were obtained by similar techniques and will be reported in detail when current work on imidazole and its derivatives reaches completion.

pK_a Measurements. Because of the low solubility of dibenzylmethylamine (*ca.* 7 × 10^{-4} M at 30°) it was necessary to measure K_A at pH <4, near the equivalence point, and a differential potentiometric method[38] was used. The concentration of R_3NHCl in six independent experiments ranged from 0.02 to 0.2 M; pK_A appeared to be independent of concentration and was 7.72 ± 0.04 at 30°. Saunders and Yamada[17] have reported that pK_A = 7.5 ± 0.1 at 25°, somewhat lower than our value.

Kinetic Results. Rates of NH-OH proton exchange between dibenzylmethylammonium chloride and water were measured by nmr techniques described previously[7,39] in the presence of 10^{-4} to 1 M HCl. The NH-HOH chemical shift used in the interpretation was 4.48 ppm. The rate law was found to be (18).

$$R = k[R_3NH^+]/(1 + Q[H^+]) + k_2[R_3NH^+][R_3N] \quad (18)$$

Because of the low solubility of the amine, the accuracy of k_2, which depends on measurements in the high pH end of the pH range, was less than usual. The accuracy of k and Q and the test of the rate law at pH <3 were satisfactory. On interpreting k and Q by the mechanism in eq 3 and 4, we obtained at 30°: $k_a = (2.4 \pm 0.3) \times 10^2$ sec^{-1}; $k_{-a} = (1.25 \pm 0.16) \times 10^{10}$ sec^{-1} M^{-1}; $k_H = (2.7 \pm 0.5) \times 10^9$ sec^{-1}; $k_2 = (1.5 \pm 0.4) \times 10^7$ sec^{-1} M^{-1}.

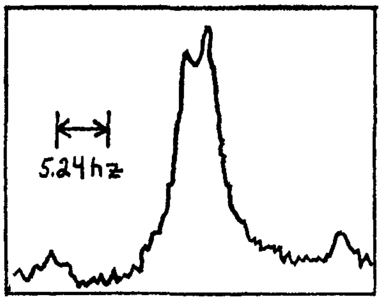

Figure 3. CH_2 proton resonance spectrum of dibenzylmethylammonium chloride at 56.4 MHz in 0.134 M DCl in D_2O. The scale of the abscissa is 5.24 Hz per large division.

Confirmation of the Rate Constant for Walden Inversion about Nitrogen. Saunders and Yamada, in their measurement of $k_{\text{inversion}}$, treat the nuclear magnetic resonance of the CH_2 protons as a partially exchange-averaged AB spectrum.[17] Unfortunately, because of the strong background nmr absorption due to the water protons, they could not show that an AB spectrum is actually obtained in the absence of exchange, in strong acid. In Figure 3 we show our measurement of the CH_2 proton resonance at 56.4 MHz of dibenzylmethylammonium chloride in 0.134 M DCl in D_2O. The resonance is in good agreement with prediction for an AB spectrum for which δ = 0.132 ppm and J = 13.1 Hz.

---

[38] E. Grunwald, *J. Am. Chem. Soc.*, 73, 4934 (1951).

[39] E. Grunwald and E. Price, *ibid.*, **86**, 2965, 2970 (1964).

Aromatic Protonation. III. Kinetic Hydrogen Isotope Effects on Acid-Catalyzed Aromatic Hydrogen Exchange in 1,3,5-Trimethoxybenzene[1]

A. J. Kresge[2] and Y. Chiang[2b]

Contribution from the Department of Chemistry, Illinois Institute of Technology, Chicago, Illinois 60616, and the Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139.

Received March 14, 1967

Abstract: Rates of aromatic hydrogen exchange in 1,3,5-trimethoxybenzene catalyzed by dilute aqueous perchloric acid were measured for four systems which used the three isotopes of hydrogen as tracers in different pairwise combinations. Kinetic analysis of the results in terms of the known two-step mechanism of this reaction shows that secondary isotope effects must be taken into account and that the Swain relation between deuterium and tritium isotope effects is valid. The product of primary and secondary isotope effects on hydrogen ion transfer from the hydronium ion to isotopically identical substrates is 3.59 ± 0.11 (k_H/k_D), and the secondary isotope effect produced by hybridization changes in the nonreacting bond of the aromatic substrate in this step of the reaction is 0.90 ± 0.03 (k_H/k_D). The quotient of primary and secondary isotope effects on hydrogen ion loss from the phenonium ion intermediate is 8.1 ± 0.3 (k_H/k_D). The secondary isotope effect on this step of the reaction is also produced by hybridization changes in the nonreacting bond of the aromatic substrate, and there is reason to expect it to be the reciprocal of the corresponding isotope effect on the other step of the reaction. This gives the primary isotope effect on hydrogen ion loss from the phenonium ion intermediate the value 9.0 ± 0.4 (k_H/k_D).

Ever since Melander's pioneering work,[3] kinetic hydrogen isotope effects have played a prominent role in mechanistic investigations of electrophilic aromatic substitution.[4] Acid-catalyzed aromatic hydrogen exchange is the most elementary electrophilic aromatic substitution, and isotope effects on this reaction are therefore of special significance in this respect. Quite apart from their value to electrophilic aromatic substitution, however, isotope effects on aromatic hydrogen exchange are important because one of the rate-determining steps of this reaction is slow proton transfer from the catalyzing acid to the substrate. Proton

---

[1] (a) This research was supported by the U. S. Atomic Energy Commission under Contract No. AT(11-1)-1025 to the Illinois Institute of Technology. (b) Part I: A. J. Kresge and Y. Chiang, *J. Am. Chem. Soc.*, **83**, 2877 (1961). (c) Part II: A. J. Kresge, L. E. Hakka, S. Mylonakis, and Y. Sato, *Discussions Faraday Soc.*, **39**, 75 (1965).

[2] (a) Guggenheim Fellow. (b) Guest of the Institute, Massachusetts Institute of Technology.

[3] L. Melander, *Arkiv Kemi*, **2**, 213 (1950).

[4] For recent reviews, see H. Zollinger, *Advan. Phys. Org. Chem.* **2**, 164 (1964); E. Berliner, *Progr. Phys. Org. Chem.*, **2**, 253 (1964).

transfer from catalyst to substrate is an elementary reaction step common to many chemical processes, but it has received relatively little detailed study for it usually appears as a rapid step preceding other slower reactions. In aromatic hydrogen exchange, however, it occurs in a form amenable to close investigation, and hydrogen isotope effects are a valuable tool which can be used in such a study. Very recently, moreover, isotope effects on aromatic hydrogen exchange have provided the first experimental support[5,6] of the theoretical prediction[7] that the magnitude of isotope effects will pass through a maximum value as reaction parameters are varied in a regular way.

The measurement of isotope effects on aromatic hydrogen exchange encounters a difficulty which is the result of a situation common to the determination of isotope effects on all isotope exchange reactions: two isotopes of the exchanging element must be used to measure a single exchange rate, and a third isotope must be supplied to provide an isotope effect.[8] In the case of aromatic hydrogen exchange, this is complicated by the fact this reaction consists of two proton transfer steps neither one of which is fully rate determining.[1b,c,9,10] The rates of these two steps are affected in different ways by isotopic substitution in either the catalyzing acid or the aromatic substrate, and simple comparison of two rates of exchange using different pairs of hydrogen isotopes is not sufficient to determine an isotope effect. These difficulties are usually overcome by making use of the Swain relation[11] between deuterium and tritium isotope effects (eq 1). This

$$(k_H/k_D)^{1.442} = k_H/k_T \qquad (1)$$

method, however, as usually applied,[12-15] neglects any secondary isotope effects which may be operative. The Swain relation, moreover, has had few empirical tests and its general validity has recently been questioned on theoretical grounds.[16]

It is possible to circumvent some of these objections by using more than two exchange rates to determine isotope effects on aromatic hydrogen exchange. In this paper we report the results of experiments using four different combinations of the three isotopes of hydrogen taken in pairs. The set of data which this provides is still not sufficient both to avoid the use of the Swain relation and to include consideration of all secondary isotope effects. It does, however, permit some conclusions to be drawn about the validity of this relation in the present case and about the magnitude of secondary isotope effects on aromatic hydrogen exchange.

Results

The four isotopically different systems employed in this investigation had the following initial compositions: I, ArT + HA; II, ArT + DA; III, ArD + HA; and IV, ArH + DA. In all cases, the aromatic substrate was 1,3,5-trimethoxybenzene and the catalyst was dilute perchloric acid; the actual catalyst species was therefore the hydronium ion. The solvent was wholly aqueous: in the systems using HA, it was H_2O, and in the systems using DA, D_2O. All of the systems were homogeneous, *i.e.*, the aromatic substrate was always supplied at a concentration less than its saturation solubility of *ca.* 2×10^{-3} *M*.

In systems I and II, rates of hydrogen exchange were measured by using liquid scintillation counting to determine the decrease in radioactivity of the substrate, 1,3,5-trimethoxybenzene-2-*t*, as a function of time. Data were collected over at least four half-lives; these obeyed first-order kinetic laws exactly. Observed second-order rate constants (Table I) were calculated by dividing first-order exchange constants by the known perchloric acid concentrations of the reaction mixtures.

Table I. Rates of Loss of Tritium from 1,3,5-Trimethoxybenzene to 0.0490 *M* Aqueous Perchloric Acid at 24.62°

	10^3k_{obsd}, M^{-1} sec^{-1}	
	In H_2O	In D_2O[a]
	6.14	10.49
	6.35	10.50
	6.03	10.44
	6.25	10.50
	6.39	10.45
	6.27	
	6.29	
	6.15	
	5.95	
Av	6.20 ± 0.05[b]	10.48 ± 0.02[b]

[a] Deuterium, 99.5 atom %. [b] Standard deviation of the mean value.

In system II, as tritium was lost from 1,3,5-trimethoxybenzene-2-*t*, the hydrogens at positions 4 and 6 were also being replaced by deuterium at a comparable rate. This produced some 1,3,5-trimethoxybenzene-2-*t*-4-*d* and 1,3,5-trimethoxybenzene-2-*t*-4,6-d_2, which later lost tritium, and this, in turn, introduced the possibility of complications arising from a time-dependent secondary isotope effect. The fact that all of the experiments with system II conformed accurately to first-order kinetic laws over their entire course indicates that this secondary isotope effect was essentially unity. In order, however, to determine whether or not small differences, undetectable as deviations from first-

---

(5) J. L. Longridge and F. A. Long, *J. Am. Chem. Soc.*, **89**, 1292 (1967). This work puts on a sound basis the original proposal[6] that isotope effects on aromatic hydrogen exchange pass through a maximum; it demonstrates also that, for catalysis by the hydronium ion, the maximum occurs with azulene as the aromatic substrate, not with anisole as was once[6] believed to be the case.

(6) A. J. Kresge, *Pure Appl. Chem.*, **8**, 517 (1964); *Discussions Faraday Soc.*, **39**, 48 (1965).

(7) F. Westheimer, *Chem. Rev.*, **61**, 265 (1961); J. Bigeleisen, *Pure Appl. Chem.*, **8**, 217 (1964); A. V. Willi and M. Wolfsberg, *Chem. Ind.* (London), 2097 (1964); R. P. Bell, *Discussions Faraday Soc.*, **39**, 16 (1965); further experimental support of this prediction appears in R. P. Bell and D. M. Goodall, *Proc. Roy. Soc.* (London), **A294**, 273 (1966).

(8) L. Melander, *Arkiv Kemi*, **7**, 287 (1954).

(9) (a) A. J. Kresge and Y. Chiang, *J. Am. Chem. Soc.*, **81**, 5509 (1959); (b) *Proc. Chem. Soc.*, 81 (1961); (c) A. J. Kresge, Y. Chiang and Y. Sato, *J. Am. Chem. Soc.*, **89**, 4418 (1967).

(10) J. Colapietro and F. A. Long, *Chem. Ind.* (London), 1056 (1960); F. A. Long and J. Schulze, *J. Am. Chem. Soc.*, **83**, 3340 (1961); B. C. Challis and F. A. Long, *ibid.*, **85**, 2524 (1963); J. Schulze and F. A. Long, *ibid.*, **86**, 331 (1964); R. J. Thomas and F. A. Long, *J. Org. Chem.*, **29**, 3411 (1964); *J. Am. Chem. Soc.*, **86**, 4770 (1964); B. C. Challis and F. A. Long, *ibid.*, **87**, 1196 (1965); *Discussions Faraday Soc.*, **39**, 67 (1965).

(11) C. G. Swain, E. C. Stivers, J. F. Reuwer, Jr., and L. J. Schaad, *J. Am. Chem. Soc.*, **80**, 5885 (1958).

(12) S. Olsson, *Arkiv Kemi*, **9**, 85 (1959); **16**, 489 (1960); B. Ostman and S. Olsson, *ibid.*, **15**, 275 (1960).

(13) (a) V. Gold, R. W. Lambert, and D. P. N. Satchell, *J. Chem. Soc.*, 2461 (1960); (b) B. D. Batts and V. Gold, *ibid.*, 4284 (1964).

(14) A. J. Kresge and Y. Chiang, *J. Am. Chem. Soc.*, **84**, 3976 (1962).

(15) L. C. Gruen and F. A. Long, *ibid.*, **89**, 1287 (1967).

(16) J. Bigeleisen, "Tritium in the Physical and Biological Sciences," Vol. I, International Atomic Energy Agency, Vienna, 1962, p 161.

order kinetic plots, were present, this secondary isotope effect was measured directly. An authentic sample of 1,3,5-trimethoxybenzene-2-*t*-4,6-d_2 (93 atom % deuterium at the labeled positions) was prepared, and its initial rate of loss of tritium to dilute perchloric acid in H_2O was compared with that for 1,3,5-trimethoxybenzene-2-*t*. Although these reactions were followed only to 2.7% completion,[17] accurate zero-order rate constants (Table II) could be obtained by performing the radioactive assay on the aqueous portion of the reaction mixture rather than on the aromatic substrate. Zero-order rate constants for the two substrates proved to be the same within the combined experimental errors, and therefore isotopic substitution at the 4 and 6 positions of 1,3,5-trimethoxybenzene does not alter the rate of exchange at the 2 position.

Table II. Initial Rates of Loss of Tritium from Ordinary and Deuterated 1,3,5-Trimethoxybenzene to 5 × 10^{-3} *M* Aqueous Perchloric Acid at 24.62°

Substrate		k_{obsd}, % reaction min^{-1}
1,3,5-Trimethoxy-benzene-2-*t*		0.172
		0.168
	Av	0.170 ± 0.002[a]
1,3,5-Trimethoxy-benzene-2-*t*-4,6-d_2		0.170
		0.176
	Av	0.173 ± 0.003[a]
k_H/k_D = 0.98 + 0.02		

[a] Standard deviation of the mean value.

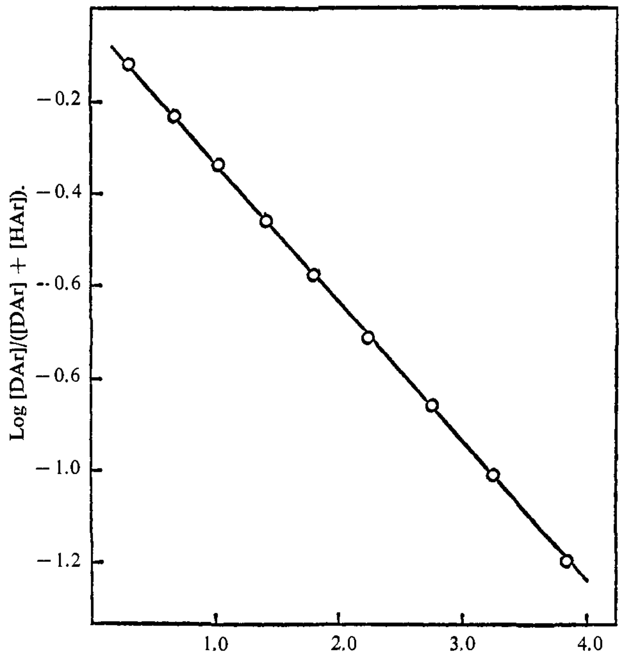

Figure 1. Kinetic plot for loss of deuterium from 1,3,5-trimethoxybenzene-2-*d* to 4.92 × 10^{-2} *M* aqueous perchloric acid at 24.62°; k_{obsd} = 1.408 × 10^{-2} M^{-1} sec^{-1}.

In systems III and IV, rates of hydrogen exchange were measured by determining the change in deuterium content of 1,3,5-trimethoxybenzene as a function of time. In our original work,[14] we used an infrared spectrometric method of deuterium assay: 1,3,5-trimethoxybenzene-2-*d* has a strong absorption band at 1115 cm^{-1} which is absent from the spectrum of the unlabeled material. It is difficult, however, to measure the intensity of this band with precision, and we therefore changed to a mass spectral method of isotopic assay for the work reported here. Molecular ions were generated at low ionizing potentials and the heights of the parent ion peaks were compared. This method produced very good results; a sample kinetic plot is shown in Figure 1.

Observed second-order rate constants for protium–deuterium exchange in systems III and IV are summarized in Table III. Each of the exchange rate constants was calculated on the basis of total loss of all of the label, and the rate constants for the reactions of ordinary 1,3,5-trimethoxybenzene and 1,3,5-trimethoxybenzene-2,4,6-d_3 therefore contain statistical factors of three which are absent from the rate constants for 1,3,5-trimethoxybenzene-2-*d* (and from the rate constants of Table I for systems I and II). When this difference is taken into account, the rate constant for loss of deuterium from 1,3,5-trimethoxybenzene-2-*d*, (1.385 ± 0.013) × 10^{-2} M^{-1} sec^{-1}, is identical with that for loss of the first deuterium from 1,3,5-trimethoxybenzene-2,4,6-d_3, $^1/_3$ × (4.14 ± 0.03) × 10^{-2} M^{-1} sec^{-1} = (1.381 ± 0.010) × 10^{-2} M^{-1} sec^{-1}; this supports the conclusion reached previously (Table II) that isotopic substitution at the other nuclear positions of 1,3,5-trimethoxybenzene does not affect the rate of hydrogen exchange at the 2 position.

Table III. Rates of Protium–Deuterium Exchange between 1,3,5-Trimethoxybenzene and Aqueous Perchloric Acid at 24.62°

Substrate	Catalyst	10^2k_{obsd}, M^{-1} sec^{-1}
1,3,5-Trimethoxy-benzene-2-*d*	0.0493 *M* $HClO_4$ in H_2O	1.408
1,3,5-Trimethoxy-benzene-2-*d*	0.0492 *M* $HClO_4$ in H_2O	1.408
1,3,5-Trimethoxy-benzene-2-*d*	0.0491 *M* $HClO_4$ in H_2O	1.358
1,3,5-Trimethoxy-benzene-2-*d*	0.0504 *M* $HClO_4$ in H_2O	1.367
	Av	1.385 ± 0.013[a]
1,3,5-Trimethoxy-benzene-2,4,6-d_3	0.0165 *M* $HClO_4$ in H_2O	4.10
1,3,5-Trimethoxy-benzene-2,4,6-d_3	0.0165 *M* $HClO_4$ in H_2O	4.13
1,3,5-Trimethoxy-benzene-2,4,6-d_3	0.0165 *M* $HClO_4$ in H_2O	4.20
	Av	4.14 ± 0.03[a]
1,3,5-Trimethoxy-benzene	0.00813 *M* $DClO_4$ in D_2O[b]	8.35
1,3,5-Trimethoxy-benzene	0.00813 *M* $DClO_4$ in D_2O[b]	8.42
1,3,5-Trimethoxy-benzene	0.00813 *M* $DClO_4$ in D_2O[b]	8.35
	Av	8.37 ± 0.02[a]

[a] Standard deviation of the mean value. [b] Deuterium, 99.5 %.

The best values of the observed second-order rate constants, adjusted for exchange of one hydrogen, for the four systems used in this study are summarized in

---

(17) It can be shown, using the rate constants of Table IV, that during the time required for loss of 2.7% of the tritium of 1,3,5-trimethoxybenzene-2-*t*-4,6-d_2, only 7% of the deuterium will be replaced by hydrogen.

Table IV. Summary of Observed Rate Constants for Aromatic Hydrogen Exchange of 1,3,5-Trimethoxybenzene in Dilute Aqueous Perchloric Acid at 24.62°

System	$10^2 k_{\text{obsd}}$, M^{-1} sec^{-1}
I, ArT + H_3O^+	0.620 ± 0.005^b
II, ArT + D_3O^+ [a]	1.048 ± 0.002^b
III, ArD + H_3O^+	1.384 ± 0.008^b
IV, ArH + D_3O^+ [a]	2.79 ± 0.01^b

[a] Deuterium, 99.5 atom %. [b] Standard deviation of the mean value.

Table IV. Three of these rate constants have recently been measured in another laboratory; the values reported[13b] are 6.0, 4.8, and 5.0% greater than those of Table IV for systems I, II, and III, respectively. These other experiments, however, were performed at a temperature slightly higher than that used in the present study, and, when this difference is taken into account using the known temperature dependence of this reaction,[9c] the discrepancies are reduced to 3.0, 1.3, and 1.5%. These are very probably within the combined experimental uncertainties of the two sets of measurements.

Discussion

Kinetic Analysis. A considerable body of evidence[1b,c,9,10] indicates that acid-catalyzed aromatic hydrogen exchange occurs by a two-step reaction mechanism. An intermediate species, the phenonium ion $L'ArL^+$,[18] is first formed by transfer of positively charged hydrogen from the catalyst, LA, to the substrate, L'Ar.

$$LA + L'Ar \longrightarrow L'ArL^+ + A^- \qquad (2)$$

This intermediate is then destroyed by transfer of a different but equivalent hydrogen to the conjugate base of the catalyst.

$$L'ArL^+ + A^- \longrightarrow LAr + L'A \qquad (3)$$

Since isotope exchange can occur with comparable facility in either direction, each of these reaction steps must be reversible. Although this doubles the number of distinguishable processes taking place in the system, it does not increase the number of kinds of elementary steps, but for isotope effects, the reverse of the reaction of eq 2 is identical with the reaction of eq 3, and the reverse of the reaction of eq 3 is identical with the reaction of eq 2.[19] Thus, only two rate constants are needed to describe the kinetics of this system. In this discussion these rate constants, k_1 and k_2 for the reactions of eq 2 and 3, respectively, will be specified further by superscripts to designate the isotope of hydrogen being transferred in the reaction steps to which they refer.

Isotope exchange reactions can be made essentially nonreversible in practice, and such was the case for the four examples of aromatic hydrogen exchange in 1,3,5-trimethoxybenzene investigated here. In each system, rate constants were determined by measuring the velocity with which an isotope of hydrogen in the aromatic substrate was replaced by a different isotope of hydrogen from an essentially isotopically homogeneous and completely aqueous solvent. In no case was the concentration of 1,3,5-trimethoxybenzene greater than 2×10^{-3} *M*, and the concentration of aromatic hydrogens, therefore, could not have exceeded 6×10^{-3} *M*. The concentration of solvent hydrogens was of course much greater, of the order of 10^2 *M*, and once the isotopic label left the aromatic substrate, it stood very little chance of returning from this large pool of solvent hydrogens.

This nonreversibility introduces a simplification in the kinetic analysis in that the reverse of the reaction of eq 3 need not be considered. The isotope exchange process then reduces to

$$LA + L'Ar \underset{k_2^L}{\overset{k_1^L}{\rightleftarrows}} L'ArL^+ + A^- \xrightarrow{k_2^{L'}} LAr + L'A \qquad (4)$$

The concentration of the reaction intermediate, $L'ArL^+$, is always very low,[20] and the steady-state approximation[22] may therefore be applied to this system. This provides the following expression for the reaction velocity

$$\frac{-d[L'Ar]}{dt} = \frac{k_1^L}{1 + k_2^L/k_2^{L'}}[L'Ar][LA] \qquad (5)$$

First-order exchange constants were determined experimentally as $-d[L'Ar]/[L'Ar]dt$, and these were divided by the acid concentration, [LA], in order to obtain observed second-order rate constants (k_{obsd} of Table IV). Observed second-order rate constants are therefore functions of the following general form consisting of rate constants for the various individual reaction steps.

$$k_{\text{obsd}} = \frac{k_1^L}{1 + k_2^L/k_2^{L'}} \qquad (6)$$

When this general expression is particularized for the four examples of aromatic hydrogen exchange in 1,3,5-trimethoxybenzene represented by Table IV, the following set of four equations is obtained.

$$ArT + H_3O^+\text{:} \quad (k_{\text{obsd}})_{\text{I}} = \frac{k_1^H}{1 + k_2^H/k_2^T} \qquad (7)$$

$$ArT + D_3O^+\text{:} \quad (k_{\text{obsd}})_{\text{II}} = \frac{k_1^D}{1 + k_2^D/k_2^T} = \frac{k_1^D}{1 + \dfrac{k_2^H/k_2^T}{k_2^H/k_2^D}} \qquad (8)$$

$$ArD + H_3O^+\text{:} \quad (k_{\text{obsd}})_{\text{III}} = \frac{k_1^H}{1 + k_2^H/k_2^D} \qquad (9)$$

$$ArH + D_3O^+\text{:} \quad (k_{\text{obsd}})_{\text{IV}} = \frac{k_1^D}{1 + k_2^D/k_2^H} \qquad (10)$$

These equations contain only four independent unknown variables: k_1^H, k_1^D, k_2^H/k_2^D, and k_2^H/k_2^T. They

---

[18] The symbol "L" is used throughout this discussion to designate an atom of hydrogen without specification of its isotopic identity; "H" is reserved for protium.

[19] This is strictly true only in cases such as those of interest here in which the hydrogens L and L' occupy chemically identical positions in the intermediate species $L'ArL^+$. For a discussion of systems in which this is not the case, see R. L. Burwell and R. G. Pearson, *J. Phys. Chem.*, 70, 300 (1966).

[20] Extrapolation of the known acidity dependence of the equilibrium protonation of 1,3,5-trimethoxybenzene[9c,21] shows that the fraction of substrate present in the protonated form never exceeded 10^{-7} at the acidities employed in this kinetic study.

[21] A. J. Kresge, G. W. Barry, K. R. Charles, and Y. Chiang, *J. Am. Chem. Soc.*, **84**, 4343 (1962); W. M. Schubert and R. H. Quacchia, *ibid.*, **84**, 3778 (1962); **85**, 1278 (1963).

[22] A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," John Wiley and Sons, Inc., New York, N. Y., 1953, p 172.

can therefore be solved exactly, and the solution will provide an isotope effect on the first step of the reaction, $k_1{}^{H}/k_1{}^{D}$, in addition to the two isotope effects on the second step, $k_2{}^{H}/k_2{}^{D}$ and $k_2{}^{H}/k_2{}^{T}$.

This analysis, however, assumes that only the isotopic identity of the hydrogen which is actually undergoing transfer is of consequence in determining the values of k_1 and k_2. It regards isotopic substitutions made elsewhere in the system as being of no importance. A number of such secondary isotopic substitutions were necessarily made in this investigation, and some of these are of a kind known to produce secondary isotope effects of appreciable magnitude. This might have a significant effect on the solution of eq 7–10. It could make the calculated values of the isotopic rate ratios $k_1{}^{H}/k_1{}^{D}$, $k_2{}^{H}/k_2{}^{D}$, and $k_2{}^{H}/k_2{}^{T}$ composite functions of primary and secondary isotope effects, or it could actually prevent the direct solution of eq 7–10 by increasing the number of unknown variables beyond four.

Two different kinds of secondary isotopic substitution were made in the systems investigated here; one of these was in the solvent and therefore in the catalyzing acid, and the other was in the aromatic substrate. The isotopic substitution in the solvent—some reactions were conducted in H_2O and some in D_2O—would be expected to change the absolute magnitude of both k_1 and k_2. The rate constant k_2, however, always appears in eq 7–10 as the ratio $k_2{}^{L}/k_2{}^{L'}$, and, in each case, both parts of the ratio refer to reactions conducted in the same solvent. The effects of isotopic substitution in the solvent will therefore cancel in these ratios, and changing the solvent will, through its effect on k_2, neither introduce a secondary isotope effect into $k_2{}^{L}/k_2{}^{L'}$ nor increase the number of unknown variables in eq 7–10. The rate constant k_1, on the other hand, appears as an isolated variable in each of the eq 7–10, and effects of isotopic substitution in the solvent will persist in calculated values of $k_1{}^{H}$ and $k_1{}^{D}$. The isotopic rate ratio $k_1{}^{H}/k_1{}^{D}$ therefore contains a primary isotope effect and a secondary isotope effect as well, and the value of this secondary effect can be expected to differ appreciably from unity.[23] In all of the systems represented by eq 7–10, however, only two isotopes of hydrogen, H and D, are involved in the first step of the reaction, and, in each case, the isotope which contributes to the primary isotope effect contributes to the secondary isotope effect as well. There are therefore only two kinds of k_1 in these equations, and isotopic substitution in the solvent will once again not increase the number of unknown variables.

It is convenient to subdivide the secondary isotopic substitutions made in the aromatic substrate into two further categories: those made at the position undergoing substitution and those made at other ring positions. The latter have already been demonstrated to produce no significant secondary isotope effect (Table II). The former, however, could be of more consequence, for they take place in bonds which are undergoing changes in hybridization; this is known to produce appreciable secondary isotope effects.[24] Again, because the rate constant k_2 appears in each of eq 7–10 only as the ratio $k_2{}^{L}/k_2{}^{L'}$, the effect of this secondary isotopic substitution on this rate constant is simpler than its effect on k_1. This effect is to make the rate ratio $k_2{}^{L}/k_2{}^{L'}$ the product of primary and secondary isotope effects on the second step of the reaction. The quantity $k_2{}^{L}/k_2{}^{L'}$, however, is also an intramolecular rate ratio which measures the relative facility with which the two isotopes of hydrogen L and L′ leave the methylene group of the intermediate species $L'ArL^+$. Since there are only two hydrogens in this methylene group, then the isotope which does not contribute to the primary isotope effect must contribute to the secondary isotope effect. In any given case, therefore, only two isotopes of hydrogen are involved in both primary and secondary isotope effects on the second step of the reaction, and there are only two independent forms of the ratio $k_2{}^{L}/k_2{}^{L'}$, one involving H and D and the other involving H and T. Thus, this secondary isotopic substitution does not increase the number of unknown variables in eq 7–10 through its effect on k_2.

This kind of secondary isotopic substitution does, however, increase the number of unknown variables through its effect on k_1. This can be shown by modifying the original rate constant symbolism through addition of another superscript to designate the isotope of hydrogen occupying this kind of secondary position. Thus, for example, ${}^{T}k_1{}^{H}$ means that H is being transferred in the first step of the reaction to a carbon atom which already bears T, and ${}^{T}k_2{}^{H}$ means that H is being removed in the second step of the reaction from a methylene group composed of H and T. Equations 7–10 can then be transformed into the equivalent set.

$$(k_{\text{obsd}})_{\text{I}} = \frac{{}^{T}k_1{}^{H}}{1 + {}^{T}k_2{}^{H}/{}^{H}k_2{}^{T}} \tag{11}$$

$$(k_{\text{obsd}})_{\text{II}} = \frac{{}^{T}k_1{}^{D}}{1 + \dfrac{{}^{T}k_2{}^{H}/{}^{H}k_2{}^{T}}{{}^{D}k_2{}^{H}/{}^{H}k_2{}^{D}}} \tag{12}$$

$$(k_{\text{obsd}})_{\text{III}} = \frac{{}^{D}k_1{}^{H}}{1 + {}^{D}k_2{}^{H}/{}^{H}k_2{}^{D}} \tag{13}$$

$$(k_{\text{obsd}})_{\text{IV}} = \frac{{}^{H}k_1{}^{D}}{1 + {}^{H}k_2{}^{D}/{}^{D}k_2{}^{H}} \tag{14}$$

Each k_1 in these new equations represents a different combination of isotopic labels in primary and secondary positions and is, therefore, different. This increases the number of unknown variables in these equations to six and makes an exact solution impossible.

This situation might be remedied by application of the Swain relation. The effects of isotopic substitution in the primary position on k_1 may be eliminated by dividing eq 11 by eq 13 and eq 12 by eq 14. This leaves two equations in the four unknowns, ${}^{T}k_1/{}^{D}k_1$, ${}^{T}k_1/{}^{H}k_1$, ${}^{D}k_2{}^{H}/{}^{H}k_2{}^{D}$, and ${}^{T}k_2{}^{H}/{}^{H}k_2{}^{T}$, and these unknowns may be related in pairs.

$$({}^{T}k_1/{}^{D}k_1)^{1.442/0.442} = {}^{T}k_1/{}^{H}k_1 \tag{15}$$

$$({}^{D}k_2{}^{H}/{}^{H}k_2{}^{D})^{1.442} = {}^{T}k_2{}^{H}/{}^{H}k_2{}^{T} \tag{16}$$

The resulting system of two equations in two unknowns can be solved by successive approximations.

---

(23) A. J. Kresge and D. P. Onwood, *J. Am. Chem. Soc.*, **86**, 5014 (1964); M. M. Kreevoy and R. A. Kretchmer, *ibid.*, **86**, 2435 (1964); M. M. Kreevoy, P. W. Steinwand, and W. V. Kayser, *ibid.*, **86**, 5013 (1964); **88**, 124 (1966); V. Gold and M. A. Kessick, *Discussions Faraday Soc.*, **39**, 84 (1965).

(24) A. Streitweiser, Jr., R. H. Jagow, R. C. Fahey, and S. Suzuki, *J. Am. Chem. Soc.*, **80**, 2326 (1958); E. A. Halivi, *Progr. Phys. Org. Chem.*, **1**, 109 (1963).

This solution, of course, depends on the validity of the Swain relation when applied to both primary and secondary isotope effects on aromatic hydrogen exchange in 1,3,5-trimethoxybenzene. The soundness of this assumption is not known, but the procedure might be justified by the results it produces: if the isotope effects calculated have reasonable values, the assumptions may be judged essentially valid. The isotope effects obtained in this way may also be compared with those calculated by the set of simplified eq 7–10, and the importance of secondary isotope effects on this reaction may thereby be assessed.

Isotope Effects. The solution of eq 11–14 by the method just outlined provides the following rate constants and isotopic rate ratios.[25]

$${}^{\mathrm{T}}k_1^{\mathrm{H}} = (13.2 \pm 0.6) \times 10^{-2}\ M^{-1}\ \mathrm{sec}^{-1}$$

$${}^{\mathrm{T}}k_1^{\mathrm{D}} = (3.69 \pm 0.02) \times 10^{-2}\ M^{-1}\ \mathrm{sec}^{-1}$$

$${}^{\mathrm{D}}k_1^{\mathrm{H}} = (12.6 \pm 0.4) \times 10^{-2}\ M^{-1}\ \mathrm{sec}^{-1}$$

$${}^{\mathrm{H}}k_1^{\mathrm{D}} = (3.14 \pm 0.02) \times 10^{-2}\ M^{-1}\ \mathrm{sec}^{-1}$$

$$k_1^{\mathrm{H}}/k_1^{\mathrm{D}} = 3.59 \pm 0.11$$

$${}^{\mathrm{H}}k_1/{}^{\mathrm{D}}k_1 = 0.90 \pm 0.03 \qquad {}^{\mathrm{H}}k_1/{}^{\mathrm{T}}k_1 = 0.85 \pm 0.04$$

$${}^{\mathrm{D}}k_2^{\mathrm{H}}/{}^{\mathrm{H}}k_2^{\mathrm{D}} = 8.1 \pm 0.3 \qquad {}^{\mathrm{T}}k_2^{\mathrm{H}}/{}^{\mathrm{H}}k_2^{\mathrm{T}} = 20.3 \pm 1.0$$

Of these, the ratio ${}^{\mathrm{H}}k_1/{}^{\mathrm{D}}k_1$ is a pure secondary isotope effect, that produced by hybridization changes in the nonreactive carbon–hydrogen bond of the aromatic substrate, and the ratios $k_1^{\mathrm{H}}/k_1^{\mathrm{D}}$ and ${}^{\mathrm{D}}k_2^{\mathrm{H}}/{}^{\mathrm{H}}k_2^{\mathrm{D}}$ are products of primary and secondary isotope effects. In the case of $k_1^{\mathrm{H}}/k_1^{\mathrm{D}}$, the secondary isotope effect is that produced by changes in the nonreactive bonds of the hydronium ion and the solvent, and, in the case of ${}^{\mathrm{D}}k_2^{\mathrm{H}}/{}^{\mathrm{H}}k_2^{\mathrm{D}}$, the secondary isotope effect is that produced by hybridization changes in the nonreactive carbon–hydrogen bond of the reaction intermediate.

Neither one of the quantities $k_1^{\mathrm{H}}/k_1^{\mathrm{D}}$ and ${}^{\mathrm{D}}k_2^{\mathrm{H}}/{}^{\mathrm{H}}k_2^{\mathrm{D}}$ can be separated into its primary and secondary isotope effect components by the information supplied in this study, but an estimate of the secondary isotope effect in the latter ratio may be made in the following way. The exponent α in the Bronsted relation for aromatic hydrogen exchange in 1,3,5-trimethoxybenzene is known to be approximately one-half.[1b] This means that the changes which occur during the first step of this reaction are approximately half complete at the transition state.[27] Since the first and second steps of the reaction have the same transition state, the changes which occur during the second step must be approximately half complete at the transition state as well. It is therefore not unreasonable to assume that the secondary isotope effect on the second step of the reaction is the reciprocal of the secondary isotope effect on the first step: ${}^{\mathrm{H}}k_2/{}^{\mathrm{D}}k_2 = {}^{\mathrm{D}}k_1/{}^{\mathrm{H}}k_1 = 1.11 \pm 0.03$. The primary isotope effect on the second step may now be calculated as $k_2^{\mathrm{H}}/k_2^{\mathrm{D}} = {}^{\mathrm{D}}k_2^{\mathrm{H}}/{}^{\mathrm{H}}k_2^{\mathrm{D}} \times {}^{\mathrm{H}}k_2/{}^{\mathrm{D}}k_2 = (8.1 \pm 0.3) \times (1.11 \pm 0.03) = 9.0 \pm 0.4$.

This primary isotope effect is a very large protium–deuterium rate ratio. This is wholly consistent with expectation for aromatic hydrogen exchange in 1,3,5-trimethoxybenzene, for Brønsted's α for this reaction is one-half,[1b] the transition state is symmetrical with respect to the extent of proton transfer,[27] and the isotope effect should have its maximum value.[7] Such a large value is also consistent with the large isotope effects recently measured by a more direct method for a series of azulene derivatives;[5] these azulenes and 1,3,5-trimethoxybenzene are similar in reactivity and should therefore have similar isotope effects. The value for the rate ratio $k_1^{\mathrm{H}}/k_1^{\mathrm{D}}$ for 1,3,5-trimethoxybenzene produced by the present method of calculation (3.6) is also large, for this quantity must contain an inverse secondary isotope effect of considerable magnitude[23] in addition to the primary isotope effect on the first step of the reaction. The value $k_1^{\mathrm{H}}/k_1^{\mathrm{D}} = 3.6$ is, in fact, one of the largest rate ratios ever reported for proton transfer from the hydronium ion in dilute aqueous solution. Since both steps of this isotope exchange reaction pass through the same transition state, then the arguments used to predict a large isotope effect for the second step apply also to the first step, and such a large value for $k_1^{\mathrm{H}}/k_1^{\mathrm{D}}$ is most reasonable. Thus, the magnitude of each of the primary isotope effects produced by this method of calculation is consistent with the nature of this reaction.

Secondary isotope effects, such as that on the first step of this reaction where the change in hybridization is from sp^2 to sp^3, are known to be inverse[24] and to have a value of about 12% per deuterium atom.[28] The calculated value of 0.90 for ${}^{\mathrm{H}}k_1/{}^{\mathrm{D}}k_1$ (11%) is in very good agreement with this; it is also consistent with the inverse tritium effect of 13% recently measured for an azo coupling reaction of 1,3,5-trimethoxybenzene.[29] The secondary isotope effect produced by this method of calculation is therefore also in excellent agreement with its expected value.

In contrast to these results, solution of the simplified set of eq 7–10, which do not take into account the effects of isotopic substitution at secondary positions, gives the following set of isotopic rate ratios.

$$k_1^{\mathrm{H}}/k_1^{\mathrm{D}} = 1.25 \pm 0.06$$

$$k_2^{\mathrm{H}}/k_2^{\mathrm{D}} = 2.51 \pm 0.13 \qquad k_2^{\mathrm{H}}/k_2^{\mathrm{T}} = 6.84 \pm 0.27$$

These values are much too low; even when account is taken of the fact that they include secondary isotope effects in addition to primary isotope effects, they cannot be rationalized in terms of our present knowledge of the nature of the aromatic hydrogen exchange reaction in 1,3,5-trimethoxybenzene and the reasons underlying the magnitude of isotope effects.

Another method of calculating isotope effects on aromatic hydrogen exchange sometimes used[12–15] begins by employing only the data from systems analogous to those labeled I and III in this study. Equations 7 and 9 are assumed to apply, the Swain relation is used to eliminate $k_2^{\mathrm{H}}/k_2^{\mathrm{T}}$, and a value for $k_2^{\mathrm{H}}/k_2^{\mathrm{D}}$ is computed. Then data for the system analogous to that labeled III here is sometimes added to provide the ratio $k_1^{\mathrm{H}}/k_1^{\mathrm{D}}$.[13,14] This procedure, however, even

---

(25) Error estimates are standard deviations of mean values obtained from the uncertainties in observed rate constants by standard methods for the propagation of errors.[26]

(26) C. A. Bennett and N. L. Franklin, "Statistical Analysis in Chemistry and the Chemical Industry," John Wiley and Sons, Inc., New York, N. Y., 1954, p 51.

(27) J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1963, p 158.

(28) S. Seltzer, *J. Am. Chem. Soc.*, **83**, 2625 (1961).

(29) E. Helgstrand and B. Lamm, *Arkiv Kemi*, **20**, 193 (1962).

when the calculated rate ratios are interpreted as consisting of secondary isotope effects in addition to the primary effects, leads to erroneous results because the nonequivalence of k_1^{H} of eq 7 with k_1^{H} of eq 9 is not recognized; these rate constants are actually ${}^{T}k_1^{H}$ and ${}^{D}k_1^{H}$ (eq 11 and 13). In the present case, for example, this method of calculation gives $k_2^{H}/k_2^{D} = 7.2$; even when this is corrected for the secondary isotope effect ${}^{D}k_2/{}^{H}k_2$ which it contains, the value obtained, 8.0, is significantly less than that calculated using the complete set of eq 11–14.

These considerations point to the conclusion that secondary isotope effects must be taken into account in kinetic analyses of aromatic hydrogen exchange reactions. Furthermore, since use of the Swain relation results in a very reasonable and internally consistent set of isotope effects for aromatic hydrogen exchange in 1,3,5-trimethoxybenzene, then it seems most likely that the assumptions on which the Swain relation is based are valid when applied both to primary and to secondary isotope effects on this reaction.

Experimental Section

Materials. 1,3,5-Trimethoxybenzene-2-*t* was prepared from 2,4,5-trimethoxyphenyllithium and tritiated water by the method already described.[1b] 1,3,5-Trimethoxybenzene-2-*d* was prepared in a similar manner using deuterium oxide instead of tritiated water. Mass spectral analysis of material from two different preparations showed the following isotopic compositions: I, 1,3,5-trimethoxybenzene-d_0, 8.7 mole %; 1,3,5-trimethoxybenzene-2-*d*, 88.4 mole %; 1,3,5-trimethoxybenzene-2,4-d_2, 2.9 mole %; and II; 1,3,5-trimethoxybenzene-d_0, 6.3 mole %; 1,3,5-trimethoxybenzene-*d*, 91.4 mole %; 1,3,5-trimethoxybenzene-2,4-d_2, 2.3 mole %.

1,3,5-Trimethoxybenzene-2,4,6-d_3 was prepared by subjecting ordinary trimethoxybenzene to exchange with D_2O in the presence of an acidic catalyst. A solution of 6.6 g of 1,3,5-trimethoxybenzene in 40 ml of D_2O (99.8 atom % D) and 60 ml of purified dioxane containing 0.45 g of 70% $HClO_4$ was allowed to stand at room temperature for 1.5 days. Sufficient anhydrous pyridine was then added to neutralize the acid, and the resulting solution was diluted with about 300 ml of ordinary water. This caused the 1,3,5-trimethoxybenzene to separate as fine crystals; these were collected, washed with water, and dried. Two such exchanges produced 5.5 g of 1,3,5-trimethoxybenzene-2,4,6-d_3 which was found, by mass spectral analysis, to have the following isotopic composition: 1,3,5-trimethoxybenzene-2,4-d_2, 6.5 mole %; 1,3,5-trimethoxybenzene-2,4,6-d_3, 93.5 mole %.

1,3,5-Trimethoxybenzene-2-*t*-4,6-d_2 was prepared from 1,3,5-trimethoxybenzene-2,4,6-d_3 by decomposing the lithium derivative of the latter substance with tritiated water. Mass spectral analysis of the product of another preparation, identical in all respects with the original except that ordinary water was used to decompose 2,4,6-trimethoxyphenyl-3,5-d_2-lithium, showed that the 1,3,5-trimethoxybenzene-2,4-d_2 so obtained had the following isotopic composition: 1,3,5-trimethoxybenzene-d_0, 2.4 mole %; 1,3,5-trimethoxybenzene-2-*d*, 7.8 mole %; 1,3,5-trimethoxybenzene-2,4-d_2, 75.6 mole %; 1,3,5-trimethoxybenzene-2,4,6-d_3, 14.2 mole %.

Prior to their use in kinetic experiments, all samples of 1,3,5-trimethoxybenzene were purified to constant melting point (51.5–52.0°) by alternate vacuum sublimations and recrystallizations from ethanol–water. Deuterium oxide (99.8 atom % D; Bio-Rad Laboratories, Richmond, Calif.) was distilled from $KMnO_4$ and a small amount of NaOH; all other chemicals were reagent grade substances.

Kinetic Procedure. Rates of tritium exchange were determined by two methods, one for reactions followed for several half-lives and the other for reactions followed only to a few per cent completion. Both methods were essentially those already described.[1b] In the case of reactions followed for several half-lives, the aromatic substrate (concentration in reaction mixture, 2–16 × 10^{-5} *M*) was assayed for radioactivity, and first-order rate constants were calculated from slopes of lines drawn by eye through plots of log cpm *vs.* time. In the case of reactions followed to only a few per cent completion, aqueous portions of the reaction mixtures were assayed for radioactivity after the aromatic substrate (concentration in reaction mixture, 1 × 10^{-4} *M*) had been removed completely and zero-order rate constants were obtained from plots of cpm *vs.* time. These were then converted into initial rate constants expressed in per cent reaction per unit time by dividing by 100 times the total tritium content of an equivalent amount of reaction mixture; the latter quantity was determined by radioactive assay of stock aqueous solutions of aromatic substrates under exactly the same conditions as those used for the kinetic samples. All radioactive assays were performed by liquid scintillation counting with a Packard Model 314-EX liquid scintillation spectrometer.

Rates of deuterium exchange were determined using reaction mixtures nearly saturated in aromatic substrate (*ca.* 2 × 10^{-3} *M*). Kinetic samples, 2 ml in volume, were quenched in 1 ml of 0.2 *M* NaOH; the resulting solutions were shaken with 1 ml of carbon tetrachloride, and the carbon tetrachloride extracts were carefully removed by capillary pipet and were transferred directly into a mass spectrometer sample tube. The carbon tetrachloride was evaporated off, first by judicious application of vacuum and later, when only a little liquid remained, by passage of a gentle stream of filtered air through the sample tube. Mass spectral analyses were performed directly on the residues using a Consolidated Electrodynamics Corp. Model 21-130 spectrometer operating at an ionizing potential of 3.3 ev. Pilot experiments showed that these conditions produced only molecular ions. Deuterium contents were calculated assuming the natural abundance of carbon-13 to be 1.11%; rate constants were obtained from slopes of lines drawn by eye through plots of log (atom fraction D) *vs.* time.

All kinetic experiments were performed in constant temperature baths operating at 24.62 ± 0.02°; temperatures were measured using a platinum resistance thermometer which had been calibrated by the National Bureau of Standards.

Acknowledgment. The authors are indebted to the members of the Chemistry Department of the Massachusetts Institute of Technology, especially to Professor C. G. Swain, for the hospitality shown them while part of this work was being done.