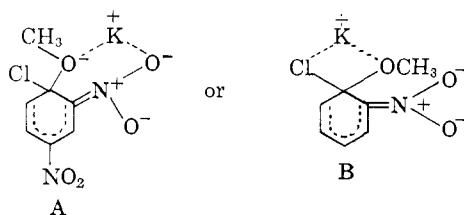


which the $-\text{OCH}_3$ can replace a methanol of solvation. Because of its smaller size, the Li^+ makes the H^+ atom on the methanol of solvation somewhat more acidic than the other two cations. Loss of this H^+ to the solution and its subsequent neutralization provides a mechanism by which an *intimate ion pair* is formed readily. However, the ion pair association of Li^+ with other anions may well be less, for the more extensive solvation of Li^+ has increased its apparent size.⁸

If one makes the assumption that $k_{ip} > k_i$ for KOCH_3 , $k_{ip} = k_i$ for NaOCH_3 and $k_{ip} < k_i$ for LiOCH_3 , the data of Fig. 4 may be explained by eq. 2. On the basis of eq. 2, since α decreases as concentration rises, the contribution of k_{ip} ($1 - \alpha$) to k_{obs} becomes larger. From this, it follows that k_{obs} for KOCH_3 will increase, k_{obs} for NaOCH_3 will not change, and k_{obs} for LiOCH_3 will decrease with increasing MOCH_3 concentration.

The implication of eq. 2 is that the transition state for the ion pair (K^+ , $-\text{OCH}_3$) and 2,4-DNCB is more favorable than that of $-\text{OCH}_3$ and 2,4-DNCB. Possibilities of a cyclic intermediate of the type A or B are suggested.

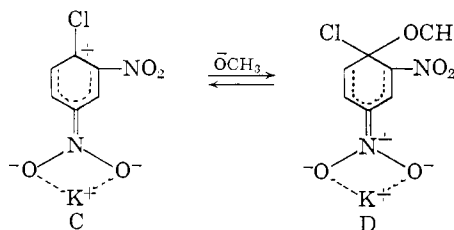


The objection to the analysis of eq. 2 is given by Brändström⁷ as follows: "From the fact that elec-

(8) J. R. Graham, G. S. Kell and A. R. Gordon, *J. Am. Chem. Soc.*, **79**, 2352 (1957).

trons are withdrawn to some extent from the anion in forming the ion pair, it might be expected that the ion pair has a much lower reactivity than the free anion, if there is no steric factor that makes the reaction with the ion pair especially favored." It is to be noted, however, that a cyclic mechanism to account for the reactivity of the ion pair is postulated in several reactions by Brändström.

The second hypothesis is that the rate depends upon the concentration of free methoxide ion and the reactivity of 2,4-DNCB. This assumes that $k_{ip} = 0$. The rate observed should be less than k_i for all concentrations if the reactivity of 2,4-DNCB does not change as the ionic strength increases, for α decreases with all three alkali methoxides. To account for the rate increase with KOCH_3 , some increase in the reactivity of 2,4-DNCB must occur, due to association of the salt with 2,4-DNCB. A possible form is



The association of the K^+ in form C facilitates the attack of the OCH_3^- , or in form D stabilizes the transition state. To account for Fig. 4, the association of M^+ in form C or D would have to be in the order $\text{K}^+ > \text{Na}^+ > \text{Li}^+$. This is the order of ion pairing, as noted by Gordon⁸ for (M^+ , Cl^-).

Acknowledgment.—The authors gratefully acknowledge helpful suggestions by the referees.

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, BROOKHAVEN NATIONAL LABORATORY, UPTON, N. Y.]

Slow Proton Transfer Reactions. III. The Mechanism of Acid-catalyzed Aromatic Hydrogen Exchange in 1,3,5-Trimethoxybenzene^{1,2}

BY A. J. KRESGE³ AND Y. CHIANG

RECEIVED FEBRUARY 7, 1961

General acid catalysis has been detected in the exchange of aromatic hydrogen of trimethoxybenzene: rates of loss of tritium from 1,3,5-trimethoxybenzene-2-*t* to seven acids ranging in strength from H_3O^+ to H_2O conform to the Brønsted relation $k_A = 4.72 \times 10^{-2} (K_A)^{0.518}$. This fact is inconsistent with a previously assigned mechanism for aromatic hydrogen exchange; that is, the scheme consisting of reversible formation of a loose complex between proton and aromatic substrate followed by slow intramolecular isomerization of this complex. Instead, general acid catalysis indicates a simple slow proton transfer mechanism for exchange. The loss of tritium from 1,3,5-trimethoxybenzene-2-*t* is not catalyzed by bases. This shows that this proton transfer is not a concerted process, but that reaction takes place in two discrete steps: proton addition to give a phenonium ion followed by proton abstraction to give exchanged trimethoxybenzene. This mechanism, unlike the one first proposed for aromatic hydrogen exchange, is wholly consistent with generally accepted mechanistic schemes for other electrophilic aromatic substitutions.

Introduction

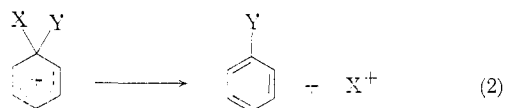
The simplest mechanism which is consistent with all existing data for electrophilic aromatic substi-

(1) Research performed under the auspices of the U. S. Atomic Energy Commission.

(2) Presented in part at the 137th National Meeting of the American Chemical Society, Cleveland, Ohio, April 12, 1960. For papers I and II in this series see A. J. Kresge and D. P. N. Satchell, *Chemistry & Industry*, 1328 (1958); A. J. Kresge and Y. Chiang, *J. Am. Chem. Soc.*, **81**, 5509 (1959).

tution, with the sole exception of substitution by hydrogen, is the two-step reaction sequence. In this scheme, either of the steps can be rate-controlling, and perhaps the strongest evidence for this mechanism comes from recent attempts to show which step is slow. For the special case of substitution for hydrogen ($\text{X} = \text{H}$), hydrogen iso-

(3) Department of Chemistry, Illinois Institute of Technology, Chicago 16, Ill.



topo rate effects are absent from nitration,⁴ some halogenations,^{4a,5} and diazo-coupling under certain conditions.⁶ On the other hand, mercuration⁷ and diazo-coupling under other conditions⁶ show large isotope effects, while sulfonation⁸ and some halogenations^{5b,9} give isotope effects of intermediate size. These data are interpreted most easily in terms of a two-step mechanism with no isotope effect on the first step and a large isotope effect on the second step. In bromodesulfonation, spectral changes during the course of the reaction suggest the transient existence of a substance with quinoid structure¹⁰ such as the phenonium ion in eq. 1 and 2. There is, moreover, a common ion effect on the concentration of this quinoid substance, which indicates that it is a rapidly and reversibly formed intermediate. In diazo-coupling, base-catalysis can be demonstrated.⁶ This catalysis is of a form which permits the incursion of base only in the second step of a two-step sequence (eq. 2), and the extent of catalysis can be related to the magnitude of the hydrogen isotope effect. These facts have led to the general acceptance of a two-step mechanism for electrophilic aromatic substitution.

It has been argued, however, that the situation is different for aromatic substitution by hydrogen. Logarithms of rates of exchange of ring hydrogens for a number of aromatic substrates have been found to be linear functions of the Hammett acidity function H_0 . It has been assumed, therefore, that, according to the Zucker-Hammett hypothesis, this reaction must proceed by an A-1 mechanism.¹¹ This mechanism requires that the scheme represented by eq. 1 and 2 be modified to include two additional steps: rapidly attained equilibria between electrophilic reagent (in this case, the proton) and aromatic substrate (eq. 3 and 6) precede and follow slower reaction steps which constitute the actual substitution process (eq. 4 and 5). In these rapid steps conjugate acids of the aromatic are formed; these generally have been assigned the non-classical structures commonly known as outer- or π -complexes. Such a mechanism has been

(4) (a) L. Melander, *Arkiv Kemi*, **2**, 211 (1950); (b) W. M. Lauer and W. E. Noland, *J. Am. Chem. Soc.*, **75**, 3689 (1953); T. G. Bonner, F. Bowyer and G. Williams, *J. Chem. Soc.*, 2650 (1953).

(5) (a) P. B. D de la Mare, T. M. Dunn and J. T. Harvey, *ibid.*, 923 (1957); (b) F. M. Vainshtein and E. A. Shilov, *Doklady Akad. Nauk S.S.S.R.*, **123**, 93 (1958).

(6) H. Zollinger, *Helv. Chim. Acta*, **38**, 1597, 1617, 1623 (1955).

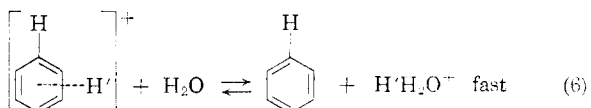
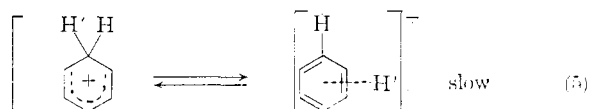
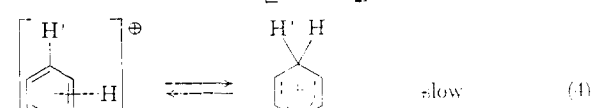
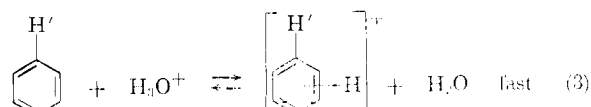
(7) A. J. Kresge, unpublished work.

(8) U. Berglund-Larsson and L. Melander, *Arkiv Kemi*, **6**, 219 (1953).

(9) E. Grovenstein and D. C. Kilby, *J. Am. Chem. Soc.*, **79**, 2972 (1957).

(10) L. G. Cannell, *ibid.*, **79**, 2927, 2932 (1957).

(11) (a) V. Gold and D. P. N. Satchell, *J. Chem. Soc.*, 3609, 3619, 3622 (1955); 1635 (1956); E. L. Machor, P. J. Smit and J. H. van der Waals, *Trans. Faraday Soc.*, **53**, 1309 (1957); (b) V. Gold, R. W. Lambert and D. P. N. Satchell, *Chemistry & Industry*, 1312 (1959); *J. Chem. Soc.*, 2461 (1960).



suggested as the general one for aromatic substitution,¹² but this is clearly incompatible with the observed base-catalysis in diazo-coupling.⁶

The validity of this mechanism can be questioned even for aromatic hydrogen exchange insofar as its assignment rests on the Zucker-Hammett hypothesis. Quite apart from the recent general breakdown of this hypothesis,¹³ it has been shown that at least some carbonium ions are not Hammett bases.¹⁴ The Zucker-Hammett criterion of mechanism can, of course, apply only to substrates which function as Hammett bases.

The acidity dependence of a reaction in concentrated aqueous acid, moreover, is a criterion of mechanism always subject to some uncertainty because approximations must necessarily be made concerning the behavior of activity coefficients. Acidity dependences in dilute acid, on the other hand, are not subject to this shortcoming: in sufficiently dilute solution activity coefficients are known to approach the limiting value 1.00. Diagnostic tests applied in dilute solution, therefore, are to be preferred over those carried out in concentrated acid. Fortunately, the form of the acidity dependence of aromatic hydrogen exchange in dilute solution can be used to distinguish between the two principle mechanisms for this reaction: in dilute solutions of strong and weak acids the scheme represented by eq. 1 and 2 will give different behavior from the scheme represented by eq. 3 through 6.

In the four-step mechanism, the first step is the only one, before the position of maximum free energy for the entire sequence, in which acid or base takes part. The only influence acid can have on this reaction, then, is its effect on the concentration of the first intermediate. Since this intermediate is a Brönsted acid, its concentration will be governed only by the pH or hydronium ion concentration of the reaction mixture. This is true

(12) K. L. Nelson and H. C. Brown in "Chemistry of Petroleum Hydrocarbons," Brooks, Boord, Kurtz and Schmerling, editors, Vol. III, Chapter 6, Reinhold Publishing Corp., New York, N. Y., 1955.

(13) J. Koskikallio and E. Whalley, *Trans. Faraday Soc.*, **55**, 815 (1959); G. Archer and R. P. Bell, *J. Chem. Soc.*, 3228 (1959); R. H. Boyd, R. W. Taft, Jr., A. P. Wolf and D. R. Christman, *J. Am. Chem. Soc.*, **82**, 4729 (1960); J. F. Bunnett, *ibid.*, **82**, 499 (1960).

(14) (a) N. C. Deno, P. T. Groves and G. Saines, *ibid.*, **81**, 5790 (1959); (b) A. J. Kresge and Y. Chiang, *Proc. Chem. Soc.*, 81 (1961).

even though this first intermediate can be formed by proton transfer from any other (undissociated) acid in the solution as well as by proton transfers from hydronium ion. Any increase in the concentration of undissociated acid must be accompanied by a corresponding increase in the concentration of its conjugate base, if the pH of the solution is to remain constant. Any increase in the rate of the forward reaction in eq. 3 produced by an increased undissociated acid concentration, then, will be offset by a corresponding increase in the rate of the reverse reaction. Thus, if the four-step mechanism for aromatic hydrogen exchange is operative, exchange rates will be proportional to hydronium ion concentration alone; this is known as specific hydronium ion catalysis. The two-step mechanism for aromatic hydrogen exchange, on the other hand, is nothing more than a slow proton transfer reaction. As such, its rate, just as the rate of the forward reaction in the first step of the four-step reaction, will be proportional to the concentrations of all acidic species present. This is known as general acid catalysis.

We have applied this criterion of general acid *versus* specific hydronium ion catalysis to the exchange of ring hydrogens in 1,3,5-trimethoxybenzene. In this paper, we present the results of our work in mixtures of hydronium ion with six undissociated acids.

Experimental Results

Kinetic Technique.—We determined exchange rates by measuring the rate of loss of radioactivity from tritiated 1,3,5-trimethoxybenzene. The bulk of this material was prepared by the exchange of normal trimethoxybenzene with aqueous hydrochloric acid- t in dioxane solution. In order, however, to show that this reaction placed tritium on the ring and not in the methyl groups, another preparation of tritiated trimethoxybenzene was made by the action of tritiated water on 2,4,6-trimethoxyphenyllithium. (The latter, in a separate experiment, gave 2,4,6-trimethoxybenzoic acid on treatment with carbon dioxide.) Both labeled materials lost tritium in 1 M aqueous perchloric acid at the same rate.

The absence of any chemical reaction other than hydrogen exchange in these reaction mixtures is indicated by the good first-order kinetics which were observed. This is further supported by the constant ultraviolet spectra of the reaction mixtures, as well as by the recovery of trimethoxybenzene of good melting point in 70% yield from a perchloric acid solution after 100 exchange half-lives.

Because the acids used to effect exchange differ widely in strength (17 pK_A units), large differences in exchange rates were encountered; observed half-lives ranged from 30 minutes to 11,000 days. Consequently, two different kinetic techniques were used. Runs with half-lives up to one month were followed by the conventional method of measuring the decrease in tritium activity of trimethoxybenzene to at least 60% reaction; this decrease was accurately first order to as much as 97% reaction (Fig. 1). Slower reactions were followed by measuring initial rates. Trimethoxybenzene of

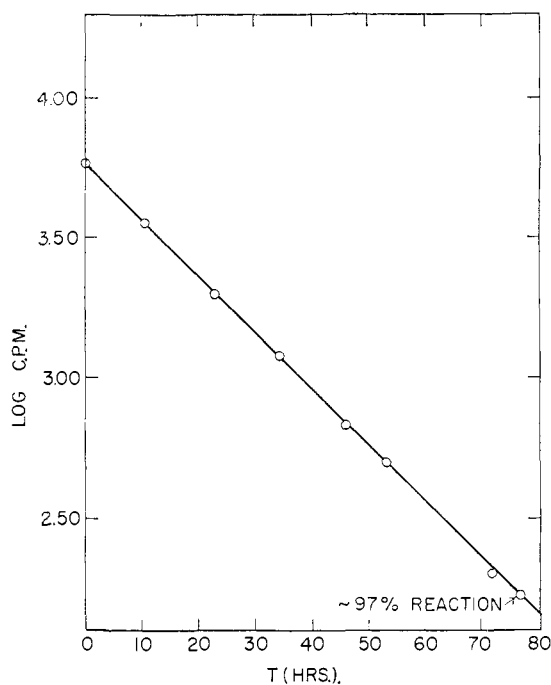


Fig. 1.—Sample plot of first-order exchange reaction followed by measuring loss of tritium activity in aromatic.

high specific activity was used to determine the linear increase of tritium activity in the aqueous fraction of the reaction mixture; these reactions were followed to less than 3% completion (Fig. 2).

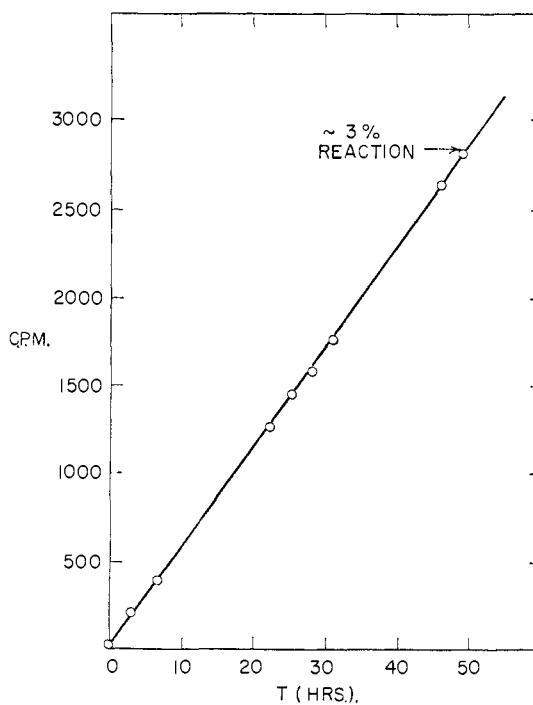


Fig. 2.—Sample plot of first-order exchange reaction followed by measuring increase of tritium activity in acid.

To demonstrate that both these methods were measuring the same reaction, the initial-reaction technique was used to measure several rates of exchange with acids for which the bulk of the data

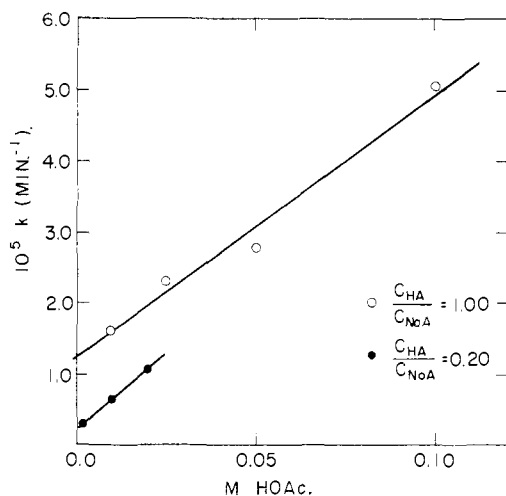


Fig. 3.—Dependence of the rate of aromatic hydrogen exchange in 1,3,5-trimethoxybenzene on acetic acid concentration in acetate buffers.

had been obtained by the other method. Table I shows that both techniques give the same specific rate constant.

TABLE I

COMPARISON OF THE TWO KINETIC TECHNIQUES USED FOR MEASURING RATES OF LOSS OF TRITIUM FROM 1,3,5-TRIMETHOXYBENZENE-2-*t*

HA	$10^3 k_2$ HA, min. ⁻¹ M ⁻¹ Init. rate method ^a	Conventional method ^b
CH ₂ FCO ₂ H	5.8	5.2
HCO ₂ H	0.64	0.65
	.73	
CH ₃ CO ₂ H	.42	0.37
	.41	
	.40	

^a Individual experiments. ^b Best values obtained from all experiments using this method.

Exchange with Dilute Hydrochloric Acid.—The rate of exchange between trimethoxybenzene and hydronium ion in the presence of no undissociated acid was measured by using dilute aqueous hydrochloric acid at various concentrations. Sodium chloride was added as the inert electrolyte to keep ionic strength constant. The data summarized in Table II give $4.0 \times 10^{-1} \text{ min.}^{-1} M^{-1}$ as the best value of the specific bimolecular rate constant for exchange between trimethoxybenzene and hydronium ion.

TABLE II

RATES OF LOSS OF TRITIUM FROM 1,3,5-TRIMETHOXYBENZENE-2-*t* TO AQUEOUS HYDROCHLORIC ACID AT 25°, IONIC STRENGTH = 0.100

M_{HA}	$10^3 k_1$ obs., min. ⁻¹	$k_2 \text{ H}_3\text{O}^+$, min. ⁻¹ M ⁻¹
0.05	19.4	0.39
.04	15.0	.38
.03	12.5	.42
.02	7.7	.38
.01	4.8	.48

Exchange with Acetic, Formic and Fluoroacetic Acid Buffer Solutions.—These experiments were designed to observe the effect on exchange velocity

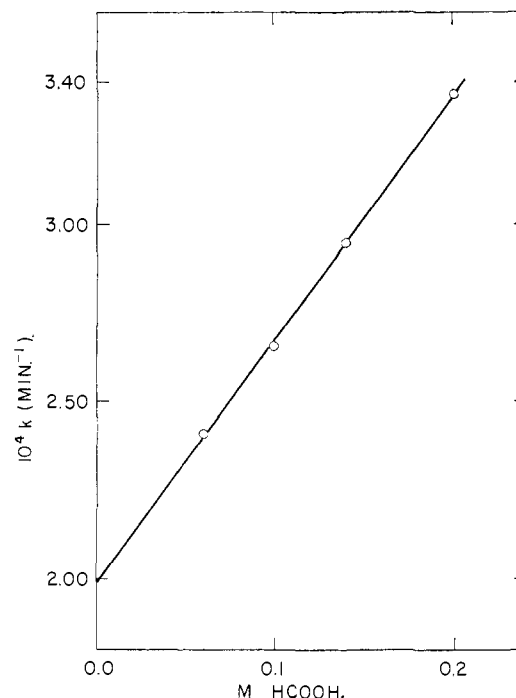


Fig. 4.—Dependence of the rate of aromatic hydrogen exchange in 1,3,5-trimethoxybenzene on formic acid concentration in formate buffers.

of changes in undissociated acid concentration at constant hydronium ion concentration. Series of kinetic runs were carried out at a constant buffer ratio ($M_{\text{HA}}/M_{\text{NaA}}$) but different buffer concentrations. Sodium chloride was added where necessary to keep ionic strength at 0.100. In each case general acid catalysis was observed: rates of exchange were linear functions of the concentration of undissociated acid.

The acetic acid reaction was studied at two different buffer ratios: 1.00 and 0.200; in the former case, a tenfold change in buffer concentration produced a threefold change in observed rate; in the latter case, a similar change in buffer concentration changed the observed rate by a factor of 3.5 (Table III, Fig. 3). Specific bimolecular rate constants for exchange between trimethoxybenzene and acetic acid were calculated from the slopes of plots of observed rate against buffer concentration. The best values of these (least squares) are 3.72×10^{-4} , $\sigma = 0.24 \times 10^{-4} \text{ min.}^{-1} M^{-1}$ and 4.15×10^{-4} , $\sigma = 0.20 \times 10^{-4} \text{ min.}^{-1} M^{-1}$ for the buffer ratios 1.00 and 0.200, respectively; the mean of these, calculated assigning relative weights to the values proportional to the number of experiments represented by each, is 3.84×10^{-4} , $\sigma = 0.23 \times 10^{-4} \text{ min.}^{-1} M^{-1}$. Hydronium ion contributions to the observed rates were calculated by extrapolating the data for each series of runs to $M_{\text{HA}} = 0.0$. From these values (1.22×10^{-6} and $2.26 \times 10^{-6} \text{ min.}^{-1}$ for the buffer ratios 1.00 and 0.200, respectively) and the known bimolecular rate constant for exchange with hydronium ion, hydronium ion concentrations and apparent dissociation constants for acetic acid in these reaction mixtures were calculated. These dissociation constants,

3.0×10^{-5} and 2.8×10^{-5} , agree well with the known value of 2.8×10^{-5} for acetic acid in 0.10 *M* sodium chloride solution.¹⁵

The formic acid reaction was studied at a buffer ratio of 2.00; here a threefold change in buffer concentration changed the observed rate by a factor of 1.4 (Table III, Fig. 4). These experi-

TABLE III

RATES OF LOSS OF TRITIUM FROM 1,3,5-TRIMETHOXYBENZENE-2-*t* TO VARIOUS AQUEOUS BUFFER SOLUTIONS AT 25°,

M_{HA}	IONIC STRENGTH = 1.00		
	$10^3 k_1$ obs., min. ⁻¹	$10^3 k_1$ H_3O^+ , min. ⁻¹	$10^3 k_2$ HA , min. ⁻¹ M^{-1}
	CH ₃ CO ₂ H, $M_{HA}/M_{NaA} = 1.00$		
0.100	0.0505	0.0122	0.38
.050	.0278	.0122	.31
.025	.0230	.0122	.43
.010	.0163	.0122	.41
	CH ₃ CO ₂ H, $M_{HA}/M_{NaA} = 0.200$		
0.020	0.0106	0.00226	0.42
.010	.00638	.00226	.41
.0020	.00310	.00226	.42
	HCO ₂ H, $M_{HA}/M_{NaA} = 2.00$		
0.20	0.336	0.198	0.69
.14	.295	.198	.69
.10	.265	.198	.67
.060	.241	.198	.72
	CH ₂ FCO ₂ H, $M_{HA}/M_{NaA} = 1.00$		
0.100	1.65	1.12	5.3
.050	1.25	1.04	4.2
.029	1.15	1.00	5.2
.025	1.13	0.96	6.8
.010	0.78	0.74	4

ments gave a specific rate of exchange with formic acid of 6.89×10^{-4} , $\sigma = 0.15 \times 10^{-4}$ min.⁻¹ M^{-1} and a hydronium ion contribution to each of the observed rates of 1.98×10^{-4} min.⁻¹. From the latter, an apparent dissociation constant for formic acid of 2.5×10^{-4} was calculated; this is again in good agreement with the value of 2.8×10^{-4} for formic acid in 0.10 *M* sodium chloride calculated on the assumption that the thermodynamic constant (1.77×10^{-4})^{16a} changes in the same way with sodium chloride concentration as does the thermodynamic constant for acetic acid.

In fluoroacetic acid buffers at the concentrations used (buffer ratio 1.00, buffer concentration 0.10 to 0.010 *M*) hydronium ion concentrations were not constant throughout the series but dropped by roughly 30% as undissociated acid concentration was lowered. Observed rates, therefore, reflected changes in the rate of exchange by undissociated acid and changes in hydronium ion contribution as well. For this reason, the method of calculating bimolecular rate constants used previously could not be employed. Nor could corrections be applied to the observed rates by calculating hydronium ion contributions at each buffer concentration: such corrections calculated using the two available values of dissociation constant for fluoroacetic acid,

(15) H. S. Harned and B. B. Owen, "The Physical Chemistry of Electrolyte Solutions," Reinhold Publishing Corp., New York, N. Y., 1958, p. 676.

(16) R. P. Bell, "The Proton in Chemistry," Cornell University Press, Ithaca, N. Y., 1959; (a) p. 64, (b) 155, (c) p. 163.

the value at infinite dilution (2.59×10^{-3})¹⁷ and the value for 0.10 *M* sodium chloride (4.17×10^{-3}), fit the observed data very poorly. A least squares procedure therefore was adopted which permitted calculation of the best values of these hydronium ion contributions as well as the best value of the bimolecular rate constant for exchange with fluoroacetic acid. This procedure made use of the fact that relative hydronium ion concentrations in buffer mixtures are less sensitive functions of dissociation constant than are the actual hydronium ion concentrations themselves (see Table IV). Relative hydronium ion concentrations using the two dissociation constants 2.59×10^{-3} and 4.17×10^{-3} were averaged, and these average values were used to fit observed rates to the ex-

$$k_{obs.} = k_2' H_3O^+ M_{H_3O^+}^{rel} + k_2 HA M_{HA} \quad (7)$$

pression (7) treating $k_2' H_3O^+$ and $k_2 HA$ as adjustable parameters. In this way the unknown hydronium ion concentrations were absorbed in the product $k_2' H_3O^+ M_{H_3O^+}^{rel}$. From the value of $k_2' H_3O^+$ obtained here (1.12×10^{-3} min.⁻¹ M^{-1}) and the known value of $k_2' H_3O^+$ (0.40 min.⁻¹ M^{-1}) a hydronium ion concentration for each buffer solution was calculated. These are listed in Table IV together with apparent dissociation constants calculated for each of these buffer mixtures. The relative constancy of these dissociation constants justifies to some extent the approximations inherent in this method of calculation. The method gives 5.17×10^{-3} min.⁻¹ M^{-1} as the bimolecular rate constant for exchange between trimethoxybenzene and fluoroacetic acid.

Exchange with Biphosphate and Ammonium Ions.—These substances are very weak acids, and in the solutions used for exchange reaction mixtures, hydronium ion concentrations were very low. Hydronium ion contributions, therefore, were 1% or less of the observed rates (see Table V), and bimolecular rate constants could be evaluated from exchange data at a single acid concentration. These data are summarized in Table V.

Exchange with Water.—The rate of loss of tritium from trimethoxybenzene to water acting as an acid was too slow at 25° to be measured accurately even by using the initial-rate technique. Kinetics were therefore measured at higher temperatures and a value for 25° was obtained by extrapolation. Sodium hydroxide was added to these reaction mixtures in order to keep exchange with hydronium ion at a negligible value. That sodium hydroxide itself has no effect on the reaction is demonstrated by the constancy of the rate over a fourfold variation in sodium hydroxide concentration. In this way a specific bimolecular rate constant for exchange between trimethoxybenzene and water at 25° of 5.7×10^{-10} M^{-1} min.⁻¹ was obtained.

Base-catalyzed Exchange.—Acetic acid was the only acid for which exchange reactions were carried out at two different buffer ratios and for which, therefore, base catalysis by the acid anion could in principle have been detected. Here the bimolecular rate constants calculated from data at the two buffer ratios were not significantly dif-

(17) D. J. G. Ives and J. H. Pryor, *J. Chem. Soc.*, 2104 (1955).

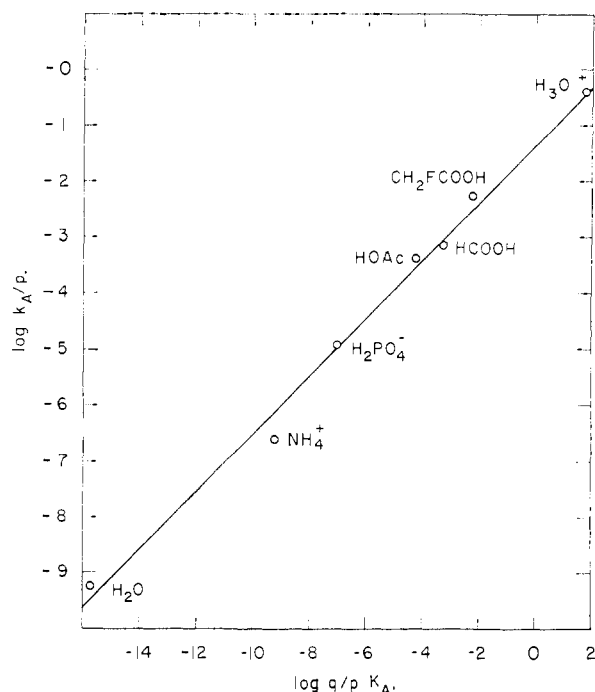


Fig. 5.—Brønsted plot for acid-catalyzed aromatic hydrogen exchange in 1,3,5-trimethoxybenzene.

ferent: their difference was less than the sum of the two standard deviations.

Further support for the lack of catalysis by base was obtained from the exchange with water acting as an acid. The rate of loss of tritium from trimethoxybenzene to water at 82° was measured at two different concentrations of added sodium hydroxide, 0.05 and 0.2 *M*. The rate constants observed were 1.04×10^{-6} and 1.01×10^{-6} min.⁻¹, respectively.

These data do not, of course, exclude the possibility that a small amount of exchange occurs by a mechanism involving base in addition to the main reaction requiring only acid. But they do definitely eliminate, as the main reaction, any scheme in which acid and base react with the substrate simultaneously; the latter demands direct proportionality between rate and base concentration.

Discussion

Brønsted Relation.—Reactions subject to general acid catalysis usually conform to a relation between catalytic constant (k_{HA}) and acid ionization constant of the catalyzing acid (K_{HA}) which is commonly known as the Brønsted relation^{16b,18a}

$$\frac{k_{HA}}{p} = G \left(\frac{q}{p} k_{HA} \right) \quad (8)$$

Bimolecular rate constants for exchange between trimethoxybenzene and the seven acids studied here give a Brønsted relation which is good considering the range of the data. Numerically, these cover nine powers of ten in specific rate and seventeen *pK* units in ionization constant (Fig. 5). From the point of view of structure of the catalyzing acid, these data include exchange with one

(18) R. P. Bell, "Acid-Base Catalysis," Oxford University Press, New York, N. Y., 1941; (a) p. 82, (b) p. 87, (c) p. 92.

TABLE IV
HYDRONIUM ION CONCENTRATIONS OF FLUOROACETIC ACID BUFFERS CALCULATED USING VARIOUS DISSOCIATION CONSTANTS, BUFFER RATIO = 1.00

<i>M</i> _{HA}	<i>K</i> = 2.592×10^{-2}		<i>K</i> = 4.167×10^{-2}		Kinetic data	
	<i>M</i> _{H₃O⁺}	Rel.	<i>M</i> _{H₃O⁺}	Rel.	<i>M</i> _{H₃O⁺}	<i>K</i> _{HA}
0.100	2.47	1.000	3.86	1.000	2.8	3.0
.0500	2.36	0.955	3.61	0.945	2.6	2.9
.0291	2.22	.898	3.31	.878	2.5	3.0
.0250	2.18	.882	3.22	.859	2.4	2.9
.0100	1.80	.729	2.32	.665	1.9	2.8
					Av.	2.9

^a Thermodynamic dissociation constant (D. J. G. Ives and J. H. Pryor, *J. Chem. Soc.*, 2104 (1955)). ^b Estimated dissociation constant for 0.1 *M* NaCl solution.

TABLE V
RATES OF LOSS OF TRITIUM FROM 1,3,5-TRIMETHOXYBENZENE-2-*t* TO AQUEOUS BIPHOSPHATE AND AMMONIUM IONS AT 25°

HA	<i>k</i> ₁ obs., min. ⁻¹	<i>k</i> ₁ H ₃ O ⁺ , min. ⁻¹	<i>k</i> ₂ HA, min. ⁻¹ <i>M</i> ⁻¹
H ₂ PO ₄ ^{-a}	2.34×10^{-6}	0.025×10^{-6}	2.31×10^{-5}
	2.36×10^{-6}	$.025 \times 10^{-6}$	2.33×10^{-5}
	2.36×10^{-6}	$.025 \times 10^{-6}$	2.34×10^{-5}
NH ₄ ^{+b}	5.7×10^{-8}	$.022 \times 10^{-8}$	2.6×10^{-7c}
	6.5×10^{-8}	$.022 \times 10^{-8}$	3.4×10^{-7c}

^a As 0.10 *M* NaH₂PO₄-NaH₂PO₄ buffer. ^b As 0.10 *M* NH₄Cl-NH₃ buffer. ^c Corrected for exchange with H₂O using 3.1×10^{-8} min.⁻¹ as the H₂O rate at 25°.

nitrogen acid and six oxygen acids as well as with acids of three different charge types. The best value of the exponent α is 0.518 with a standard deviation of 0.007. The standard deviation in log k_{HA}/p is 0.10 which corresponds to a factor of about 1.3 in rate constant. Table VI shows that, on the whole, the largest deviations from this relation occur for the cases where rate measurements were the least accurate (fluoroacetic acid and the two slowest rates, ammonium ion and water), and that the best agreement is found in those cases where rate measurements were the most reliable (acetic acid, hydronium ion and biphosphate ion). There seems to be no trend in the deviations: their distribution is random.

TABLE VI
COMPARISON OF OBSERVED RATES OF AROMATIC HYDROGEN EXCHANGE IN TRIMETHOXYBENZENE WITH VALUES CALCULATED FROM THE BRÖNSTED RELATION

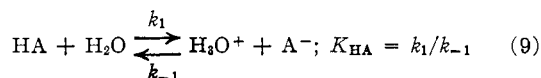
$$\frac{k_{2,HA}}{p} = 4.72 \times 10^{-2} \left(\frac{q}{p} K_{HA} \right)^{0.518}$$

HA	<i>K</i> _{HA}	<i>k</i> _{2,HA} Obsd.	min. ⁻¹ <i>M</i> ⁻¹ Calcd.	$\frac{100(\text{Obsd.}) - (\text{calcd.})}{(\text{calcd.})}$
H ₃ O ⁺	5.5×10	4.0×10^{-1}	3.76×10^{-1}	+6
CH ₂ FCO ₂ H	2.9×10^{-3}	5.2×10^{-3}	3.28×10^{-3}	+58
HCO ₂ H	2.85×10^{-4}	6.9×10^{-4}	9.85×10^{-4}	-30
CH ₃ CO ₂ H	2.82×10^{-5}	3.84×10^{-4}	2.97×10^{-4}	+22
H ₂ PO ₄ ⁻	6.23×10^{-8}	2.32×10^{-6}	2.16×10^{-6}	-7
NH ₄ ⁺	5.5×10^{-10}	3.0×10^{-7}	7.54×10^{-7}	-60
H ₂ O	1.79×10^{-16}	5.7×10^{-10}	3.35×10^{-10}	+70

This fit is somewhat unusual. Over so wide a range of data Brønsted plots may begin to show signs of curvature caused by changing values of α .^{16c} A correlation between catalyst charge type and deviations from the relationship is also sometimes found.^{18a} In the present case, though neu-

tral, singly positive and singly negative charged acids were used, no correlation of this sort could be discerned. Another unusual feature of the present relationship is the fact that the points for both the hydronium ion reaction and the water reaction fit quite well: one or the other of these almost invariably offers the worst fit, and differs from the calculated value by several powers of ten.^{18c}

This good compliance with the Brønsted relation over the entire range of data indicates that exchange between trimethoxybenzene and each of these acids occurs by a single mechanism which operates in much the same form for exchange with each acid. This mechanism must be quite similar to the process which governs the value of the equilibrium constant, K_{HA} , in the ionization reaction



It is now known that, for oxygen and nitrogen acids, the rate of the reverse reaction in this ionization process is, to a large extent, diffusion controlled: the value of k_{-1} (eq. 9) does not change appreciably over wide variations in K_{HA} .¹⁹ Changes in K_{HA} , therefore, reflect changes in k_1 , the rate constant for the forward step in eq. 9. Hydrogen exchange in trimethoxybenzene, then, must be a process similar to the forward reaction in eq. 9. Since this is a proton transfer from acid to neutral substrate, it is reasonable to expect the rate-determining process in aromatic hydrogen exchange of trimethoxybenzene to be a proton transfer from acid to neutral substrate as well.

The Mechanism of Exchange.—This compliance with the Brønsted relation as well as the experiments in buffer solutions establish beyond a doubt that aromatic hydrogen exchange in trimethoxybenzene is subject to general acid catalysis. This fact is in disagreement with the A-1 mechanism (eq. 3, 4, 5 and 6) proposed for aromatic hydrogen exchange. The latter was supported by the Zucker-Hammett hypothesis, but this hypothesis is a mechanistic criterion subject to considerable shortcomings and is, moreover, inapplicable to the case under discussion.^{14b} It seems reasonable, therefore, to accept the evidence supplied by general acid catalysis and to conclude that the A-1 mechanism for aromatic hydrogen exchange is untenable for the case of trimethoxybenzene.

Elimination of the A-1 reaction leaves two general classes of mechanism for this reaction: A-2 and A-SE2. Both of these are compatible with general acid catalysis.

The usual A-2 mechanism, that requiring two steps for complete reaction, can be eliminated immediately on the ground that it consists of an unsymmetrical reaction sequence. Isotope exchange reactions must be symmetrical except for the small differences introduced by isotope effects. The A-2 mechanism can, however, be made symmetrical by the addition of two more steps to the usual two step sequence; this was done for the A-1 mechanism to make it fit aromatic exchange.¹¹ This lengthened A-2 mechanism will differ from the A-1 mechanism depicted in eq. 3 through 6 only

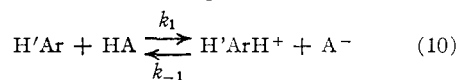
in the respect that the slow isomerization of the first intermediate to the second intermediate (eq. 4) must be assisted by a molecule of base. Two kinds of assistance are possible: one in which the base acts directly on the proton, and one in which the base stabilizes the positive charge developing at the positions *ortho* and *para* to the reaction site.

In the former case, with the base acting directly on the proton which had been donated to the aromatic substrate in the previous step, the original acid must be partially reformed. The system, then, re-assumes some of the character of the initial state. It seems doubtful that such a scheme, involving as it does a partly backward step in the forward process, could be a lower free energy route to the formation of a symmetrical intermediate than would be the direct transfer of a proton in a single step. Simple processes are always to be preferred over the more complex.

The second kind of assistance by base, that in which the base stabilizes positive charge developing on carbon, requires the molecule of base to function as a nucleophile or a base in the Lewis sense. In a Brønsted relation, however, reaction rate is compared to basicity in the Brønsted sense. A mixture of Brønsted and Lewis basicity, such as results from a comparison of nucleophilic reaction rates with Brønsted ionization constant, is known to give a poor Brønsted relation.²⁰ In the present reaction, a very good Brønsted relation was observed.

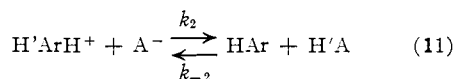
This leaves only the A-SE2 or slow proton transfer mechanism to be considered. In this general classification, two separate schemes are possible: a concerted slow proton transfer, that is, one in which the arrival of the incoming proton and departure of the leaving proton are simultaneous; and a consecutive slow proton transfer, that is, one in which proton arrival occurs in a separate step before proton departure. The consecutive process differs from the concerted process in that it involves the formation of an intermediate species. It would be preferred, therefore, on the basis of the evidence which points to the existence on an intermediate phenonium ion in several other electrophilic aromatic substitution reactions. But this same choice can also be based on the absence of base catalysis in this reaction. The concerted reaction demands simultaneous catalysis by both acid and base, the former to supply the incoming proton and the latter to receive the leaving proton. The consecutive process, for the special case of both steps occurring at nearly equal rates, which must be the case in an isotope exchange reaction, requires only acid catalysis: base is involved in the proton-removal step, but it is also produced in the proton-supplying step. Base catalysis was not observed in the present investigation.

By these arguments, the mechanism for exchange of aromatic hydrogen in 1,3,5-trimethoxybenzene must be a consecutive slow proton transfer



(19) R. P. Bell, *Quart. Revs.*, **13**, 169 (1959).

(20) G. F. Smith, *J. Chem. Soc.*, 521 (1943).



This mechanism not only fits all the experimental observations made in this investigation, but it is also consistent with the generally accepted scheme for electrophilic aromatic substitution (eq. 1 and 2).

A kinetic expression for the velocity of the reaction sequence represented by eq. 10 and 11 can be derived through use of the steady-state approximation (spectral evidence indicates that the intermediate H'ArH^+ is present only in very low concentrations at the acidities employed in these experiments^{14b})

$$v = -\frac{d(\text{H'Ar})}{dt} = \frac{d(\text{HAr})}{dt} = \frac{k_1 k_2 (\text{H'Ar})(\text{HA}) - k_{-1} k_{-2} (\text{HAr})(\text{H'A})}{k_{-1} + k_2} \quad (12)$$

The pairs of rate constants k_1, k_{-2} and k_{-1}, k_2 differ in magnitude only by isotope effects. If, then, the isotope effects α and β be defined as the rate ratios for bond-breaking in the intermediate phenonium ion, HArH^+ , and bond-breaking in the acid, HA , respectively

$$\alpha = (k_{\text{H}'} / k_{\text{H}})_{\text{HArH}^+} = k_2 / k_{-1} \quad (13)$$

$$\beta = (k_{\text{H}'} / k_{\text{H}})_{\text{HA}} = k_{-2} / k_1 \quad (14)$$

eq. 12 becomes

$$v = \frac{k_1}{1 + \alpha} [\alpha (\text{H'Ar})(\text{HA}) - \beta (\text{HAr})(\text{H'A})] \quad (15)$$

This expression consists of two terms; the first gives the rate of the forward reaction, and the second, the rate of the reverse reaction. The second term can be shown to make a negligible contribution to the total expression over essentially the entire course of the reaction under the conditions used in this investigation. At the concentrations employed ($10^{-3} M$ HAr , $55 M$ $\text{HA} + \text{H}_2\text{O}$), there are 10^5 times as many exchangeable hydrogens in the aqueous fraction as in the aromatic. If, as was the case, initially the isotopic tracer is present in the aromatic and is absent from the acid, the rate at which the tracer is re-incorporated in the aromatic will not become equal to the rate at which it is lost until the level of tracer in the aromatic has dropped to 10^{-5} of its initial value. Thus, the velocity of the reaction studied here can be represented quite simply as

$$v = \frac{\alpha k_1}{1 + \alpha} (\text{H'Ar})(\text{HA}) \quad (16)$$

This shows that the loss of tritium from 1,3,5-trimethoxybenzene-2-*t* to aqueous acids is a bimolecular process, first order in aromatic and first order in general acid. The rate of exchange, moreover, is not dependent on base concentration.

These arguments supporting a new mechanism for aromatic hydrogen exchange in trimethoxybenzene bring up the question of the validity of the old mechanism for exchange in other substrates. General acid catalysis has been detected for exchange in one other aromatic substrate, azulene²¹; no other systems have been investigated from this

(21) J. Colapietro and F. A. Loug, *Chemistry & Industry*, 1056 (1960).

point of view. The phenomenon, therefore, may be general, though two cases are hardly enough to permit the drawing of fast conclusions.

These two substrates for which general acid catalysis has been found have necessarily been very much more reactive toward electrophilic aromatic substitution than the substrates used in the kinetic studies which led to the proposal of the A-1 mechanism for exchange. It has been argued, therefore, that exchange in these highly reactive substrates may well proceed by a different mechanism.^{11b,22} In opposition to this view is the fact that exchange between trimethoxybenzene and the various acids used in this investigation covered a range of reaction rate roughly as great as the difference in reactivity between trimethoxybenzene and benzene; no change in mechanism was apparent here. A single mechanism for all exchange is further supported by the close similarity between exchange in trimethoxybenzene and exchange in the less reactive substrates at all points where comparison is possible. The rate of exchange in trimethoxybenzene in concentrated aqueous acid is h_0 -dependent in the same sense as are the rates of the less reactive aromatics.^{11,23} The slope of the straight line obtained by plotting $\log k_{\text{exch}}$ against $-\log h_0$ for trimethoxybenzene in perchloric acid is 1.07^{14b}; the corresponding slopes for exchange at the *o*- and *p*-positions of anisole in sulfuric acid are both 1.18.²⁴ But these slopes are known to be generally lower in perchloric acid than in sulfuric acid. The solvent isotope effect for exchange in trimethoxybenzene catalyzed by 0.05 *M* perchloric acid is 1.67($k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}}$)²⁵; the solvent isotope for exchange in *p*-cresol catalyzed by 4 *M* hydrochloric acid is 1.62.^{11b}

It must be borne in mind that the only evidence on which assignment of the A-1 mechanism for exchange rests is the acidity dependence of rate in concentrated aqueous acid. The argument here, however, is losing force both from the recent breakdown of the Zucker-Hammett hypothesis¹³ and from a re-determination of exchange rates.²³ To this must be added the fact that the " h_0 -dependence" of exchange rates can be explained quite satisfactorily in terms of a slow proton transfer mechanism.^{14b}

A single mechanism for a class of reactions must always be a more satisfactory situation than a multiplicity of mechanisms. Since the A-SE2 mechanisms seems firmly established for some aromatic exchanges whereas the A-1 mechanism may be in doubt, we are inclined, at this time, to favor the view that all aromatic hydrogen exchange proceeds by way of slow proton transfers.

Experimental

Materials. 1,3,5-Trimethoxybenzene-2-*t* (I).—Unlabeled 1,3,5-trimethoxybenzene²⁶ (2.00 g.) was dissolved in 30 ml. of purified dioxane containing 0.5 ml. of concentrated hydrochloric acid and 0.5 ml. of tritiated water. This solution was allowed to stand at room temperature 10 hours; the trimethoxybenzene then was precipitated by addition of 100 ml. of water. The solid was collected by filtration, was

(22) L. Melander, private communication.

(23) C. Eaborn and R. Taylor, *J. Chem. Soc.*, 3301 (1960).

(24) D. P. N. Satchell, *ibid.*, 3911 (1956).

(25) A. J. Kresge and Y. Chiang, unpublished work.

(26) H. Brederick, I. Hennig and W. Rau, *Ber.*, **86**, 1085 (1953).

washed with water, and was dried *in vacuo* over silica gel. It was purified to constant specific activity by alternate vacuum sublimations (50–60° (0.1 mm.)) and recrystallizations from aqueous ethanol.

1,3,5-Trimethoxybenzene-2-*t* (II).—The lithium derivative of 1,3,5-trimethoxybenzene was prepared by the method of Gilman.²⁷ A twofold excess of tritiated water was added to a suspension of lithium aryl in ether and the mixture was stirred rapidly at room temperature for 10 minutes. The reaction mixture was decomposed by the addition of water, layers were separated, and the ether solution was washed with dilute aqueous sodium hydroxide and with water. The ether solution was then dried over calcium chloride and ether was removed. The residue was sublimed *in vacuo* and the sublimate was purified to constant activity as before.

In a separate experiment, lithium trimethoxybenzene, prepared in the same way, was treated with carbon dioxide; 2,4,6-trimethoxybenzoic acid was isolated in 60% yield, m.p. 144.5–145.0° (reported²⁸ m.p. 142–144°).

Fluoroacetic Acid.—A sample purchased from K. & K. Laboratories was distilled at atmospheric pressure through a 15-plate column. A middle fraction consisting of about one-third of the original charge was collected at 167–168°.

All other materials were reagent grade chemicals. Buffer solutions were prepared either by using appropriate volumes of aqueous acid and sodium hydroxide solutions of known strength, or by diluting accurately weighed amounts of reagent chemicals to known volumes. Aqueous solutions of trimethoxybenzene were prepared by suspending solid trimethoxybenzene in distilled water (a quantity less than that necessary to make a saturated solution was always used; the solubility of trimethoxybenzene in H₂O at 25° was determined to be 0.43 mg./ml.), heating the mixture past the melting point of trimethoxybenzene (52°), and shaking the suspension mechanically as it cooled to room temperature.

Kinetic Procedure. Conventional Method.—Reaction mixtures were prepared either by mixing equal volumes of buffer solution and aqueous trimethoxybenzene-*t* or by mixing 100 volumes of buffer solution with one volume of either aqueous or alcoholic trimethoxybenzene-*t*. The presence of 1% of ethyl alcohol in the reaction mixture had no effect on the rate of exchange. The reaction mixtures were placed in a constant temperature bath (24.62 ± 0.01°) and samples (10, 2 or 1 ml. depending on the concentration and activity of the trimethoxybenzene used) were withdrawn at suitable intervals of time. These samples were quenched in at least a twofold excess of aqueous sodium hydroxide. The

resultant mixtures were shaken mechanically for 1 minute with 15.0-ml. portions of xylene or toluene, the aqueous layers were withdrawn, and the organic solutions were dried with anhydrous CaCl₂. (A second extraction showed that this procedure removed 99.8% of the trimethoxybenzene-*t* from aqueous solution). Ten-ml. aliquots of the dried solutions were assayed for tritium in a Packard Tri-Carb liquid scintillation counter. The counting data were used directly to calculate first-order rate constants: using machine computation (IBM 704), the data were fitted to the expression $A = ae^{bt}$ where A is activity at time t , a is $A_0 - A_\infty$ and b is the negative of the first-order rate constant.

Initial Rate Method.—Reaction mixtures were prepared by mixing equal volumes of acid solution and a nearly saturated solution of high specific activity trimethoxybenzene in water. These were placed in a constant temperature bath (24.62 ± 0.01°) and 1.00-ml. samples were withdrawn at suitable intervals of time. The samples were quenched in 2.00 ml. of water containing a twofold excess of sodium hydroxide and the resultant mixtures were shaken mechanically with 15 ml. of xylene. The aqueous layers were withdrawn and were washed twice with 15-ml. portions of ethyl ether (control experiments showed that this was sufficient to remove all organically bound tritium). One-ml. aliquots of the washed aqueous solutions were assayed for tritium in a Packard Tri-Carb liquid scintillation counter. These counting data were plotted against time and a straight line was fitted by eye. The slope of this line gave the rate of reaction in c.p.m. per unit time. This was converted to the fraction of reaction (x) per unit time from a knowledge of the total activity present in a kinetic sample and the counting efficiency of the aqueous solutions which were assayed. The total activity in a kinetic sample was determined by counting an aliquot of the first xylene extraction of a sample against an aliquot of a xylene solution of benzoic-*t* acid of known activity. The counting efficiency of the aqueous solutions assayed was determined by carrying a sample of water-*t* of known activity through the separation procedure for kinetic samples and then determining its activity under counting conditions similar to those used for kinetic samples. The activities of the standards used in these determinations, benzoic-*t* acid and water-*t*, were each measured several times by a gas-phase counting method which is known to give absolute activities.²⁹ From the fraction of reaction per unit time, rate constants were calculated using the relationship

$$k_1 = \frac{1}{t} \ln \frac{1}{1-x} \approx \frac{x}{t} \text{ for small } x$$

(27) H. Gilman, C. E. Arntzen and F. J. Webb, *J. Org. Chem.*, **10**, 374 (1954).

(28) J. Herzog and F. Wenzel, *Monatsh.*, **23**, 96 (1902).

(29) D. Christman, *Chemist Analyst* (J. T. Baker Chemical Co.), **46**, No. 1, 5 (1957).

[CONTRIBUTION FROM THE B. F. GOODRICH RESEARCH CENTER AND GOODRICH-GULF CHEMICALS, INC., BRECKSVILLE, OHIO]

The Rate of Reaction of Maleic Anhydride with 1,3-Dienes as Related to Diene Conformation

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The rate of reaction of fifteen open-chain 1,3-dienes with equivalent concentrations of maleic anhydride has been measured in benzene solution at 25°. Several of the rates were also measured at other temperatures so that heats of activation could be calculated. The heats for the reaction of maleic anhydride with low molecular weight, open-chain dienes are higher than those for 1,3-cyclopentadiene, 2-*t*-butyl-1,3-butadiene or 2-neopentyl-1,3-butadiene. The two highly-branched, open-chain, 2-substituted dienes react very rapidly, the 2-neopentyl derivative reacting about twice as fast as the 2-*t*-butyl and much less rapidly than the cyclic diene. The Raman and infrared spectra of 2-*t*-butyl-1,3-butadiene are consistent with the presence of both *cisoid* and *transoid* conformations. However, spectra studies clearly revealed that the 2-neopentyl derivative is *transoid*. The high rate and low heat of activation for 2-*t*-butyl-1,3-butadiene is understandable on the basis of the presence of more *cisoid* than *transoid* molecules. The *cisoid* form appears to be favored at the expense of the *transoid* the lower the temperature. The 2-neopentyl derivative may react rapidly and with a low heat of activation as a result of the ease of rotation in the complexed state around the diene single bond, which ease appears to be a function of electron availability enhanced by the substituent in the 2-position.

The rate of reaction of 1,3-butadiene with maleic anhydride in benzene solution has been reported by Eisler and Wassermann.¹ They found for

(1) B. Eisler and A. Wassermann, *J. Chem. Soc.*, 1943 (1953); 979 (1953).

equimolecular concentrations a second-order dependence on time for any single mixture. Within experimental error the constants did not change as the starting concentration of the reactants was increased. They reported a heat of activation of