Aromatic Protonation. IV. Activation Parameters for Acid-Catalyzed Aromatic Hydrogen Exchange in 1,3-Dimethoxybenzene and 1,3,5-Trimethoxybenzene[1]

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Abstract: The loss of tritium from 1,3-dimethoxybenzene-4-*t* was found to be catalyzed by formic acid in dilute aqueous buffer solutions. This indicates that the two-step, protonation–deprotonation reaction sequence established as the mechanism for aromatic hydrogen exchange in more reactive substrates applies to this substance as well; the range of substrate reactivity over which this mechanism is known to be operative now extends to 10^7. Rates of loss of tritium from 1,3-dimethoxybenzene-4-*t* catalyzed by formic and perchloric acids and from 1,3,5-trimethoxybenzene-2-*t* catalyzed by biphosphate ion and perchloric acid were each measured at several temperatures. These data permit the calculation of enthalpies and entropies of activation for proton transfer from these acids to the respective aromatic substrates. These activation parameters describe a pattern which can be understood in terms of solvation changes, and this, in turn, suggests that these proton transfers are, at least in part, adiabatic processes.

One of the rate-determining steps of acid-catalyzed aromatic hydrogen exchange is proton transfer from the catalyzing acid to the aromatic substrate. This reaction step is an example of an importqnt elementary process which occurs frequently in chemical transformations; it must, for example, take place in all acid-catalyzed reactions conducted in protic solvents. Quite often, however, this kind of proton transfer occurs in a rapidly established pseudo-equilibrium preceding the rate-determining step of the over-all reaction. In these cases, it is difficult to study the kinetics of proton transfer directly, and, as a consequence, this elementary process has not received the direct, detailed study warranted by its importance. Acid-catalyzed aromatic hydrogen exchange provides an opportunity for remedying this situation.

In this paper, we describe experiments which measure the rates of aromatic hydrogen exchange in 1,3-dimethoxybenzene and 1,3,5-trimethoxybenzene catalyzed by several acids. This provides data from which the enthalpies and entropies of activation for proton transfer from these acids to these substrates may be calculated. But before we could interpret the results of these experiments in this way, we first had to demonstrate that aromatic hydrogen exchange in these two substrates proceeds by the same mechanism, and we also had to examine the relationship between the observed activation parameters and those for the various steps of the exchange reaction. The results obtained will be seen to have a bearing on the recent proposal that a system undergoing proton transfer may not be in continuous equilibrium with the solvent and that proton transfer may therefore be a nonadiabatic process.[2]

Results

Kinetics of aromatic hydrogen exchange were measured by determining the rate at which tritium was lost from labeled aromatic substrates. All reaction mixtures were homogeneous solutions in a wholly aqueous solvent. Radioactive assay was usually performed on the aromatic substrate and data were collected over four to five exchange half-lives; these obeyed first-order kinetic laws exactly. In some experiments, determinations were extended to more than ten half-lives, and even here no deviations from first-order kinetics could be detected (Figure 1). This demonstrates that during these kinetic experiments the aromatic substrates were undergoing no reaction other than aromatic hydrogen exchange.

Under some of the conditions employed, loss of tritium from aromatic substrates was very slow: half-lives as great as 5 years were encountered. In these cases it was impractical to collect data for any appreciable extent of reaction, and an initial-rate method which measured the rate of increase of radioactivity in the aqueous portions of the reaction mixtures[1b,3] was used. Since these reactions were never followed to more than 3% completion, the increase of radioactivity in the solvent was linear with time. Good zero-order kinetic plots could be obtained, and zero-order rate constants were converted to first-order exchange constants by making use of the known total radioactivity of the aromatic substrate. It has already been demonstrated[3] that this initial-rate method gives exchange rate constants which are identical with those obtained by the other method.

Exchange of 1,3-Dimethoxybenzene-4-*t* with Formic Acid Buffers. Rates of loss of tritium from 1,3-dimethoxybenzene-4-*t* to formic acid–sodium formate buffer solutions were measured at 25 and 96°. The first-order exchange rate constants are presented in Table I. Figure 2 shows that these rate constants increase linearly with the concentration of undissociated formic acid present in the buffer solutions, and that this reaction is therefore subject to general acid catalysis.

Least-squares fitting of these data to linear expression by standard methods[4a] produced the equations[5]

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(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 III: A. J. Kresge and Y. Chiang, *J. Am. Chem. Soc.*, 89, 4411 (1967).

(2) (a) M. M. Kreevoy and R. A. Kretchmer, *ibid.*, 86, 2435 (1964); (b) E. Grunwald and E. Price, *ibid.*, 86, 2965, 2970 (1964); R. P. Bell, *Discussions Faraday Soc.*, 39, 16 (1965).

(3) A. J. Kresge and Y. Chiang, *J. Am. Chem. Soc.*, 83, 2877 (1961).

(4) 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: (a) p 222; (b) p 51.

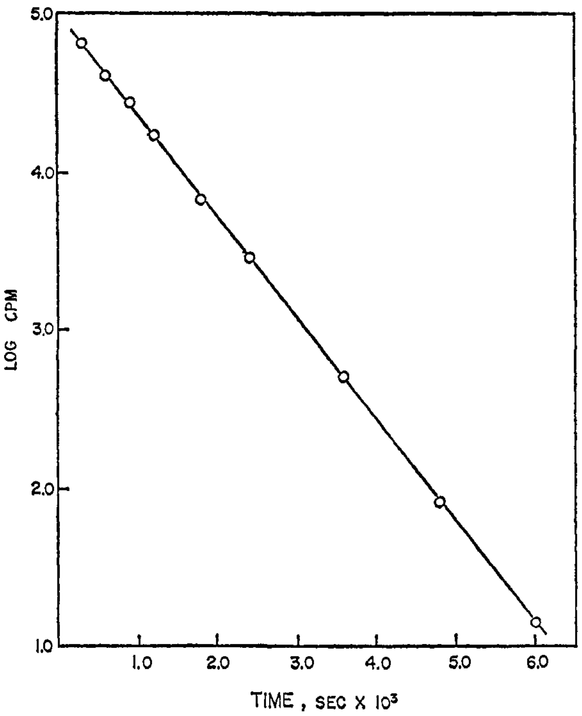

Figure 1. Kinetic plot for loss of tritium from 1,3-dimethoxybenzene-4-*t* to 5.23 *M* aqueous perchloric acid at 15.01°; k_{obsd} = 1.48×10^{-3} sec^{-1}. The data cover 12 exchange half-lives.

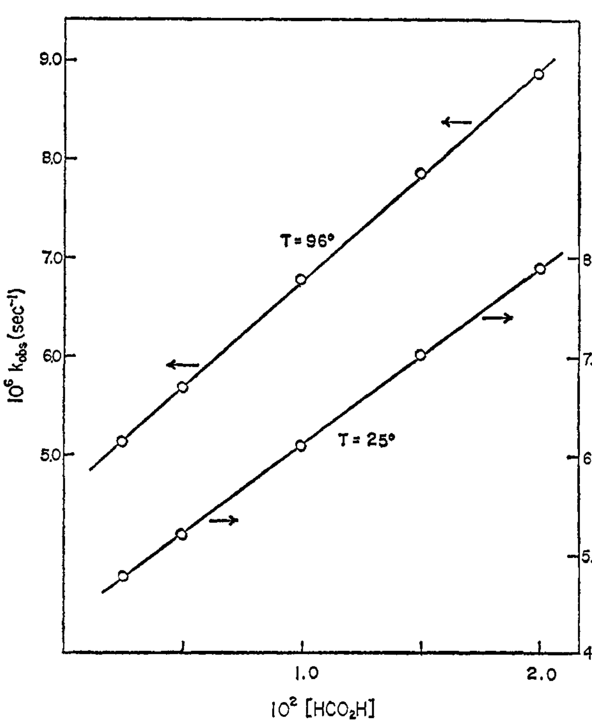

Figure 2. Relationship between formic acid concentration and observed rate constants for loss of tritium from 1,3-dimethoxybenzene-2-*t* to aqueous formic acid buffer solutions at 25 and 96°; buffer ratio = 1.00, μ = 0.100.

$$25°{:}\quad k_{obsd}(\text{sec}^{-1}) = (4.308 \pm 0.015) \times 10^{-9} + (1.787 \pm 0.012) \times 10^{-8}[\text{HA}] \quad (1)$$

$$96°{:}\quad k_{obsd}(\text{sec}^{-1}) = (4.611 \pm 0.017) \times 10^{-6} + (2.143 \pm 0.014) \times 10^{-5}[\text{HA}] \quad (2)$$

The intercepts of these expressions represent catalysis by the hydronium ion which is present at constant concentration in each set of buffer solutions. The catalytic constants for exchange through the hydronium ion at these temperatures were determined by measuring the rates of loss of tritium from 1,3-dimethoxybenzene-4-*t* to dilute perchloric acid solutions (Table I), and the hydronium ion concentration of each set of buffer solutions was then calculated. When these were combined with the buffer ratios in an appropriate manner, the following concentration ionization constants for formic acid at an ionic strength of 0.100 were obtained: 25°, 2.71×10^{-4} *M;* 96°, 2.14×10^{-4} *M*. These compare well with the values 2.91×10^{-4} *M* and 1.95×10^{-4} *M* estimated for these temperatures from the thermodynamic dissociation constants for infinitely dilute solutions[6a] and activity coefficients calculated using the Debye–Hückel equation with an ion-size parameter of 4.8 A.[6b] (The thermodynamic dissociation constant for 96° was obtained by extrapolating the known[6a] temperature dependence of this quantity.) This good agreement demonstrates that these kinetic results for catalysis in dilute acid solutions are internally consistent.

Table I. Rates of Loss of Tritium from 1,3-Dimethoxybenzene-4-*t* to Dilute Aqueous Acids

Catalyst	10^2[HA], *M*	T = 24.69° $10^9 k_{obsd}$, sec^{-1}	T = 95.82° $10^6 k_{obsd}$, sec^{-1}
HCO_2H[a]	2.50	4.748	5.133
HCO_2H[a]	5.00	5.198	5.680
HCO_2H[a]	10.00	6.103	6.773
HCO_2H[a]	15.00	7.008	7.841
HCO_2H[a]	20.00	7.866	8.878
		k_{HCO_2H}, M^{-1} sec^{-1}	
		17.87 ± 0.12[b]	21.43 ± 0.13[b]
$HClO_4$	0.2111	. . .	22.77
$HClO_4$	0.2192	17.57	. . .
$HClO_4$	1.055	. . .	114.1
$HClO_4$	1.096	86.5	. . .
		$k_{H_3O^+}$, M^{-1} sec^{-1}	
		7950 ± 70[b]	10,800 ± 200[b]

[a] In buffer solutions; [HA]/[NaA] = 2.00 and ionic strength = 0.100 (maintained by addition of NaCl). [b] Error estimates are standard deviations of mean values.

Exchange of 1,3-Dimethoxybenzene-4-*t* with Moderately Concentrated Perchloric Acid. Rates of loss of tritium from 1,3-dimethoxybenzene-4-*t* to moderately concentrated perchloric acid solutions were measured at 15, 25, 35, and 45°. The first-order exchange rate constants are presented in Table II. Figure 3 shows that the logarithums of these rate constants are linearly related to the acidity function H_0; least-squares fitting of the data produced the equations[5,7]

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(5) Error estimates are standard deviations of mean values.

(6) R. A. Robinson and R. H. Stokes, "Electrolyte Solutions," Butterworth and Co. (Publishers) Ltd., London, 1959: (a) p 519; (b) p 229.

(7) The temperature dependence of the H_0 scale in $HClO_4$ has not been determined, but the variations with temperature of this scale in H_2SO_4[8] and that of the H_R scale in H_2SO_4[9] are known to be small. Values of H_0 measured at 25°[10] were therefore used throughout this work.

(8) A. A. Gelbshtein, G. G. Shcheglova, and M. I. Temkin, *Zh. Neorgan. Khim.*, 1, 506 (1956).

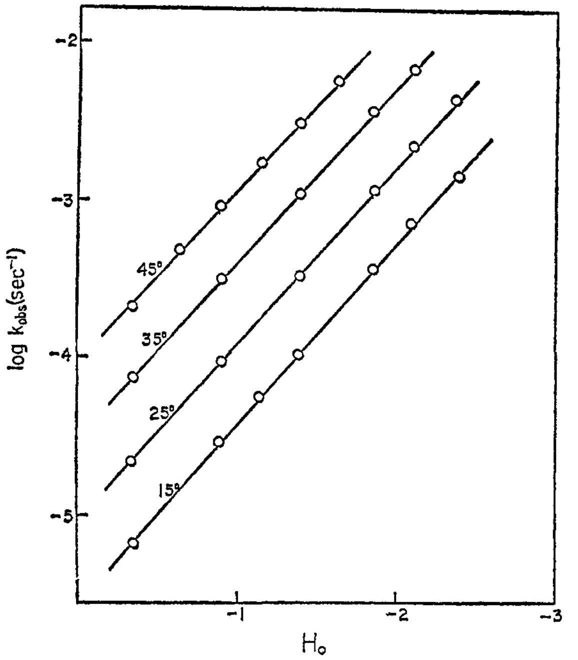

Figure 3. Relationship between the acidity function H_0 and logarithms of observed rate constants for loss of tritium from 1,3-dimethoxybenzene-2-*t* to aqueous perchloric acid solutions at 15, 25, 35, and 45°.

$$15.01°:\ \log k_{\text{obsd}}(\text{sec}^{-1}) = -(5.010 \pm 0.011) - (1.151 \pm 0.007)H_0 \quad (3)$$

$$24.69°:\ \log k_{\text{obsd}}(\text{sec}^{-1}) = -(4.495 \pm 0.017) - (1.139 \pm 0.009)H_0 \quad (4)$$

$$35.03°:\ \log k_{\text{obsd}}(\text{sec}^{-1}) = -(3.950 \pm 0.031) - (1.112 \pm 0.021)H_0 \quad (5)$$

$$45.01°:\ \log k_{\text{obsd}}(\text{sec}^{-1}) = -(3.463 \pm 0.005) - (1.085 \pm 0.005)H_0 \quad (6)$$

Table II. Rates of Loss of Tritium from 1,3-Dimethoxybenzene-4-*t* to Moderately Concentrated Aqueous Perchloric Acid

Temp, °C	Wt % $HClO_4$	$[HClO_4]$, *M*	$-H_0$[a]	$10^6 k_{\text{obsd}}$, sec^{-1}
15.01	10.04	1.065	0.36	0.6865
15.01	18.75	2.098	0.90	2.995
15.01	22.84	2.603	1.15	5.783
15.01	26.70	3.149	1.38	10.70
15.01	33.84	4.191	1.86	37.52
15.01	37.01	4.692	2.10	72.57
15.01	40.34	5.233	2.39	148.1
24.69	9.94	1.05	0.35	2.233
24.69	18.82	2.08	0.91	9.700
24.69	26.82	3.12	1.39	33.48
24.69	33.95	4.17	1.86	118.0
24.69	37.10	4.69	2.11	225.7
24.69	40.21	5.17	2.37	444.3
35.03	9.995	1.049	0.35	7.665
35.03	18.96	2.108	0.91	31.95
35.03	26.93	3.137	1.40	111.5
35.03	33.96	4.172	1.86	373.7
35.03	37.24	4.662	2.12	702.3
45.01	10.08	1.060	0.36	22.42
45.01	14.61	1.576	0.64	48.67
45.01	18.97	2.098	0.91	93.27
45.01	23.11	2.630	1.16	175.0
45.01	26.94	3.126	1.40	311.3
45.01	30.65	3.655	1.63	562.7

[a] K. Yates and H. Wai, *J. Am. Chem. Soc.*, **86**, 5408 (1964).

Table III. Rates of Loss of Tritium from 1,3,5-Trimethoxybenzene-2-*t* to Aqueous Perchloric Acid

Temp, °C	$10^2[HClO_4]$, *M*	$10^4 k_{\text{obsd}}$, sec^{-1}	$k_{H_3O^+}$, $M^{-1}\ \text{sec}^{-1}$
0.00	4.91	0.253	
0.00	4.91	0.282	
0.00	4.91	0.267	5.44 ± 0.20[a]
24.62	0.490	3.05 ± 0.02[a,b]	62.0 ± 0.5[a,b]
36.83	0.488	9.27	
36.83	0.488	9.30	
36.83	0.488	9.27	190.1 ± 0.3[a]

[a] Error estimates are standard deviations of mean values. [b] See ref 1b.

Table IV. Rates of Loss of Tritium from 1,3,5-Trimethoxybenzene-2-*t* to Aqueous Monohydrogen Phosphate–Dihydrogen Phosphate Buffer Solutions[a]

Temp, °C	$10^2[H_2PO_4^-]$, *M*	$10^7 \cdot [H_3O^+]$, *M*	$10^8 k_{\text{obsd}}$, sec^{-1}	$10^8 k_{H_3O^+} \cdot [H_3O^+]$, sec^{-1}	$k_{H_2PO_4^-}$, $M^{-1}\ \text{sec}^{-1}$
24.62	10.00	2.77	3.89	0.17	
24.62	10.00	2.77	3.92	0.17	
24.62	10.00	2.77	3.94	0.17	$(3.75 \pm 0.02) \times 10^{-7}$[b]
39.91	9.95	2.87	14.58	0.68	
39.91	9.95	2.87	14.74	0.68	
39.91	9.95	2.87	14.04	0.68	$(13.84 \pm 0.27) \times 10^{-7}$[b]
55.40	9.89	2.85	43.6	2.3	
55.40	9.89	2.85	43.6	2.3	
55.40	9.89	2.85	44.8	2.3	$(42.1 \pm 0.5) \times 10^{-7}$[b]

[a] $[NaH_2PO_4] = [Na_2HPO_4] = 0.100\ M$. [b] Error estimates are standard deviations of mean values.

Exchange of 1,3,5-Trimethoxybenzene-2-*t* with Dilute Perchloric Acid. Rates of loss of tritium from 1,3,5-trimethoxybenzene-2-*t* to solutions approximately 0.05 *M* in perchloric acid were measured at 0, 25, and 37°. The data obtained at 25° have already been reported;[1b] a summary of these together with a listing of the data for the other temperatures appears in Table III.

Exchange of 1,3,5-Trimethoxybenzene-2-*t* with Phosphate Buffers. Rates of loss of tritium from 1,3,5-trimethoxybenzene-2-*t* to sodium dihydrogen phosphate–sodium monohydrogen phosphate buffer solutions were measured at 25, 40, and 55°. First-order exchange rate constants appear in Table IV. At the buffer ratio used (1.00), most of the isotope exchange reaction occurs through catalysis by dihydrogen phosphate ion, but a significant amount does take place through catalysis by the hydronium ion. In order to correct for this secondary reaction, the hydronium ion concentration of each buffer solution was calculated using the known infinite dilution ionization constants of dihydrogen phosphate ion at the necessary temperatures[11a] and activity coefficients obtained from the Debye–Hückel equation with an ion-size parameter of 4.8 A.[6b] From the known temperature dependence of the hydronium

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(9) E. M. Arnett and R. D. Bushick, *J. Am. Chem. Soc.*, **86**, 1564 (1964).

(10) K. Yates and H. Wai, *ibid.*, **86**, 5408 (1964).

(11) H. S. Harned and B. B. Owen, "The Physical Chemistry of Electrolytic Solutions," Reinhold Publishing Corp., New York, N. Y., 1958: (a) p 760; (b) p 667.

ion catalyzed reaction (Table III), hydronium ion contributions to the observed first-order exchange rate constants were then estimated. These amounted to about 5% of the observed rates of exchange.

Calculation of Activation Parameters. Ethalpies and entropies of activation were calculated using the following version of the thermodynamic formulation of reaction rates.

$$\log (k_2/T) = 10.319 + \Delta S^{\ddagger}/4.574 - \Delta H^{\ddagger}/4.574T \quad (7)$$

Here k_2 is a bimolecular rate constant expressed in units of M^{-1} sec^{-1} and the other symbols have their usual meanings. In no case could deviations from a linear dependence of log (k_2/T) on $1/T$ be detected. The activation parameters obtained are presented in Table V; listed error estimates were obtained either from the goodness of the least-squares fit of values of log (k_2/T) and $1/T$ to eq 7[6a] or, when data for only two temperatures were available, by propagation of the observed uncertainties in the average values of k_2.[6b] These procedures produced errors of variable magnitude; a uniform and yet conservative estimate of the reliability of these results would be an uncertainty of 0.5 kcal/mole in enthalpy of activation and 1.0 cal deg^{-1} mole^{-1} in entropy of activation.

Table V. Activation Parameters for Tritium Loss from Labeled Aromatic Substrates

Substrate	Catalyst	$\Delta H^{\ddagger}$,[a] kcal mole^{-1}	$\Delta S^{\ddagger}$,[a] cal deg^{-1} mole^{-1}
1,3-Dimethoxybenzene-4-*t*	H_3O^+ [b]	21.5 ± 0.1	-9.7 ± 0.1
1,3-Dimethoxybenzene-4-*t*	H_3O^+ [c]	22.1 ± 0.3	-7.9 ± 0.9
1,3-Dimethoxybenzene-4-*t*	HCO_2H	21.1 ± 0.1	-23.1 ± 0.1
1,3,5-Trimethoxybenzene-2-*t*	H_3O^+	15.6 ± 0.1	-16.3 ± 0.6
1,3,5-Trimethoxybenzene-2-*t*	$H_2PO_4^-$	14.7 ± 0.1	-38.4 ± 0.4

[a] Error estimates are standard deviations of mean values. [b] Dilute solutions. [c] Concentrated solutions.

The standard state to which these activation parameters refer is unit molar concentration of both the aromatic substrate and the catalyst acid. In dilute acid solutions, the systems behaved ideally (first-order exchange constants increased linearly with acid concentrations) and calculation of k_2 for this standard state was straightforward. In moderately concentrated perchloric acid solutions, however, appreciable deviations from ideal behavior were encountered: exchange rate constants increased much more rapidly than acid concentration and were, in fact, proportional to the acidity function h_0 raised to some power slightly greater than unity. Equations 3–6 were therefore used to calculate values of exchange rate constants (k_{obsd}) at $h_0 = 0.100$, which is the acidity of aqueous perchloric acid at which acid concentration first begins to deviate from h_0.[12] These first-order rate constants were then converted to values of k_2 by dividing by the concentration of perchloric acid at this acidity (0.100 M). This method of obtaining activation parameters from data for concentrated acid solutions produced values which agree well with those determined from data for dilute solutions (Table V).

Discussion

Reaction Mechanism. The available experimental evidence indicates that acid-catalyzed aromatic hydrogen exchange occurs through a two-step reaction sequence.

$$\text{H'Ar} + \text{HA} \rightleftharpoons \text{H'ArH}^+ + \text{A}^- \rightleftharpoons \text{HAr} + \text{H'A} \quad (8)$$

This reaction mechanism implies general acid catalysis and observation of this form of catalysis in dilute buffer solutions constitutes the most compelling argument for this reaction sequence. General acid catalysis in aromatic hydrogen exchange was first detected with 1,3,5-trimethoxybenzene as the aromatic substrate,[3,13] then with azulene,[14] and most recently with guaiazulene,[14b] 2-methyl- and 1,2-dimethylindole,[15] and cycl[3.2.2]azine.[16] All of these substrates are very reactive toward aromatic hydrogen exchange; the least reactive member of the group, 1,3,5-trimethoxybenzene, undergoes hydronium ion catalyzed exchange 10^{10} times faster than benzene. It has been pointed out that a change in exchange mechanism may occur with decreasing substrate reactivity,[17] and, since one of the substrates used in the present study, 1,3-dimethoxybenzene, is nearly 10^3 times less reactive than 1,3,5-trimethoxybenzene, it would seem advisable to look into the matter of reaction mechanism with this substance.

The alternative mechanism proposed for aromatic hydrogen exchange in substrates of low reactivity differs from the sequence of eq 8 in that proton transfer from catalyst to substrate occurs in a rapidly established pseudo-equilibrium preceding rate-determining, unimolecular isomerization of the substrate conjugate acid. This sequence of reactions implies specific hydrogen ion catalysis, and the change in reaction mechanism will therefore be accompanied by a shift from general acid catalysis to catalysis only by the hydrogen ion. But the data presented in Figure 2 show clearly that exchange in 1,3-dimethoxybenzene is subject to general acid catalysis. It is therefore safe to conclude that no change of reaction mechanism has occurred and that exchange in 1,3-dimethoxybenzene and 1,3,5-trimethoxybenzene is mechanistically homogeneous. This extends to some seven powers of ten the range of reactivity over which the reaction mechanism of eq 8 is known to operate.

Relationship between Observed Activation Parameters and Those for the First Forward Step. The transition states of the two steps of the reaction mechanism presented in eq 8 are isotopic isomers. The free energies of these transition states can therefore differ by no more than an isotope effect, and neither of these two steps can be fully rate determining. This means that observed activation parameters obtained from rate constants for the over-all reaction must be composite functions of activation parameters for each of the individual reaction steps.[18] It is possible to show, however, that the observed values consist principally

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[12] A. J. Kresge and H. J. Cheng, unpublished data.

[13] A. J. Kresge and Y. Chiang, *J. Am. Chem. Soc.*, **81**, 5509 (1959).

[14] (a) J. Colapietro and F. A. Long, *Chem. Ind.* (London), 1056 (1960); (b) J. Schulze and F. A. Long, *J. Am. Chem. Soc.*, **86**, 331 (1964); R. J. Thomas and F. A. Long, *ibid.*, **86**, 4770 (1964).

[15] B. C. Challis and F. A. Long, *ibid.*, **85**, 2524 (1963).

[16] R. J. Thomas and F. A. Long, *J. Org. Chem.*, **29**, 3411 (1964).

[17] L. Melander, *Arkiv Kemi*, **17**, 291 (1961).

[18] M. M. Kreevoy in "Technique of Organic Chemistry," Vol. VIII, Part II, S. L. Friess, E. S. Lewis, and A. Weissberger, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, p 1372.

of activation parameters for the first step in the forward direction, and that the differences between the two are functions of quantities which either are known or can easily be estimated.

In all of the kinetic experiments reported here, the aromatic substrate was present at low concentration in a wholly aqueous solvent. Tritium was used as a tracer and it was placed initially only in the aromatic substrate. Under these conditions, reincorporation of the isotopic label into the aromatic substrate proceeds at a negligible rate and the exchange reaction may be considered to be nonreversible.[1b] The reaction scheme of eq 8 therefore reduces to

$$\mathrm{TAr} + \mathrm{HA} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{TArH^+} + \mathrm{A^-} \xrightarrow{k_2} \mathrm{HAr} + \mathrm{TA} \qquad (9)$$

and observed second-order rate constants are the following simple function of rate constants for the individual reaction steps.[1b]

$$k_{\mathrm{obsd}} = k_1/(1 + k_{-1}/k_2) \qquad (10)$$

It then follows that

$$\Delta F^{\ddagger}_{\mathrm{obsd}} = \Delta F_1^{\ddagger} + RT\ln(1 + k_{-1}/k_2) \qquad (11)$$

and, using the relationships

$$(\mathrm{d}/\mathrm{d}T)(\Delta F^{\ddagger}/T) = -\Delta H^{\ddagger}/T^2 \qquad (12)$$

$$T\Delta S^{\ddagger} = \Delta H^{\ddagger} - \Delta F^{\ddagger} \qquad (13)$$

it can be shown that

$$\Delta H^{\ddagger}_{\mathrm{obsd}} = \Delta H_1^{\ddagger} + \frac{(k_{-1}/k_2)(\Delta H_2^{\ddagger} - \Delta H_{-1}^{\ddagger})}{1 + k_{-1}/k_2} = \Delta H_1^{\ddagger} + A \qquad (14)$$

$$\Delta S^{\ddagger}_{\mathrm{obsd}} = \Delta S_1^{\ddagger} + \frac{(k_{-1}/k_2)(\Delta H_2^{\ddagger} - \Delta H_{-1}^{\ddagger})}{T(1 + k_{-1}/k_2)} - R\ln(1 + k_{-1}/k_2) = \Delta S_1^{\ddagger} + B \qquad (15)$$

The ratio of rate constants, k_{-1}/k_2, which appears in eq 14 and 15 is the intramolecular hydrogen–tritium isotope effect on acid-catalyzed aromatic hydrogen exchange.[19] This isotope effect has been evaluated as 20.3 for exchange in 1,3,5-trimethoxybenzene catalyzed by the hydronium ion,[1b] and it can be estimated for the other substrate–catalyst pairs of Table V from its observed dependence on ΔpK_a (pK_a substrate − pK_a catalyst) in a number of systems.[20] Values of k_{-1}/k_2 obtained in this way are listed in Table VI. Hydrogen isotope effects of this magnitude are likely to be largely zero-point energy effects, and the quantity $\Delta H_2^{\ddagger} - \Delta H_{-1}^{\ddagger}$ can therefore be approximated by $RT\ln k_{-1}/k_2$. This permits complete evaluation of the terms A and B of eq 14 and 15, the quantities by which the observed activation parameters differ from $\Delta H_1^{\ddagger}$ and $\Delta S_1^{\ddagger}$. In none of the cases of interest here is either of these quantities more than a few per cent of $\Delta H^{\ddagger}_{\mathrm{obsd}}$ or $\Delta S^{\ddagger}_{\mathrm{obsd}}$ (Table VI), and the approximations made in their calculation are therefore not critical. The derived values of $\Delta H_1^{\ddagger}$ and $\Delta S_1^{\ddagger}$ are listed in Table VI.

Table VI. Calculation of Activation Parameters on the First Forward Step of Aromatic Hydrogen Exchange

Systems	k_{-1}/k_2 (at 25°)	A,[a] kcal mole^{-1}	B,[b] cal deg^{-1} mole^{-1}	$\Delta H_1^{\ddagger}$, kcal mole^{-1}	$\Delta S_1^{\ddagger}$, cal deg^{-1} mole^{-1}
1,3-Dimethoxybenzene-4-t + H_3O^+	13[c]	1.4	−0.2	20.4[d]	−8.3[d]
1,3-Dimethoxybenzene-4-t + HCO_2H	5[c]	0.8	−0.3	20.3	−22.2
1,3,5-Trimethoxybenzene-2-t + H_3O^+	20[e]	1.7	−0.1	13.9	−15.9
1,3,5-Trimethoxybenzene-2-t + $H_2PO_4^-$	6[c]	0.9	−0.2	13.8	−37.6

[a] See eq 14. [b] See eq 15. [c] Estimated from the correlation presented in ref 20. [d] Based on the average of the two values measured in dilute and in concentrated perchloric acid. [e] Reference 1b.

Enthalpy and Entropy of Ionization of the Hydronium Ion. It is useful, in interpreting enthalpies and entropies of activation for aromatic protonation, to be able to compare these quantities with the enthalpies and entropies of ionization of the protonating acids. These data are readily available for the weak acids of Table VI. The hydronium ion, however, presents a special problem because it itself is the species formed in the ionization of all other acids in aqueous solutions.

The usual way of handling this matter is to treat the hydronium ion as an undissociated acid and to consider its ionization as being proton transfer to a molecule of water.[21a]

$$\mathrm{H_3O^+} + \mathrm{H_2O} \rightleftharpoons \mathrm{H_3O^+} + \mathrm{H_2O} \qquad (16)$$

Since this reaction produces no net chemical change, both ΔH_i and ΔS_i must be zero. This treatment, however, implies that the ionization constant of the hydronium ion is unity. While this is correct insofar as the equilibrium constant of eq 16 is 1, it does not conform to the usual practice of including the concentration of water in the acidity constant of a weak acid.

$$\mathrm{HA} + \mathrm{H_2O} \rightleftharpoons \mathrm{H_3O^+} + \mathrm{A^-} \qquad (17)$$

$$K = \frac{(\mathrm{H_3O^+})(\mathrm{A^-})}{(\mathrm{HA})(\mathrm{H_2O})} \qquad K_a = K(\mathrm{H_2O}) = \frac{(\mathrm{H_3O^+})(\mathrm{A^-})}{(\mathrm{HA})} \qquad (18)$$

The stoichiometric concentration of water in dilute aqueous solutions is 55, and, following usual practice, the conventional acidity constant of the hydronium ion must be 55 ($K_a = K(\mathrm{H_2O}) = 1.00 \times 55 = 55$).[21a] Since the density of water changes slightly with temperature, its molar concentration and therefore this acidity constant are somewhat temperature dependent. From the variation near 25°, a value of −0.05 kcal mole^{-1} may be calculated for ΔH_i and a value of +8.1 cal deg^{-1} mole^{-1} for ΔS_i.

In a number of correlations of acid strength with catalytic power, however, the hydronium ion appears to be a less effective proton transfer agent than this value of 55 for its acidity constant would imply.[21b,22] Since an appreciable fraction of the water molecules

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[19] This is the isotope effect designated $^{\mathrm{T}}k_2{}^{\mathrm{H}}/^{\mathrm{H}}k_2{}^{\mathrm{T}}$ in ref 1b; it includes both primary and secondary effects.

[20] J. L. Longridge and F. A. Long, *J. Am Chem. Soc.*, **89**, 1292 (1967).

[21] R. P. Bell, "Acid-Base Catalysis," Oxford University Press, London, 1941: (a) p 91; (b) p 93.

[22] A. J. Kresge, L. E. Hakka, S. Mylonakis, and Y. Sato, *Discussions Faraday Soc.*, **39**, 75 (1965); M. M. Kreevoy, T. S. Straub, W. V. Kayser, and J. L. Melquist, *J. Am. Chem. Soc.*, **89**, 1201 (1967).

in dilute aqueous solutions is associated in rather large clusters, it has been suggested that only the concentration of unassociated water and not the stoichiometric water concentration should be used in calculating the hydronium ion acidity constant.[23] This proposal is supported by the recent deduction that protonic conduction in aqueous solutions at ordinary temperatures takes place by proton transfer to unassociated water molecules only.[24] The fraction of unassociated water molecules in liquid water has recently been estimated from near-infrared measurements,[25] and these results are consistent with a detailed theory of the structure of water which predicts thermodynamic functions with considerable accuracy.[26] These data give 0.314 as the fraction of unassociated water at 25°, and this makes the concentration of unassociated water molecules, and also the acidity constant of the hydronium ion, 17.4 *M*. From the temperature dependence of this quantity near 25°,[25] values of 1.10 kcal mole^{-1} and 6.0 cal deg^{-1} mole^{-1} may be calculated for ΔH_i and ΔS_i, respectively.

Enthalpies of Activation. The data of Table VI show that the enthalpy of activation for proton transfer to 1,3,5-trimethoxybenzene is *ca.* 6.5 kcal mole^{-1} less than that for proton transfer to 1,3-dimethoxybenzene. This is consistent with the electrophilic nature of this reaction and the electron-donating properties of a methoxyl group situated *ortho* to the site of the reaction.

The data also show that this substrate difference of 6.5 kcal mole^{-1} is preserved for all of the systems investigated. This would seem to imply that these enthalpies of activation are independent of the nature of the protonating acid and that all of the acids, therefore, are making the same contribution to $\Delta H^{\ddagger}$. In this connection, it is interesting to note that these acids also have similar entropies of ionization in aqueous solution: for formic acid, $\Delta H_i = -0.02$ kcal mole^{-1};[11b] for biphosphate ion, $\Delta H_i = 0.82$ kcal mole^{-1};[11b] and for hydronium ion, $\Delta H_i = 1.1$ kcal mole^{-1}. Thus, insofar as energy changes accompanying protonation are concerned, these kinetic processes are remarkably similar to related equilibrium reactions.

Entropies of Activation. In contrast to the enthalpy changes, the entropies of activation of Table VI vary markedly with the nature of the protonating acid. The data show a regular progression, covering some 30 cal deg^{-1} mole^{-1}, to increasingly negative values of $\Delta S^{\ddagger}$ as the charge type of the acid goes from positive through neutral to negative. This trend is readily understood in terms of differences in hydration of the relevant initial and transition states. The hydronium ion is known to be strongly solvated in aqueous solutions,[27] whereas there is evidence that protonated aromatics such as 1,3-dimethoxybenzene or 1,3,5-trimethoxybenzene are hydrated to a much smaller extent.[28] Proton transfer from the hydronium ion to either of these aromatic substrates will therefore be accompanied by liberation of some solvating water molecules, and this will raise the entropy of the system making a positive contribution to $\Delta S^{\ddagger}$. Proton transfer from a neutral or negatively charged acid, on the other hand, will result in an increase in solvation, for here new ionic species are being formed. This will make a negative contribution to $\Delta S^{\ddagger}$, and this contribution should be greater for a negatively charged acid where a dinegative ion is formed than for a neutral acid where a mononegative ion is formed.

This interpretation of entropy changes in terms of solvation is supported by the observed effect of a change in substrate reactivity on $\Delta S^{\ddagger}$. The data of Table VI show that, for proton transfer from the hydronium ion, $\Delta S^{\ddagger}$ for 1,3,5-trimethoxybenzene is *ca.* 7.5 cal deg^{-1} mole^{-1} more negative than $\Delta S^{\ddagger}$ for 1,3-dimethoxybenzene. Since 1,3,5-trimethoxybenzene is the more reactive of these two substrates, its transition state will occur at an earlier position on the reaction coordinate than the transition state for 1,3-dimethoxybenzene.[29] This means that less hydronium ion desolvation will have occurred at the transition state for proton transfer to 1,3,5-trimethoxybenzene than for proton transfer to 1,3-dimethoxybenzene. Since this desolvation makes a positive contribution to $\Delta S^{\ddagger}$, $\Delta S^{\ddagger}$ for 1,3,5-trimethoxybenzene should be more negative than $\Delta S^{\ddagger}$ for 1,3-dimethoxybenzene.[30,33]

The order of entropy changes seen in Table VI is also the order in which the entropies of ionization of the protonating acids stand: for the hydronium ion, $\Delta S_i = +6.0$ cal deg^{-1} mole^{-1}; for formic acid, $\Delta S_i = -18$ cal deg^{-1} mole^{-1};[11b] and for biphosphate ion, $\Delta S_i = -30$ cal deg^{-1} mole^{-1}.[11b] The individual correspondence is not as good as was seen to be the case with enthalpy changes, but this is hardly to be expected for a comparison involving a quantity whose magnitude depends strongly on solvation changes which cannot be the same for the kinetic and equilibrium processes and will, moreover, vary according to the positions the various transition states occupy on the reaction coordinate. There is, however, one relationship which presists in all the systems: $\Delta S^{\ddagger}$ is always more negative than ΔS_i. This is consistent with the bimolecular nature of the kinetic process in which translational and rotational degrees of freedom are converted into more restrictive vibrational motions.[31b] It may be significant that the difference between $\Delta S^{\ddagger}$

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(23) R. P. Bell, *Trans. Faraday Soc.*, **39**, 253 (1943).

(24) B. E. Conway, J. O'M. Bockris, and H. Linton, *J. Chem. Phys.*, **24**, 834 (1956); R. A. Horne and R. A. Courant, *J. Phys. Chem.*, **69**, 2224 (1965).

(25) K. Buijs and G. R. Choppin, *J. Chem. Phys.*, **39**, 2035 (1963).

(26) J. Vand and W. A. Senior, *ibid.*, **43**, 1869, 1873, 1878 (1965).

(27) R. P. Bell, "The Proton in Chemistry," Cornell University Press, Ithaca, N. Y., 1959, p 19.

(28) 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.*, **85**, 1278 (1963).

(29) G. S. Hammond, *ibid.*, **77**, 334 (1955).

(30) A difference in $\Delta S^{\ddagger}$ for these two substrates might also arise from the constraint imposed on the system as rotation about carbon-oxygen bonds is restricted in the transition state through increased conjugative electron release from methoxy groups or steric interference from the protonating acid. Since 1,3,5-trimethoxybenzene has one more methoxy group than 1,3-dimethoxybenzene, this would make $\Delta S^{\ddagger}$ for 1,3,5-trimethoxybenzene more negative than $\Delta S^{\ddagger}$ for 1,3-dimethoxybenzene. This effect, however, cannot account for the entire difference of 7.6 cal deg^{-1} mole^{-1}. It will contribute only about 3 cal deg^{-1} mole^{-1} provided that rotation about this bond is initially completely free;[31a] if, as is probable,[32] a barrier to rotation does exist in the initial state, the effect will be much less.[31a]

(31) (a) L. L. Schaleger and F. A. Long, *Advan. Phys. Org. Chem.*, **1**, 6 (1963); (b) *ibid.*, **1**, 24 (1963).

(32) G. W. Wheland, "Resonance in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1955, p 241.

(33) The effect of substrate reactivity on $\Delta S^{\ddagger}$ found here is opposite to that discovered in a recent correlation of these two variables for a number of rate-determining proton-transfer reactions.[34] This correlation, however, includes data for concentrated acid solutions where other effects might be operating to mask the trend noted here.

(34) S. M. A. Matesich, *J. Org. Chem.*, **32**, 1258 (1967).

and ΔS_i is largest for proton transfer from the hydronium ion, for only in this case is the bimolecular lowering of $\Delta S^{\ddagger}$ of opposite sign to the contribution made by solvation and only here, therefore, can the bimolecular effect not be masked by incomplete changes in solvation.

Nonequilibrium Transition-State Solvation. It has been suggested recently[2] that proton transfer from an acid to a substrate may not be a truly adiabatic process because the reactants may not be in continuous equilibrium with the solvent as they pass through the transition state. The dielectric relaxation time of water, 10^{-10} to 10^{-11} sec,[35] is greater than the time required for a proton jump to occur between suitably oriented and activated molecules, 10^{-12} to 10^{-13} sec.[36] This would imply that the reorganization of solvent, and therefore solvation, cannot keep up with proton transfer in aqueous solution. Additional evidence for this hypothesis has been adduced from entropies of activation: it is argued[2a] that $\Delta S^{\ddagger}$ for a number of rate-determining proton transfers in water is more negative than expected and that this is because desolvation of the proton does not take place before the transition state is reached.

The explanation of the difference in $\Delta S^{\ddagger}$ for proton transfer to 1,3-dimethoxybenzene and 1,3,5-trimethoxybenzen presented above would seem to negate this argument. In addition, the general parallelism between the activation parameters of Table VI and corresponding quantities for the equilibrium ionization of the catalyst acids is inconsistent with nonequilibrium transition-state solvation, for the ionization processes are not time dependent and cannot be subject to nonadiabatic effects of this type. The correspondence between equilibrium and kinetic parameters, on the other hand, is not perfect, and this does leave room for some nonequilibrium transition-state solvation. The presently available data, therefore, while suggesting an adiabatic kinetic situation, do not resolve the issue completely. It is hoped that a comparison of activation parameters for aromatic protonation with corresponding quantities for the more closely related equilibrium process, equilibrium aromatic protonation,[28] might be more definitive, and experiments are therefore being conducted to supply the necessary information.

Experimental Section

Materials. 1,3,5-Trimethoxybenzene-2-*t* was prepared from 2,4,6-trimethoxyphenyllithium by the method already described.[3] 1,3-Dimethoxybenzene-4-*t* was synthesized by adding an equivalent amount of tritiated water to a solution of 2,4-dimethoxyphenylmagnesium bromide prepared from 2,4-dimethoxybromobenzene and magnesium in tetrahydrofuran at 65°. The resulting mixture was hydrolyzed with saturated aqueous ammonium chloride, and the product was removed and was purified to constant specific activity by fractional distillation. When aqueous acid was used to perform this hydrolysis instead of ammonium chloride solution, the product was found to contain varying amounts (of the order of 5%) of the isomeric 1,3-dimethoxybenzene-2-*t*. This could easily be detected by kinetic experiments: plots of log (aromatic radioactivity) *vs.* time began to show curvature after a few half-lives, and suitable analysis of the data showed that two parallel detritiation reactions were occurring. The slower of the two rate constants obtained in this way was identical with that measured using an authentic sample of 1,3-dimethoxybenzene-2-*t* prepared by the reaction of tritiated water with 2,6-dimethoxyphenyllithium.

All other materials were reagent grade chemicals available commercially. Buffer solutions were prepared by weight from the pure components, and perchloric acid solutions were assayed by standard acidimetric methods. Corrections for concentration changes produced by changes in volume were made in the case of reactions carried out at temperatures different from that at which the solutions were prepared.

Kinetic Procedure. Kinetics were measured by the two methods already described.[1b,3] The initial-rate method was used for the experiments with 1,3-dimethoxybenzene in dilute acids at 25° and for the experiments with 1,3,5-trimethoxybenzene in phosphate buffers; the other method was used for all other determinations. The reactions at 96° were conducted in sealed ampoules; those at the lower temperatures, in glass-stoppered flasks. Bath temperatures were controlled to ±0.02° and were measured with a platinum resistance thermometer which had been calibrated by the National Bureau of Standards.

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(35) J. B. Hasted, *Progr. Dielectrics*, 3, 101 (1961).

(36) T. Ackermann, *Z. Physik. Chem.*, 27, 34 (1961).

The Protonation Site of a Sulfonamide and the Stereochemistry of Proton Exchange

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Abstract: Variable-temperature nmr studies of N-methyl-5-chloro-1,2-benzisothiazoline 1,1-dioxide (compound E in text) in fluorosulfonic acid prove unequivocally that (a) protonation occurs on the nitrogen of the sulfonamide and (b) the nitrogen proton of the conjugate acid of E exchanges with retention of configuration. The results are discussed in terms of the electronic structure of sulfonamides.

It has been shown with the aid of nmr spectroscopy that amides in strong acid protonate at the oxygen, thereby producing a resonance-stabilized cation in which the positive charge is distributed between the oxygen and nitrogen.[1] Sulfonamides might likewise

$$\underset{\displaystyle \text{O}}{\overset{}{\text{RC}}}\ddot{\text{N}}\text{R}_2 \xrightleftharpoons{\text{H}^+} \underset{\displaystyle {}^+\text{OH}}{\text{RC}}\ddot{\text{N}}\text{R}_2 \longleftrightarrow \underset{\displaystyle \text{OH}}{\text{RC}}{=}\overset{+}{\text{N}}\text{R}_2$$

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(1) R. J. Gillespie and T. Birchall, *Can. J. Chem.*, 41, 148 (1963).