	$10^2(\mathrm{HClO_4})$ or $10^2(\mathrm{DClO_4})$, M	$10^3(\mathrm{HAr})$, M	$R_{\mathrm{H_2O}}$ or $R_{\mathrm{D_2O}}$,[a] M^{-1} sec^{-1}
H_2O	1.32	6.77	6.30 ± 0.28
H_2O	2.20	6.68	6.67 ± 0.25
H_2O	3.54	6.19	6.25 ± 0.11
H_2O	4.41	6.55	6.30 ± 0.28
		Weighted average =	6.28 ± 0.08
D_2O	1.32	6.33	16.5 ± 0.4
D_2O	2.12	6.84	14.5 ± 0.4
D_2O	2.87	7.15	14.8 ± 0.3
D_2O	3.89	6.25	16.1 ± 0.4
		Weighted average =	15.5 ± 0.2
	$R_{\mathrm{H_2O}}/R_{\mathrm{D_2O}}$ = 0.407 ± 0.007		

[a] These rate constants all contain the same (unknown) multiplier: certain dilution factors times the ratio of the counting efficiency of the liquid scintillation counting solution used to measure the aromatic radioactivity to that of the solution used to measure the water radioactivity. Error limits are standard deviations of mean values.

In these experiments, aromatic radioactivities were determined using a liquid scintillation counting solution of different composition from that used for total radioactivity (water) assay. Since the relative counting efficiencies of these two solutions were not determined, no attempt was made to express rate constants in standard units. The bimolecular constants in the last column of Table I therefore contain an unknown multiplier. This multiplier, however, is exactly the same for the two sets of runs, and the ratio $R_{\mathrm{H_2O}}/R_{\mathrm{D_2O}}$ is an accurate representation of the quantity from which the secondary isotope effect may be calculated (eq 16). Division of $R_{\mathrm{H_2O}}/R_{\mathrm{D_2O}}$ by l (0.69) then gives 0.59 ± 0.01 $(k_{\mathrm{H}}/k_{\mathrm{D}})$ as the secondary isotope effect on hydrogen ion transfer from the hydronium ion to 1,3-dimethoxybenzene.

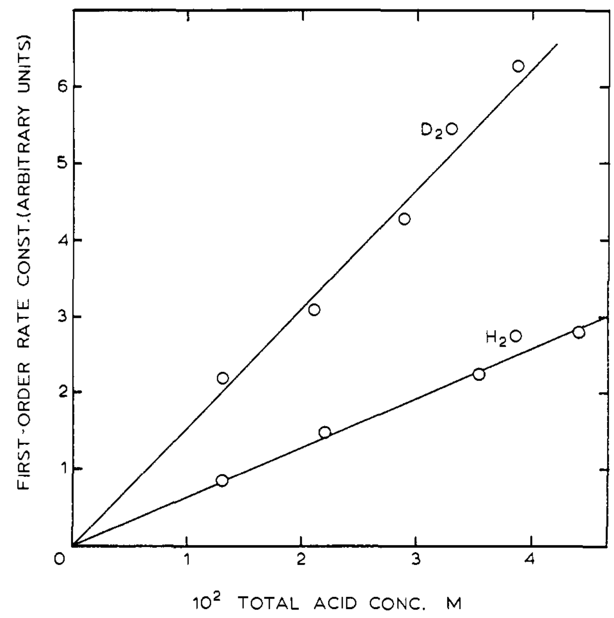

Figure 2. Relationship between first-order rate constants and total perchloric acid concentration for the tritiation of 1,3-dimethoxybenzene at 25°.

1,3,5-Trimethoxybenzene. The bromination method of determining aromatic substrate concentrations gave erratic results with this substrate; a different kind of analysis, which determines substrate concentration and water radioactivity simultaneously, was therefore used. This method depends on the fact that, at equilibrium, *i.e.*, after approximately ten tritiation half-lives, the radioactivity present in a toluene extract of reaction mixture is proportional to the amount of aromatic substrate available for exchange and the level of solvent radioactivity. In an experiment in H_2O solution, for example, the isotope exchange reaction shown in eq 17

$$\mathrm{HAr + HTO \rightleftharpoons TAr + H_2O} \quad (17)$$

is brought to equilibrium by the acidic catalyst. The expression for the equilibrium constant of this reaction can be rearranged to give eq 18, which shows that the equilibrium concentration of TAr is proportional to the product of aromatic substrate concentration and water radioactivity. The latter two quantities, of

$$(\mathrm{TAr})_{\mathrm{e}} = K_{17}(\mathrm{HAr})(\mathrm{HTO})/(\mathrm{H_2O}) \quad (18)$$

course, do not change significantly with time, for tritium is present only at tracer level and the amount of water available greatly exceeds that of aromatic substrate. The equilibrium concentrations of HAr, HTO, and H_2O are therefore the same as their initial concentrations, and $(\mathrm{TAr})_{\mathrm{e}}$ is an accurate measure of these values.

In experiments performed in D_2O solution, the aromatic substrate was furnished initially as HAr. The quantity of protium supplied in this form, however, is negligible, and the reaction occurring at equilibrium can be written in terms of deuterated species only (eq 19). The equilibrium concentration of DAr is of

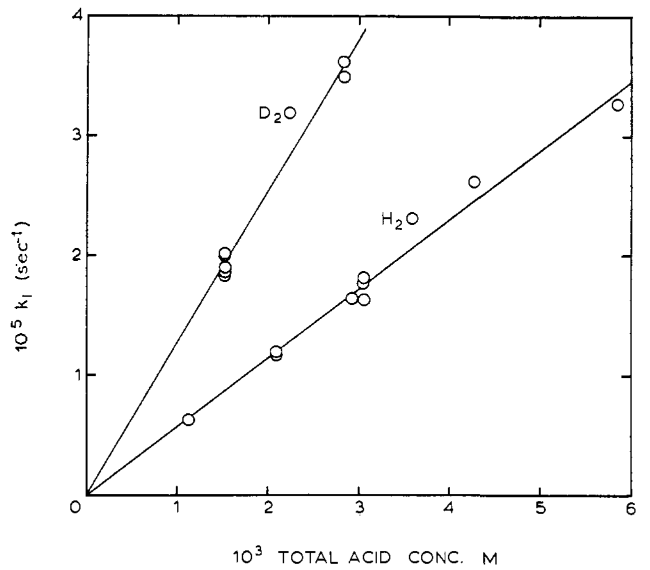

Figure 3. Relationship between first-order rate constants and total perchloric acid concentration for the tritiation of 1,3,5-trimethoxybenzene at 25°.

$$\mathrm{DAr} + \mathrm{DTO} \rightleftharpoons \mathrm{TAr} + \mathrm{D_2O} \qquad (19)$$

course equal to the initial concentration of HAr, $(\mathrm{HAr})_0$, and $(\mathrm{TAr})_e$ again accurately measures $(\mathrm{HAr})_0$ and $(\mathrm{DTO})/(\mathrm{D_2O})$ (eq 20).

$$(\mathrm{TAr})_e = K_{19}(\mathrm{DAr})_e(\mathrm{DTO})/(\mathrm{D_2O}) = K_{19}(\mathrm{HAr})_0(\mathrm{DTO})/(\mathrm{D_2O}) \qquad (20)$$

For experiments using 1,3,5-trimethoxybenzene, therefore, aromatic substrate concentrations and water radioactivities were determined by accelerating exchange in a portion of reaction mixture through addition of more acid catalyst. When equilibrium had been reached, aliquots were quenched in base and extracted with toluene, and the toluene extracts were assayed for radioactivity. Acid concentrations were determined as for runs using 1,3-dimethoxybenzene, and zero-order rates were divided by total acidities and equilibrium substrate radioactivities. This gave the bimolecular rate constants $R'_{\mathrm{H_2O}}$ and $R'_{\mathrm{D_2O}}$ shown as eq 21 and 22. The ratio $R'_{\mathrm{H_2O}}/R'_{\mathrm{D_2O}}$ could then be

$$\frac{v_{\mathrm{H_2O}}}{(\mathrm{H_3O^+})(\mathrm{TAr})_e} = \left(\frac{k_1^{\mathrm{T\text{-}OH_2}}}{1 + k_2^{\mathrm{T}}/k_2^{\mathrm{H}}}\right)\left(\frac{(\mathrm{HAr})(\mathrm{H_2TO^+})}{(\mathrm{H_3O^+})K_{17}(\mathrm{HAr})(\mathrm{HTO})/(\mathrm{H_2O})}\right) = \left(\frac{k_1^{\mathrm{T\text{-}OH_2}}}{1 + k_2^{\mathrm{T}}/k_2^{\mathrm{H}}}\right)\left(\frac{1}{K_{17}}\right)\left(\frac{(\mathrm{H_2TO^+})(\mathrm{H_2O})}{(\mathrm{H_3O^+})(\mathrm{HTO})}\right) = R'_{\mathrm{H_2O}} \qquad (21)$$

$$\frac{v_{\mathrm{D_2O}}}{(\mathrm{D_3O^+})(\mathrm{TAr})_e} = \left(\frac{k_1^{\mathrm{T\text{-}OD_2}}}{1 + k_2^{\mathrm{T}}/k_2^{\mathrm{H}}}\right)\left(\frac{(\mathrm{HAr})(\mathrm{D_2TO^+})}{(\mathrm{D_3O^+})K_{19}(\mathrm{HAr})_0(\mathrm{DTO})/(\mathrm{D_2O})}\right) = \left(\frac{k_1^{\mathrm{T\text{-}OD_2}}}{1 + k_2^{\mathrm{T}}/k_2^{\mathrm{D}}}\right)\left(\frac{1}{K_{19}}\right)\left(\frac{(\mathrm{D_2TO^+})(\mathrm{D_2O})}{(\mathrm{D_3O^+})(\mathrm{DTO})}\right) = R'_{\mathrm{D_2O}} \qquad (22)$$

reduced to eq 23 by application of the rule of the geometric mean as described in the section above on 1,3-dimethoxybenzene.

$$R'_{\mathrm{H_2O}}/R'_{\mathrm{D_2O}} = l(k_{\mathrm{H}}/k_{\mathrm{D}})_{\mathrm{sec}}K_{19}/K_{17} \qquad (23)$$

Table II summarizes the results of these experiments. Here again, first-order rate constants proved to be linear functions of total acidity with zero intercepts (Figure 3) demonstrating that this system was well behaved. In these experiments, only one kind of liquid scintillation counting solution was used; the counting efficiency in the determination of $v_{\mathrm{H_2O}}$ and $v_{\mathrm{D_2O}}$ was therefore exactly the same as that in the measurement of $(\mathrm{TAr})_e$. This (unknown) counting efficiency cancels in the calculation of $R'_{\mathrm{H_2O}}$ and $R'_{\mathrm{D_2O}}$, and these bimolecular rate constants are thus accurate measures of the specific rates of these reactions and are expressed in standard units (Table II, last column). It can be shown that $R'_{\mathrm{H_2O}}$ should have the same numerical value as the observed bimolecular rate constant for hydronium ion catalyzed loss of tritium from 1,3,5-trimethoxybenzene-2-*t* in H_2O solution. The latter quantity is reported[12] as $(6.20 \pm 0.05) \times 10^{-3}\ M^{-1}$ sec^{-1}, which is in acceptable agreement with the value of $(5.65 \pm 0.03) \times 10^{-3}\ M^{-1}$ sec^{-1} found here for $R'_{\mathrm{H_2O}}$.

Table II. Rates of Incorporation of Tritium into 1,3,5-Trimethoxybenzene Catalyzed by Perchloric Acid at 25°

Solvent	$10^3(\mathrm{HClO_4})$ or 10^3 $(\mathrm{DClO_4})$, M	$10^3R'_{\mathrm{H_2O}}$ or $10^3R'_{\mathrm{D_2O}}$,[a] M^{-1} sec^{-1}
H_2O	1.13	5.37 ± 0.05
H_2O	2.09	5.70 ± 0.08
H_2O	2.09	5.62 ± 0.09
H_2O	2.92	5.63 ± 0.08
H_2O	3.05	5.75 ± 0.16
H_2O	3.05	5.92 ± 0.18
H_2O	3.05	5.97 ± 0.14
H_2O	4.29	6.07 ± 0.32
H_2O	5.86	5.53 ± 0.18
	Weighted average =	5.65 ± 0.03
D_2O	1.53	12.00 ± 0.18
D_2O	1.53	12.97 ± 0.07
D_2O	1.53	12.40 ± 0.13
D_2O	1.53	12.05 ± 0.23
D_2O	1.53	13.03 ± 0.23
D_2O	2.85	12.22 ± 0.13
D_2O	2.85	12.68 ± 0.19
	Weighted average =	12.67 ± 0.05
	$R'_{\mathrm{H_2O}}/R'_{\mathrm{D_2O}}$ =	0.446 ± 0.003

[a] Error limits are standard deviations of mean values.

In order to calculate $(k_{\mathrm{H}}/k_{\mathrm{D}})$ from $R'_{\mathrm{H_2O}}/R'_{\mathrm{D_2O}}$, the ratio K_{19}/K_{17} must be known (eq 23). This was supplied by dissolving known amounts of 1,3,5-trimethoxybenzene in tritiated H_2O and tritiated D_2O containing acid catalysts, allowing the systems to come to equilibrium, and then comparing aromatic radioactivities with water (total) radioactivities. The value so obtained, $K_{19}/K_{17} = 1.09 \pm 0.02$, when combined with $R'_{\mathrm{H_2O}}/R'_{\mathrm{D_2O}}$ and l gives 0.59 ± 0.01 $(k_{\mathrm{H}}/k_{\mathrm{D}})$ as the secondary isotope effect on hydrogen ion transfer from the hydronium ion to 1,3,5-trimethoxybenzene.

Discussion

Rule of the Geometric Mean. The present method of determining secondary isotope effects on hydrogen ion transfer from the hydronium ion assumes that the rule of the geometric mean applies to isotopically substituted hydronium ion and water species. This rule states that partition functions, with symmetry numbers removed, of successive members of an isotopic series, formed by successive isotopic substitutions at equivalent sites in a molecule, differ by the same factor. This implies that the zero-point energies of such an isotopic series are a linear function of the number of isotopic substitutions. Although real systems do in fact obey such a relationship, the agreement, in accordance with theoretical expectation, is only approximate.[15]

Quite recently, direct experimental proof of the approximate nature of the rule of the geometric mean as applied to water species has been supplied. It was found that the equilibrium constant for the isotope disproportionation reaction between H_2O and D_2O to give HDO is 6% less than its expected statistical (rule of the geometric mean) value.[16] This means that the partition function of HDO is about 3% less than the square root of the product of the partition functions, with symmetry numbers removed, of H_2O and D_2O, and that the corresponding deviation from the equality $Q_{HTO} = (2Q_{H_2O})^{1/2}(2Q_{T_2O})^{1/2}$ used in the denominator of eq 13 is likely to be even greater. The rule of the geometric mean, however, was also applied in a similar form to hydronium ion species in the numerator of eq 13: $Q_{H_2TO} = (3Q_{H_3O})^{2/3}(3Q_{T_3O})^{1/3}$. Deviations from the rule of the geometric mean for hydronium ion species have not been measured, but experiments on a closely analogous molecule, ammonia, show deviations per bond similar in magnitude to those for water.[17] It is likely, therefore, that the deviations for hydronium ion species will be similar to those for corresponding water species, and that much of the inexactness in the numerator and denominator of eq 13 will cancel. The effects of these deviations on the quantity of interest to us here, $(k_H/k_D)_{sec}$, moreover, is likely to be even less, for calculation of the latter requires only the ratio K_{10}/K_{11} (eq 13 and 14). In equation 14, the rule of the geometric mean was applied again to deuterium and tritium species in a manner exactly analogous to that used for eq 13, and a further cancellation of deviations in the ratio of eq 13 to eq 14 is probable.

Magnitude of Secondary Isotope Effects. Both of the secondary isotope effects measured here are inverse. This agrees with the direction of the secondary isotope effect on hydrogen ion transfer from the hydronium ion measured by other methods in different systems,[6,9] and it is consistent with the fact that these isotope effects originate in bonds which are being strengthened in the process under observation. These bonds, the nonreacting bonds of the hydronium ion, become oxygen–hydrogen bonds of a molecule of water in the reaction product, and a simplified calculation employing only the stretching frequencies of the hydronium ion and water predicts a value of 0.61 for this secondary isotope effect.[4a]

It is now generally accepted that primary isotope effects will vary in magnitude as transition state structure is changed.[5b,18] This variation originates in regular changes in those force constants of the transition state which refer to the partial bonds holding the atom in transit.[19] A similar regular reorganization of nonreacting bonds affected by the reaction process should also take place, and secondary isotope effects should therefore vary in magnitude as well. Whereas primary isotope effects pass through a maximum value,[5b,18,19] however, secondary effects might be expected to vary monotonically and realize their largest size in the limit of a product-like transition state.

In this respect, the identity of the two secondary isotope effects measured here is surprising. 1,3-Dimethoxybenzene is protonated by the hydronium ion 780 times more slowly than 1,3,5-trimethoxybenzene;[1b] its transition state should therefore be significantly more product-like than the transition state for the protonation of 1,3,5-trimethoxybenzene.[20] And yet, the secondary isotope effects for hydrogen ion transfer to these two substrates are identical within the rather small experimental limits. This is true regardless of the approximations introduced by use of the rule of the geometric mean: this rule is applied in exactly the same way to both cases, and, although it may introduce some uncertainty into the absolute value of these isotope effects, it does not alter their relative magnitudes.

It is possible, of course, that a change of 10^3 in reaction velocity is insufficient to produce a marked change in transition state structure. Not much information is available on this aspect of proton transfer reactions, but it is known that a similar change of 10^3 in rate is enough to reduce the exponent α in the Brønsted relation from 0.8 to 0.6 in vinyl ether hydrolysis.[21] Brønsted's α, of course, is believed to be a fairly reliable index of the extent of proton transfer in the transition state of such reactions and therefore of the degree to which the reactants have progressed toward products.[22]

Another explanation of this unexpected similarity of secondary isotope effects is the hypothesis that those parts of the reaction coordinate which pertain to proton transfer do not change in a manner parallel to the parts which control secondary isotope effects. In fact, model system calculations being performed in this laboratory[23] indicate that the secondary isotope effect on proton transfer from the hydronium ion can lead the primary effect by a considerable margin. In our model, secondary effects reach a limiting value by the time the proton is only half-transferred. These model calculations, however, are necessarily based on arbitrary assumptions concerning variations in transition state force constants. In the absence of a good potential energy surface for the proton transfer process, the validity of these variational functions cannot be known, and the verification of this hypothesis must await more experimental work.

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It should be pointed out that secondary isotope effects different in magnitude from those measured here have been reported for other reactions: $(k_H/k_D)_{sec}$ = 0.65 and 0.66 for ethyl vinyl ether hydrolysis,[6b,9b] 0.67 for alkyl mercuric iodide cleavage,[9a] and 0.53 for isobutene hydration.[6a] These effects are all based on methods which require dissection of observed data into primary and secondary isotope effects, and it may therefore be improper to compare them with values obtained here by a method which does not assume separability of primary and secondary effects. Two of the most divergent of the above values, however, 0.65 and 0.53, were determined by a single method, analysis of rates measured in H_2O–D_2O mixtures. It can be argued, on the other hand, that this analysis is subject to all the assumptions inherent in the theory of isotope effects in H_2O–D_2O mixtures,[7] that one value (0.65) was obtained in dilute acid (0.01 *M*) whereas the other refers to moderately concentrated solutions (0.4 *M*), and that the value of 0.53 is subject to considerable experimental error due to the difficulties inherent in measuring rates of isobutene hydration. Nevertheless, it would seem prudent to refrain for the time being from any broad generalization concerning the relationship between the magnitude of this secondary isotope effect and transition state structure.

Experimental Section

Materials. 1,3,5-Trimethoxybenzene was prepared by the methylation of phloroglucinol[24] and was purified by alternate vacuum sublimations and recrystallizations from aqueous ethanol. 1,3-Dimethoxybenzene was purchased commercially and was purified by fractional distillation. All other materials were best quality commercial chemicals and were used without further treatment.

Kinetic Procedure. Runs using 1,3,5-trimethoxybenzene were conducted in glass-stoppered flasks, but the higher volatility of 1,3-dimethoxybenzene necessitated use of a special apparatus designed to prevent the substrate from escaping the reaction mixture. This consisted essentially of a leveling bulb immersed in a water bath and connected to its twin through flexible tubing. The reaction mixture was contained over mercury and under a stopper fitted with a curved capillary tube and a stopcock arranged so as to leave no air space. At suitable intervals, portions of the reaction mixture were expressed by applying pressure through the mercury, an initial amount was discarded, and an aliquot was pipetted from the remainder.

Runs with 1,3-dimethoxybenzene were conducted at 25.0 ± 0.02° while those with 1,3,5-trimethoxybenzene were performed at 24.62 ± 0.02°. Reaction mixtures were prepared by mixing substrate and catalyst solutions which had equilibrated with the constant-temperature bath; in the case of runs using 1,3-dimethoxybenzene, reaction mixtures were then transferred to the apparatus described above by hypodermic syringe. Samples were quenched in excess base, extracted with toluene, and the toluene extracts were washed with water a sufficient number of times (established through control experiments) to remove all nonaromatic radioactivity. (Three washings were usually sufficient.) The washed extracts were then dried over calcium chloride, and aliquots were diluted with counting solution (PPO and POPOP in toluene) and assayed by liquid scintillation counting using a Packard Model 314-EX machine. Water radioactivities were determined using Bray's counting solution.[25]

Analysis for 1,3-Dimethoxybenzene. Samples of reaction mixture were removed as described above and were added to potassium bromate–potassium bromide in a bromination flask. Dilute sulfuric acid was introduced, and the mixture was stirred thoroughly. When the color of free bromine was observed, the rapid reaction which yields 1,3-dimethoxy-4,6-dibromobenzene was complete, and potassium iodide was added. The liberated iodine was titrated with thiosulfate solution.

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Stable Carbonium Ions. LXXVI.[1a] 2,2-Dimethyltetramethylene Halonium Ions and a Study of Halogen Participation in Protonated Methyl γ-Halopropyl Ketones and 5-Halo-1-pentynes

George A. Olah, J. Martin Bollinger,[1b] and Jean Brinich[1c]

Contribution from the Department of Chemistry, Case Western Reserve University, Cleveland, Ohio 44106. *Received June 20, 1968.*

Abstract: Tertiary carbonium ions containing a halogen atom three carbon atoms removed from the positive site have been generated in antimony pentafluoride–sulfur dioxide solution and in fluorosulfuric acid–antimony pentafluoride dioxide solutions. When the halogen atom was Cl, Br, or I, the species observed in the strong acid systems were the five-membered ring 2,2-dimethyltetramethylene halonium ions. No evidence for halogen participation in protonated methyl γ-halopropyl ketones or 5-halo-1-pentynes was found with the exception of the protonation of 5-iodopentyne-1 which gave the 2-methylenetetramethyleneiodonium ion.

In previous investigations we have shown[2] that tertiary cations containing halogen on an adjacent carbon atom undergo a strong interaction with the halogen which results in the cationic site becoming tetrahedral (the more nearly tetrahedral as the size of the halogen atom increases) and in charge dispersal to the bridged halogen atom.[3] We have also demonstrated that cyclic

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