823. *The Kinetics of Hydrogen Isotope Exchange Reactions. Part XIII.* Isotope Effects in the Acid-catalysed Hydrogen Exchange of* 1,3,5-*Trimethoxybenzene.*

By B. D. Batts and V. Gold.

The ratio of the rates of the simultaneous loss of tritium and deuterium from 1,3,5-trimethoxybenzene labelled with both isotopes has been studied in aqueous perchloric acid and acetate buffer solutions. This ratio has been shown to be independent of the concentration of the catalysing acid. In D_2O–$DClO_4$ solution the loss of tritium is 1·68 times faster than in H_2O–$HClO_4$ solutions of the same acid concentration. In deuteriated acetate buffer solution the acetic acid-catalysed reaction (general acid catalysis) is 1·46 times slower than in the light medium. On the basis of a reasonable representation of the reaction path, isotope effects for the component steps of the overall reaction have been deduced. These effects should be interconnected if a common reaction mechanism holds for both forms of catalysis, and this prediction is borne out by the data.

Electrophilic hydrogen exchange in aromatic compounds has been observed in aqueous solutions of both strong acids and weak acids. In dilute solutions the exchange is subject to general acid catalysis [1-3] but no corresponding phenomenon has been detected in concentrated solutions of strong mineral acids.[4]

The present study is concerned with the interrelated problems (i) whether a single mechanism suffices to explain catalysis both by hydrogen ions and acetic acid molecules, and (ii) whether there is a progressive change in mechanism as the concentration of mineral acid is raised over an extended range. The experiments were designed to decide between alternative answers to these questions by the detailed determination of hydrogen isotope effects. Kresge and Chiang [2] have answered the first question in the affirmative on the ground that the rate constants for both the hydrogen ion and for weak acids obey the

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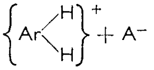
* Part XII, *J.*, 1963, 1938.

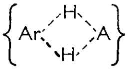
[1] Ingold, Raisin, and Wilson, *J.*, 1936, 915, 1637.
[2] Kresge and Chiang, *J. Amer. Chem. Soc.*, 1961, **83**, 2877.
[3] Colapietro and Long, *Chem. and Ind.*, 1960, 1056.
[4] Gold, Lambert, and Satchell, *J.*, 1960, 2461 and earlier Papers in the Series.

Brönsted catalysis law. However, the catalysis law is not reliable when applied to structurally dissimilar acids [5] and the experimental point for the hydrogen ion sometimes does not agree with those for other acids, even when a common mechanism is not in doubt. The evidence of the catalysis law is therefore not very strong on this issue. A further point is that the inclusion of the entire general acid species in the composition of the transition state, which follows from the observation of general acid catalysis, does not by itself establish that there is complete proton transfer in the terminal stage of the reaction concerned. Thus if we represent the exchange reaction by a sequence of steps involving an intermediate and a potential energy profile which, apart from isotope effects, is symmetrical about the hollow corresponding to the intermediate, there remain two main alternatives; for the intermediate,[6] *viz.*



(*a*)

and



(*b*)

In (*a*) the nature of the conjugate base A⁻ does not affect the structure. If (*b*) is correct, catalysis by different acids could be said not to follow the same mechanism, inasmuch as different symmetrical intermediates of structure (*b*) incorporate different groups A. There may then also be a bigger difference in mechanism between hydroxonium ions and weak acids in the role of HA. While structure (*b*) is reasonable for a carboxylic acid, it is improbable, especially on stereochemical grounds, for the hydroxonium ion. A change in mechanism thus appears possible. Of course, there is conclusive evidence that a structure corresponding to (*a*) exists and is stable for certain aromatic compounds,[7] but such evidence has not so far extended to reactions in carboxylic acid buffers in which association with base [to give (*b*)] is more likely.

The isotope effect studies now reported largely resolve these problems, at least for 1,3,5-trimethoxybenzene as the substrate. This substance was selected because it is the only benzenoid aromatic compound for which general acid catalysis in hydrogen exchange has been studied in some detail [2] and also because a repetition of some isotope-effect measurements on this compound [8] would provide a test of the reliability of both the earlier and our own values. The agreement of our isotope effect results with Kresge and Chiang's measurements [8] in the perchloric acid-catalysed exchange is excellent (Tables 1 and 2), but our conclusions and calculations are entirely based on the coherent set of our own more extensive data. Our individual rate constants are systematically a few percent larger than the values given by Kresge and Chiang.[8]

EXPERIMENTAL

1,3,5-*Trimethoxybenzene*.—This was prepared in 80% yield by the methylation of anhydrous phloroglucinol [9] (1 mole) by purified [10] dimethyl sulphate (5 moles) in a dry acetone (1200 ml.)–potassium carbonate (5·5 moles) solution. After distillation (131°/11 mm.) the product was thrice recrystallized from alcohol–water mixture and then had m. p. 52°.

Labelled 1,3,5-*Trimethoxybenzene*.—The rate of loss of deuterium from the aromatic molecule was followed by determination of its deuterium content by infrared spectroscopy. For this purpose the compound must not be labelled randomly. A specimen of 1,3,5-trimethoxy[2-D_1]-benzene was therefore synthesised. Specimens of tritiated and normal trimethoxybenzene were prepared by the same method so as to provide exactly comparable samples.

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[5] Bell, " Proton in Chemistry," Oxford University Press, 1959.

[6] Gold, in " Friedel–Crafts and Related Reactions," ed. G. A. Olah, Vol. 2, ch. 29, Interscience, New York and London, 1964; presented at Gordon Conference on the Physics and Chemistry of Isotopes, New Hampton, N.H., July 1962.

[7] Gold and Tye, *J.*, 1952, 2172; MacLean, van der Waals, and Mackor, *Mol. Physics*, 1958, **1**, 247.

[8] Kresge and Chiang, *J. Amer. Chem. Soc.*, 1962, **84**, 3976.

[9] Clark-Lewis, *Austral. J. Chem.*, 1957, **10**, 505.

[10] Vogel and Cowan, *J.*, 1943, 23.

The labelled compounds were prepared by the decomposition of a suspension of 2,4,6-trimethoxyphenyl-lithium in ether by water containing the appropriate hydrogen isotope.[11] The " water " was added slowly (10 min.) with rapid stirring at 0°. The mixture was allowed to come to room temperature and stirring was continued for a further 30 min. Water was added and the layers were allowed to separate. The ether layer was withdrawn, twice washed with water, and the ether distilled off. The residue was purified by repeated recrystallization (m. p. 52°) from alcohol–water mixtures (yield of crude product 85—88%).

The aryl-lithium compound was prepared * by the reaction of n-butyl-lithium with 2-bromo-1,3,5-trimethoxybenzene in ether suspension at 0° with vigorous stirring.[11] The suspension was then allowed to warm to room temperature and stirred for a further 16 hr.

The activity of the tritiated water used to decompose the aryl-lithium compound was found to be 2·8 times that of the 1,3,5-trimethoxy[2-T]benzene formed as a product of the reaction. This isotope effect is somewhat larger than that (1·0—1·6) recently reported for the protolysis reaction of Grignard compounds.[12]

2-Bromo-1,3,5-trimethoxybenzene was prepared by the slow (2½ hr.) addition with vigorous stirring of bromine (59 g., 0·37 mole) dissolved in chloroform (500 ml.) to 1,3,5-trimethoxybenzene (69 g., 0·41 mole) dissolved in chloroform (1 l.) at room temperature. The chloroform solution was washed with 2N-sodium hydroxide solutions in order to remove any phenolic compounds. The chloroform layer was separated, chloroform distilled off, and the residue thrice crystallized from alcohol. [Bromine and methoxyl group analyses agreed with the formula $C_9H_{11}O_3Br$.] The product had m. p. 98° (lit.,[13] 99°).

Solutions of acetic acid in deuterium oxide were prepared by hydrolysis of a weighed quantity of acetic anhydride in deuterium oxide. After 3 days the solution was made up to the mark. Aqueous solutions of acetic acid of normal isotopic abundance used for rate comparisons with the reaction in deuterated buffer solution were prepared by a similar technique.

Acetate buffer solutions used in the study of the simultaneous loss of tritium and deuterium were prepared by partially neutralizing 8N-acetic acid with 8N-sodium hydroxide solution. Buffer solutions used for the comparison of the acetic acid-catalysed loss of tritium in deuteriated and normal solutions were prepared by the partial neutralization of acetic acid of the correct isotopic abundance by freshly ignited sodium carbonate. Dissolved carbon dioxide was removed by vibrating the flask with a Pifco Massager. The solution was then made up to the correct volume with water of the required isotopic abundance. A stock solution of deuteriated perchloric acid was prepared by diluting a weighed quantity (0·1 ml.) of 70% aqueous perchloric acid to 10 ml. with deuterium oxide.

Tritiated water with a nominal activity of 0·2 curies/ml. was purchased from the U.K.A.E.A.

An Ekco liquid scintillation counter (N 612 B) was used in conjunction with an Ekco scaler (N 530 F) and an Isotope Development Limited E.H.T. unit (532 A) for radioactivity measurement. A Grubb–Parsons S 4 double-beam infrared spectrometer with rock-salt optics was used for deuterium assay.

Kinetic Procedure.—The rates of the following reactions were determined: (1) loss of tritium in aqueous perchloric acid solution; (2) loss of deuterium in aqueous perchloric acid solution; (3) loss of tritium in acetate buffer solution; (4) loss of deuterium in acetate buffer solution; (5) loss of tritium in perchloric acid-deuterium oxide solution; (6) loss of tritium in acetate buffer–deuterium oxide solution.

In order to reduce errors in rate comparisons the following procedures were followed where possible: (*a*) both experiments were carried out simultaneously in the same thermostat bath; (*b*) the tritium samples from one experiment were assayed for radioactivity along with those of the other experiment in a random sequence; (*c*) the tritium and deuterium assays were carried out on the same sample of trimethoxybenzene; (*d*) the reaction mixtures were prepared by the same technique.

In most experiments the total concentration of 1,3,5-trimethoxybenzene (labelled and unlabelled) was about 2×10^{-3}M. The temperature for all experiments was 25°.

Rate Comparisons of Reactions (1) *and* (2).—For experiments in which the faster reaction

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* We thank Dr. D. Bryce-Smith for advice concerning this preparation.

[11] Jones and Gilman, " Organic Reactions," Vol. VI, John Ainley and Sons, Inc., New York, 1951.

[12] Assarson, *Arkiv Kemi*, 1963, **20**, 259.

[13] Hesse, *Annalen*, 1893, **276**, 328.

has a half-life of more than 6 min., eight samples of aqueous trimethoxybenzene solution in 500-ml. volumetric flasks were allowed to come to thermal equilibrium, and the reactions were started in each flask by addition of standard perchloric acid solution. After suitable time intervals the reactions were quenched by pouring the solutions into a five-fold excess of aqueous sodium hydroxide solution.

The 1,3,5-trimethoxybenzene was extracted from the neutralized reaction mixture with freshly distilled peroxide-free ether (250 ml.). The ether layer was separated off, twice washed with water, and then evaporated to dryness. The residue, dried in a vacuum desiccator, was crystalline and melted sharply at 52°. The deuterium assay was performed on 100-mg. samples dissolved in 4 ml. of carbon disulphide by measurement of the intensity of the infrared absorption band at 8·97 μ with a cell of *ca.* 0·05-mm. path length. The tritium activity was measured on a 1-ml. sample of a solution in ethanol containing *ca.* 0·2 mg. of the sample per ml. The exact concentration of 1,3,5-trimethoxybenzene in this solution was determined by measuring the optical density at 266 mμ. The activity was then corrected so as to correspond to a constant concentration or optical density. This technique is possible since the compound has a negligible quenching effect. The counting solution used was 10 ml. of 0·3% P.P.O. (2,5-diphenyloxazole) in toluene solution.

For experiments in which the half-life was less than 6 min. aqueous trimethoxybenzene (500 ml.) was placed in a thermostatted open polythene box ($7\frac{1}{2} \times 2\frac{1}{2}$ in., and $4\frac{1}{2}$ in. deep) which was stirred by two glass twisted-leaf paddles driven at 1500 r.p.m. The reaction was started by breaking a bulb containing 6·09M-perchloric acid solution under the surface of the trimethoxybenzene solution. The reaction was quenched by the addition of excess of sodium hydroxide solution, using the same technique. (6·09M-Perchloric acid has a small heat of dilution.[14]) Mixing was complete in about 0·1 sec. The experiment was repeated for eight different time intervals. The neutralized mixture was filtered to remove glass particles, and the 1,3,5-trimethoxybenzene was extracted and analysed for tritium and deuterium as above.

Because of limitations in the size of the bath, 12M-perchloric acid was used for the fastest experiment attempted. In order to allow for the temperature change due to the heat of mixing (9·8°) the reaction was started when the reagents were at 15·2°. The temperature was measured by using " Pallador " thermocouples (Johnson, Matthey and Co. Ltd.) in conjunction with a sensitive galvanometer.

Rate Comparisons of Reactions (3) *and* (4).—To aqueous 1,3,5-trimethoxybenzene solution (4 l.) the appropriate amount of acetate buffer was added. Eight 500-ml. volumetric flasks, each filled with the reaction mixture to a minimum air space, were placed in the thermostat bath. At suitable time intervals the flasks were withdrawn and the contents mixed with sufficient sodium hydroxide to quench the reaction. The 1,3,5-trimethoxybenzene was extracted and analysed for tritium and deuterium as above.

Rate Comparisons of Reactions (1) *and* (5).—The reaction mixtures were made up separately and the rates determined by the same experimental methods. For reaction (5), 5 ml. of a 1,3,5-trimethoxybenzene solution in deuterium oxide were mixed with $(5 - x)$ ml. of deuterium oxide, and the reaction started by the addition of x ml. of the stock deuteriated perchloric acid solution. At suitable time intervals 1-ml. portions were withdrawn by pipette and run into 2 ml. aqueous sodium hydroxide solution. The neutralized mixture was shaken (2 min.) with AnalaR toluene (20 ml.). The dried ($CaCl_2$) toluene extract (2 ml.) was used for counting. The extraction procedure was shown to be at least 99·8% efficient.

Rate Comparisons of Reactions (3) *and* (6).—Essentially the same techniques were used as for the rate comparisons of reactions (1) and (5).

RESULTS

All runs followed precise first-order kinetics. The observed first-order rate constants for the replacement of the hydrogen isotope Y in the substrate by the isotope X from the solvent is denoted by the symbol ${}^{\mathrm{X}}_{\mathrm{Y}}\lambda$. The catalytic coefficient or second-order rate constant for the reaction in which the hydrogen isotope Y is displaced from the aromatic molecule by the isotope X in the hydrogen ion (${}^{\mathrm{X}}_{\mathrm{Y}}\lambda$/[strong acid]) is given as ${}^{\mathrm{X}}_{\mathrm{Y}}k$. The second-order rate constant for a similar displacement by the acid XA (${}^{\mathrm{XA}}_{\mathrm{YA}}\lambda$/[XA]) is given as ${}^{\mathrm{XA}}_{\mathrm{YA}}k$, where ${}^{\mathrm{XA}}_{\mathrm{YA}}\lambda$ is the contribution

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[14] Bidinosti and Bierman, *Canad. J. Chem.*, 1956, **34**, 1591.

to the total rate due to XA. A bar over a symbol indicates that the value relates to a deuteriated medium.

TABLE 1.

Leaving-atom isotope effect in aqueous perchloric acid solution at 25°.

$[\mathrm{HClO_4}]$	$10^5\,{}^{\mathrm{H}}_{\mathrm{D}}\lambda$ (sec.$^{-1}$)	$10^2\,{}^{\mathrm{H}}_{\mathrm{D}}k$ (sec.$^{-1}$ l. mole^{-1})	$10^5\,{}^{\mathrm{H}}_{\mathrm{T}}\lambda$ (sec.$^{-1}$)	$10^3\,{}^{\mathrm{H}}_{\mathrm{T}}k$ (sec.$^{-1}$ l. mole^{-1})	${}^{\mathrm{H}}_{\mathrm{D}}k/{}^{\mathrm{H}}_{\mathrm{T}}k$
0·00609	8·95	$1{\cdot}47_0$	4·11	6·75	2·18
0·0122	17·2	$1{\cdot}41_0$	7·85	6·43	2·19
0·0609	88·9	$1{\cdot}46_0$	40·0	6·57	2·22
0·122	196	$1{\cdot}60_7$	92·7	7·60	2·11
1·06	2640	$2{\cdot}49_1$	1180	11·13	2·24
1·42	4850	$3{\cdot}41_5$	2370	16·69	2·05
2·04	13,400	6·57	5990	29·36	2·24
		1·45 *		$6{\cdot}5_8$ *	2·18

* Limiting value at low acid concentration. Kresge and Chiang's values [8] for 0·05M-perchloric acid are $10^2\,{}^{\mathrm{H}}_{\mathrm{D}}k = 1{\cdot}330$ sec.$^{-1}$ l. mole^{-1}; $10^3\,{}^{\mathrm{H}}_{\mathrm{T}}k = 6{\cdot}20$ sec.$^{-1}$ l. mole^{-1}; ${}^{\mathrm{H}}k/{}^{\mathrm{H}}_{\mathrm{T}}k = 2{\cdot}15$.

TABLE 2.

Solvent isotope effect in perchloric acid solution at 25°.

$[\mathrm{DClO_4}]$	$10^4\,{}^{\mathrm{D}}_{\mathrm{T}}\bar{\lambda}$ (sec.$^{-1}$)	$10^2\,{}^{\mathrm{D}}_{\mathrm{T}}\bar{k}$ (sec.$^{-1}$ l. mole^{-1})	$[\mathrm{HClO_4}]$	$10^4\,{}^{\mathrm{H}}_{\mathrm{T}}\lambda$ (sec.$^{-1}$)	$10^3\,{}^{\mathrm{H}}_{\mathrm{T}}k$ (sec.$^{-1}$ l. mole^{-1})	${}^{\mathrm{D}}\bar{k}/{}^{\mathrm{H}}_{\mathrm{T}}k$
0·06312	6·88	1·09	0·06105	3·98	6·52	1·67
0·03787	4·17	1·10	0·03663	2·39	6·52	1·69
0·02433	2·72	1·12	0·02400	1·59	6·63	1·69
	Average *	1·10			6·56	1·68

* Kresge and Chiang's values [8] for 0·05M-perchloric acid are $10^2\,{}^{\mathrm{D}}\bar{k} = 1{\cdot}031$ sec.$^{-1}$ l. mole^{-1}; $10^3\,{}^{\mathrm{H}}_{\mathrm{T}}k = 6{\cdot}20$ sec.$^{-1}$ l. mole^{-1}; ${}^{\mathrm{D}}_{\mathrm{T}}\bar{k}/{}^{\mathrm{H}}_{\mathrm{T}}k = 1{\cdot}66$.

TABLE 3.

Leaving-atom isotope effect for catalysis by acetic acid at 25°.

$\frac{[\mathrm{HA}]}{[\mathrm{NaA}]}$	I *	pK_c †	$10^6[\mathrm{H^+}]$	$10^7\,{}^{\mathrm{H}}_{\mathrm{D}}\lambda$ (sec.$^{-1}$)	$10^7\,{}^{\mathrm{H}}_{\mathrm{T}}\lambda$ (sec.$^{-1}$)	$10^8\,{}^{\mathrm{H}}_{\mathrm{D}}k[\mathrm{H^+}]$ ‡ (sec.$^{-1}$)	$10^8\,{}^{\mathrm{H}}_{\mathrm{T}}k[\mathrm{H^+}]$ ‡ (sec.$^{-1}$)	$10^7\,{}^{\mathrm{HA}}_{\mathrm{DA}}\lambda$ (sec.$^{-1}$)	$10^7\,{}^{\mathrm{HA}}_{\mathrm{TA}}\lambda$ (sec.$^{-1}$)	${}^{\mathrm{HA}}_{\mathrm{DA}}k/{}^{\mathrm{HA}}_{\mathrm{TA}}k$
0·10	0·47	4·48	3·31	6·21	3·18	4·80	2·18	5·73	2·95	1·94
0·15	0·20	4·51	4·64	4·10	2·09	6·73	3·05	3·43	1·78	1·93
0·25	0·20	4·51	7·73	6·92	3·61	11·2	5·09	5·80	3·10	1·87
0·50	0·20	4·51	15·5	13·8	7·35	22·5	10·2	11·5	6·33	1·82
1·00	0·20	4·51	30·9	28·2	14·4	44·8	20·3	23·7	12·4	1·91
									Average:	1·89

* I = [NaA] = ionic strength. † Interpolated from figures of Harned and Hickey, *J. Amer. Chem. Soc.*, 1937, **59**, 1284, 2303, for aqueous sodium chloride solutions. ‡ For values of ${}^{\mathrm{H}}_{\mathrm{D}}k$ and ${}^{\mathrm{H}}_{\mathrm{T}}k$ see Table 1.

TABLE 4.

Solvent isotope effect for catalysis by acetic acid at 25°.

[NaA] = Ionic Strength = 0·20; pK_c($\mathrm{CH_3COOH}$) = 4·51; pK_c($\mathrm{CH_3COOD}$) = 4·51 + 0·50 * = 5·01.

$\frac{[\mathrm{HA}]}{[\mathrm{NaA}]}$	$10^6[\mathrm{D^+}]$	$10^6[\mathrm{H^+}]$	$10^7\,{}^{\mathrm{D}}_{\mathrm{T}}\bar{\lambda}$ (sec.$^{-1}$)	$10^7\,{}^{\mathrm{H}}_{\mathrm{T}}\lambda$ (sec.$^{-1}$)	$10^8\,{}^{\mathrm{D}}_{\mathrm{T}}\bar{k}[\mathrm{D^+}]$ † (sec.$^{-1}$)	$10^8\,{}^{\mathrm{H}}_{\mathrm{T}}k[\mathrm{H^+}]$ † (sec.$^{-1}$)	$10^7\,{}^{\mathrm{DA}}_{\mathrm{T}}\bar{\lambda}$ (sec.$^{-1}$)	$10^7\,{}^{\mathrm{HA}}_{\mathrm{TA}}\lambda$ (sec.$^{-1}$)	${}^{\mathrm{DA}}_{\mathrm{TA}}\bar{k}/{}^{\mathrm{HA}}_{\mathrm{TA}}k$
0·25	2·44	7·73	2·43	3·65	2·68	5·07	2·16	3·14	0·688
0·50	4·89	15·5	4·67	7·01	5·38	10·2	4·13	5·99	0·690
0·75	7·33	23·2	7·42	11·0	8·06	15·2	6·61	9·5	0·696
1·00	9·77	30·9	9·87	14·6	10·8	20·3	8·79	12·6	0·698
								Average:	0·693

* Gold and Lowe—unpublished results. † For values of ${}^{\mathrm{D}}_{\mathrm{T}}\bar{k}$ and ${}^{\mathrm{H}}_{\mathrm{T}}k$ see Table 2.

DISCUSSION

The mechanistic alternatives set out at the beginning in terms of the structures (*a*) and (*b*) can be tested by analysing the results of the isotope-effect measurements in terms of specific mechanisms. For any aromatic hydrogen exchange reaction following general acid catalysis we may write the general scheme

$$\mathrm{XA} + \mathrm{ArY} \underset{{}^{\mathrm{X}}_{\mathrm{Y}}{}^{\mathrm{A}}k_{-1}}{\overset{{}^{\mathrm{X}}_{\mathrm{Y}}{}^{\mathrm{A}}k_{1}}{\rightleftarrows}} \text{Symmetrical intermediate} \underset{{}^{\mathrm{Y}}_{\mathrm{X}}{}^{\mathrm{A}}k_{1}}{\overset{{}^{\mathrm{YA}}_{\mathrm{XA}}k_{-1}}{\rightleftarrows}} \mathrm{YA} + \mathrm{ArX}$$

where X and Y denote two different hydrogen isotopes. (If the exchange reaction path should exhibit no minimum for the symmetrical disposition of the entering and leaving nuclei, the intermediate is considered to have infinitesimal stability.) Under the conditions of all our experiments the reaction is practically irreversible, *i.e.*, the step with rate constant ${}^{\mathrm{YA}}_{\mathrm{XA}}k_1$ can be neglected. The experimental second-order rate constant (${}^{\mathrm{XA}}_{\mathrm{YA}}k$) for the above reaction proceeding from left to right is then given by [15,4]

$${}^{\mathrm{XA}}_{\mathrm{YA}}k = \frac{{}^{\mathrm{XA}}_{\mathrm{YA}}k_1}{(1 + {}^{\mathrm{XA}}_{\mathrm{YA}}k_{-1}/({}^{\mathrm{YA}}_{\mathrm{XA}}k_{-1})} \tag{1}$$

Our measurements relate to three such exchange reactions, the replacement of (i) tritium or (ii) deuterium in the aromatic compound by protium (derived from an entirely light medium) or (iii) the replacement of tritium by deuterium (from a fully deuteriated medium). Each of these three exchanges has been studied in dilute mineral acid and in acetate buffer.

According to equation (1), the comparison of reactions (i) and (ii) (the " leaving-atom " isotope effect) is [4]

$$\frac{{}^{\mathrm{HA}}_{\mathrm{DA}}k}{{}^{\mathrm{HA}}_{\mathrm{TA}}k} = \frac{{}^{\mathrm{HA}}_{\mathrm{DA}}k_1(1 + {}^{\mathrm{HA}}_{\mathrm{TA}}k_{-1}/{}^{\mathrm{TA}}_{\mathrm{HA}}k_{-1})}{{}^{\mathrm{HA}}_{\mathrm{TA}}k_1(1 + {}^{\mathrm{HA}}_{\mathrm{DA}}k_{-1}/{}^{\mathrm{DA}}_{\mathrm{HA}}k_{-1})} \tag{2}$$

and the comparison of (i) and (iii) (" solvent isotope effect ") is

$$\frac{{}^{\mathrm{DA}}_{\mathrm{TA}}\bar{k}}{{}^{\mathrm{HA}}_{\mathrm{TA}}k} = \frac{{}^{\mathrm{DA}}_{\mathrm{TA}}\bar{k}_1(1 + {}^{\mathrm{HA}}_{\mathrm{TA}}k_{-1}/{}^{\mathrm{TA}}_{\mathrm{HA}}k_{-1})}{{}^{\mathrm{HA}}_{\mathrm{TA}}k_1(1 + {}^{\mathrm{DA}}_{\mathrm{TA}}\bar{k}_{-1}/{}^{\mathrm{TA}}_{\mathrm{DA}}\bar{k}_{-1})} \tag{3}$$

The preceding formulæ are in the following taken to relate to catalysis by acetic acid. Analogous equations using symbols ${}^{\mathrm{H}}_{\mathrm{D}}k_1$, in place of ${}^{\mathrm{HA}}_{\mathrm{DA}}k_1$ etc. represent the isotope effects for hydrogen-ion catalysis.

The following isotope effects p_{A}, q_{A}, r_{A}, and s_{A} will affect the overall effects to varying extents: [6]

$$p_{\mathrm{A}} = {}^{\mathrm{XA}}_{\mathrm{HA}}k_1/{}^{\mathrm{XA}}_{\mathrm{DA}}k_1 \tag{4}$$

$$q_{\mathrm{A}} = {}^{\mathrm{XA}}_{\mathrm{DA}}k_{-1}/{}^{\mathrm{XA}}_{\mathrm{HA}}k_{-1} \tag{5}$$

$$r_{\mathrm{A}} = {}^{\mathrm{HA}}_{\mathrm{YA}}k_{-1}/{}^{\mathrm{DA}}_{\mathrm{YA}}k_{-1} \tag{6}$$

$$s_{\mathrm{A}} = {}^{\mathrm{HA}}_{\mathrm{YA}}k_1/{}^{\mathrm{DA}}_{\mathrm{YA}}\bar{k}_1 \tag{7}$$

(p, q, r, and s without subscript refer to hydrogen-ion catalysis). It is assumed that these relations hold irrespective of the nature of the isotopes X and Y (so long as they remain constant for a particular comparison). The ratio p_{A} is a small secondary isotope effect to the attachment of X. In other electrophilic substitution reactions the rate of attachment of the electrophilic reagent to the aromatic ring has been found to be unaffected by the isotopic nature of the hydrogen atom at the seat of substitution. However, the results do not rule out an effect of a few percent.[17] In the absence of definite information, p and p_{A} will be assumed to be 1. The secondary isotope effect to X-detachment is likewise expected to be close to unity, but the 30% difference [18] in the rate of ionisation of a single C–D bond in $\mathrm{PhCH_2D}$ and $\mathrm{PhCD_3}$ suggests that the value of q and q_{A} may be as

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[15] Melander and Olsson, *Acta Chim. Scand.*, 1956, **10**, 879.

[16] Willi, *Chimia*, 1961, **15**, 239; *Z. Naturforsch.*, 1961, **16***a*, 162.

[17] Zollinger, " Advances in Physical Organic Chemistry," Vol. 2, ed. V. Gold, Academic Press, London and New York, 1964.

[18] Streitwieser, *Ann. N.Y. Acad. Sci.*, 1960, **84**, 576.

low as 0·85. The two ratios p and q are related; their product is the (unknown) equilibrium constant (here written on the assumption that the intermediate is a free cation)

$$pq = \frac{\left(\overset{+}{\mathrm{Ar}}{<}^{\mathrm{H}}_{\mathrm{X}}\right)(\mathrm{Ar{-}D})}{\left(\overset{+}{\mathrm{Ar}}{<}^{\mathrm{D}}_{\mathrm{X}}\right)(\mathrm{Ar{-}H})}$$

which again must be close to unity. The isotope effects r_{A}, the ratio of the rates of breaking C–H and C–D bonds in the intermediate, and s_{A}, the ratio of the rate of protonation of the aromatic species in ordinary water to the rate of deuteronation in heavy water, are expected to be the more significant contributors to the overall isotope effects. With equations (4)—(7), and assuming Schaad's formula [19] for relating deuterium and tritium isotope effects to apply to both primary and secondary isotope effects (*e.g.*, ${}^{\mathrm{X}}_{\mathrm{T}}k_1/{}^{\mathrm{X}}_{\mathrm{H}}k_1 = ({}^{\mathrm{X}}_{\mathrm{D}}k_1/{}^{\mathrm{X}}_{\mathrm{H}}k_1)^{1\cdot442}$), equations 2 and 3 can be developed as follows:

$$\frac{{}^{\mathrm{HA}}_{\mathrm{DA}}k}{{}^{\mathrm{HA}}_{\mathrm{TA}}k} = p_{\mathrm{A}}{}^{0\cdot442}\,\frac{1+\dfrac{{}^{\mathrm{HA}}_{\mathrm{TA}}k_{-1}}{{}^{\mathrm{HA}}_{\mathrm{HA}}k_{-1}}\cdot\dfrac{{}^{\mathrm{HA}}_{\mathrm{HA}}k_{-1}}{{}^{\mathrm{TA}}_{\mathrm{HA}}k_{-1}}}{1+\dfrac{{}^{\mathrm{HA}}_{\mathrm{TA}}k_{-1}}{{}^{\mathrm{HA}}_{\mathrm{HA}}k_{-1}}\cdot\dfrac{{}^{\mathrm{HA}}_{\mathrm{HA}}k_{-1}}{{}^{\mathrm{DA}}_{\mathrm{HA}}k_{-1}}} = p_{\mathrm{A}}{}^{0\cdot442}\,\frac{1+(q_{\mathrm{A}}r_{\mathrm{A}})^{1\cdot442}}{1+q_{\mathrm{A}}r_{\mathrm{A}}} \tag{8}$$

$$\frac{{}^{\mathrm{DA}}_{\mathrm{TA}}\bar{k}}{{}^{\mathrm{HA}}_{\mathrm{TA}}k} = \frac{1}{s_{\mathrm{A}}}\cdot\frac{1+\dfrac{{}^{\mathrm{HA}}_{\mathrm{TA}}k_{-1}}{{}^{\mathrm{HA}}_{\mathrm{HA}}k_{-1}}\cdot\dfrac{{}^{\mathrm{HA}}_{\mathrm{HA}}k_{-1}}{{}^{\mathrm{TA}}_{\mathrm{HA}}k_{-1}}}{1+\dfrac{{}^{\mathrm{DA}}_{\mathrm{TA}}\bar{k}_{-1}}{{}^{\mathrm{DA}}_{\mathrm{DA}}\bar{k}_{-1}}\cdot\dfrac{{}^{\mathrm{DA}}_{\mathrm{DA}}\bar{k}_{-1}}{{}^{\mathrm{TA}}_{\mathrm{DA}}\bar{k}_{-1}}} = \frac{1+(q_{\mathrm{A}}r_{\mathrm{A}})^{1\cdot442}}{s_{\mathrm{A}}[1+(q_{\mathrm{A}}r_{\mathrm{A}})^{0\cdot442}]} \tag{9}$$

By setting $p_{\mathrm{A}} = 1$, these equations can be solved for s_{A} and $(q_{\mathrm{A}}r_{\mathrm{A}})$ [and similarly the analogous equations for s and (qr)], with the results given in Table 5.

TABLE 5.

Kinetic isotope effects in the acid-catalysed hydrogen exchange reaction of aromatic compounds at 25°.

Compound	Catalyst	${}^{\mathrm{H}}_{\mathrm{D}}k/{}^{\mathrm{H}}_{\mathrm{T}}k$*	${}^{\mathrm{D}}_{\mathrm{T}}\bar{k}/{}^{\mathrm{H}}_{\mathrm{T}}k$**	qr	r***	s
p-Cresol ‡	H_3O^+	2·5	1·62	8·93	10·5	4·3
1,3,5-Trimethoxybenzene	H_3O^+	2·17	1·68	6·84	8·05	3·0
1,3,5-Trimethoxybenzene	CH_3CO_2H	1·89	0·693	5·14	6·05	5·5

* Leaving-atom isotope effect. ** Solvent isotope effect. *** Calc. with $q = 0\cdot85$. ‡ Gold, Lambert, and Satchell, *J.*, 1960, 2461. (This value of ${}^{\mathrm{H}}k/{}^{\mathrm{H}}_{\mathrm{T}}k$ is less reliable than the other results of this Table.)

Note: The symbols ${}^{\mathrm{HA}}k$, p_{A}, etc., apply to the third line.

The interest in these parameters as a test of mechanism lies in the fact that they are interrelated if the symmetrical intermediate is (a) and common to both forms of catalysis, *i.e.*, $\left\{\mathrm{Ar}{<}^{\mathrm{H}}_{\mathrm{H}}\right\}^{+}$. Under these conditions the ratios k_1/k_{-1} are the equilibrium constants for hydrogen transfer reactions, as follows:

$$\frac{{}^{\mathrm{HA}}_{\mathrm{XA}}k_1}{{}^{\mathrm{HA}}_{\mathrm{XA}}k_{-1}} = \frac{K^{\mathrm{H}}_{\mathrm{HA}}}{K^{\mathrm{H}}_{\mathrm{ArXH^+}}} \tag{10}$$

$$\frac{{}^{\mathrm{DA}}_{\mathrm{XA}}\bar{k}_1}{{}^{\mathrm{DA}}_{\mathrm{XA}}\bar{k}_{-1}} = \frac{\bar{K}^{\mathrm{D}}_{\mathrm{DA}}}{\bar{K}^{\mathrm{D}}_{\mathrm{ArXD^+}}} \tag{11}$$

$$\frac{{}^{\mathrm{H}}_{\mathrm{X}}k_1}{{}^{\mathrm{H}}_{\mathrm{X}}k_{-1}} = \frac{1}{K^{\mathrm{H}}_{\mathrm{ArXH^+}}} \tag{12}$$

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[19] Swain, Stivers, Reuwer, and Schaad, *J. Amer. Chem. Soc.*, 1958, **80**, 5885.

$$\frac{{}^{\mathrm{D}}_{\mathrm{X}}\bar{k}_1}{{}^{\mathrm{D}}_{\mathrm{X}}\bar{k}_{-1}} = \frac{1}{\bar{K}^{\mathrm{D}}_{\mathrm{ArXD+}}} \tag{13}$$

where $\bar{K}^{\mathrm{D}}_{\mathrm{ArXD+}}$ denotes the acidity constant for deuteron loss from $\mathrm{ArXD^+}$, the bar symbolising deuterium oxide medium, with corresponding meaning for the other constants.

Combining equations (10)—(13), we obtain

$$\frac{K^{\mathrm{H}}_{\mathrm{HA}}}{\bar{K}^{\mathrm{D}}_{\mathrm{DA}}} = \frac{{}^{\mathrm{HA}}_{\mathrm{XA}}k_1}{{}^{\mathrm{HA}}_{\mathrm{XA}}k_{-1}} \cdot \frac{{}^{\mathrm{DA}}_{\mathrm{XA}}\bar{k}_{-1}}{{}^{\mathrm{DA}}_{\mathrm{XA}}\bar{k}_1} \cdot \frac{{}^{\mathrm{D}}_{\mathrm{X}}\bar{k}_1}{{}^{\mathrm{D}}_{\mathrm{X}}\bar{k}_{-1}} \cdot \frac{{}^{\mathrm{X}}_{\mathrm{H}}k_{-1}}{{}^{\mathrm{H}}_{\mathrm{X}}k_1}$$

Multiplication of numerator and denominator by ${}^{\mathrm{HA}}_{\mathrm{XA}}\bar{k}_{-1}$ and ${}^{\mathrm{H}}_{\mathrm{X}}\bar{k}_{-1}$ and rearrangement of factors then yields

$$\frac{K^{\mathrm{H}}_{\mathrm{HA}}}{\bar{K}^{\mathrm{D}}_{\mathrm{DA}}} = \frac{{}^{\mathrm{HA}}_{\mathrm{XA}}k_1}{{}^{\mathrm{DA}}_{\mathrm{XA}}\bar{k}_1} \cdot \frac{{}^{\mathrm{D}}_{\mathrm{X}}\bar{k}_1}{{}^{\mathrm{H}}_{\mathrm{X}}k_1} \cdot \frac{{}^{\mathrm{DA}}_{\mathrm{XA}}\bar{k}_{-1}}{{}^{\mathrm{HA}}_{\mathrm{XA}}\bar{k}_{-1}} \cdot \frac{{}^{\mathrm{H}}_{\mathrm{X}}\bar{k}_{-1}}{{}^{\mathrm{D}}_{\mathrm{X}}\bar{k}_{-1}} \cdot \frac{{}^{\mathrm{H}}_{\mathrm{X}}k_{-1}}{{}^{\mathrm{H}}_{\mathrm{X}}\bar{k}_{-1}} \cdot \frac{{}^{\mathrm{HA}}_{\mathrm{XA}}\bar{k}_{-1}}{{}^{\mathrm{HA}}_{\mathrm{XA}}k_{-1}}$$

The first four factors can be expressed in terms of equations (6) and (7) (and their analogues for hydrogen-ion catalysis), so that

$$\frac{K^{\mathrm{H}}_{\mathrm{HA}}}{\bar{K}^{\mathrm{D}}_{\mathrm{DA}}} = \frac{s_{\mathrm{A}}r}{sr_{\mathrm{A}}} \cdot \frac{{}^{\mathrm{H}}_{\mathrm{X}}k_{-1}}{{}^{\mathrm{H}}_{\mathrm{X}}\bar{k}_{-1}} \cdot \frac{{}^{\mathrm{HA}}_{\mathrm{XA}}\bar{k}_{-1}}{{}^{\mathrm{HA}}_{\mathrm{XA}}k_{-1}} \tag{14}$$

We assume the last factor in this product to be unity, since it corresponds only to a medium isotope effect for the transfer of a *proton* from the intermediate to the acetate ion. The preceding factor represents a medium isotope effect for the loss of proton from the intermediate to protium oxide or deuterium oxide. Data have been presented [20] to suggest that this effect is likewise small, but the following evaluation of its magnitude is also possible. On the basis of the Brönsted catalysis law the rate constants of the two reactions concerned

$$\mathrm{ArXH^+} + \mathrm{H_2O} \xrightarrow{{}^{\mathrm{H}}_{\mathrm{X}}k_{-1}} \mathrm{ArX} + \mathrm{H_3O^+}\ (\text{in } \mathrm{H_2O})$$

$$\mathrm{ArXH^+} + \mathrm{D_2O} \xrightarrow{{}^{\mathrm{H}}_{\mathrm{X}}\bar{k}_{-1}} \mathrm{ArX} + \mathrm{HD_2O^+}\ (\text{in } \mathrm{D_2O})$$

should be related. Writing the expressions for the rate constants [21] with inclusion of the appropriate statistical factors,[22] we obtain

$$\frac{{}^{\mathrm{H}}_{\mathrm{X}}k_{-1}}{2} = G\left(\frac{3}{2K^{\mathrm{H}}_{\mathrm{H_3O+}}}\right)^{\alpha}$$

and

$$\frac{{}^{\mathrm{H}}_{\mathrm{X}}\bar{k}_{-1}}{2} = G\left(\frac{1}{2K^{\mathrm{H}}_{\mathrm{HD_2O+}}}\right)^{\alpha}$$

From the relationship between the acidity constants of the isotopic hydrogen ions,[21] it then follows that

$$\frac{{}^{\mathrm{H}}_{\mathrm{X}}k_{-1}}{{}^{\mathrm{H}}_{\mathrm{X}}\bar{k}_{-1}} = l^{-2\alpha}$$

Since the Brönsted exponent for k_1 is 0·52,[2] the value of α for k_{-1} is 0·48. Taking [21] $l =$ 0·69, we then obtain ${}^{\mathrm{H}}_{\mathrm{X}}k_{-1}/{}^{\mathrm{H}}_{\mathrm{X}}\bar{k}_{-1} = 1{\cdot}43$. Substituting this value, and the results from Table 5, in equation (14), we obtain $K^{\mathrm{H}}_{\mathrm{HA}}/\bar{K}^{\mathrm{D}}_{\mathrm{DA}} = 3{\cdot}5$. Bearing in mind that some assumptions have had to be made, we regard this value to be in satisfactory agreement with the experimental value for this ratio [23] (3·3). The results thus support the mechanistic ideas on

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[20] Long and Riley, *J. Amer. Chem. Soc.*, 1962, **84**, 522.

[21] Gold, *Proc. Chem. Soc.*, 1963, 141.

[22] Benson, *J. Amer. Chem. Soc.*, 1958, **80**, 5151; Gold, *Trans. Faraday Soc.*, 1964, **60**, 738.

[23] Gold and Lowe, unpublished results.

which this mathematical analysis is based, namely, that catalysis of the exchange by hydrogen ions and by acetic acid follows the same mechanism in which the conjugate acid of the aromatic substrate [*i.e.*, structure (a)] is the symmetrical intermediate.

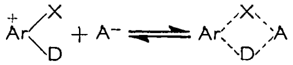
On the other hand, if the symmetrical intermediate had structure (*b*) for catalysis by the weak carboxylic acid HA, but structure (*a*) for catalysis by the hydrogen ion, the rate coefficients of the steps leading to its formation and decomposition would be related in a different way. Equations (10) and (11) would now take the form

$$\frac{{}^{\rm HA}_{\rm XA}k_1}{{}^{\rm HA}_{\rm XA}k_{-1}} = \frac{K^{\rm H}_{\rm HA}}{K^{\rm H}_{\rm ArXH^+}} \cdot \frac{1}{K^{\rm XH}_{\rm ass.}} \qquad (10')$$

and

$$\frac{{}^{\rm DA}_{\rm XA}\bar{k}_1}{{}^{\rm DA}_{\rm XA}\bar{k}_{-1}} = \frac{\bar{K}^{\rm D}_{\rm DA}}{\bar{K}^{\rm D}_{\rm ArXD^+}} \cdot \frac{1}{K^{\rm XD}_{\rm ass.}} \qquad (11')$$

where $\bar{K}^{\rm XD}_{\rm ass.}$ is the equilibrium constant for the hypothetical association reaction



(the superscripts denoting the isotopic hydrogen atoms in the intermediate, and the bar over the symbol deuterium oxide as reaction medium.) It follows that the right-hand side of equation (14) would now contain the additional factor $\bar{K}^{\rm XD}_{\rm ass.}/K^{\rm XH}_{\rm ass.}$ which is expected to differ from unity by a factor of the order of that found for hydrogen isotope effects on hydrogen bonds.[24] Such effects would be large enough to destroy the good agreement between the directly determined value of the ratio $K^{\rm H}_{\rm HA}/\bar{K}^{\rm D}_{\rm DA}$ and that calculated from the present results on the basis of structure (*a*).

A similar derivation leads from equations (12) and (13) to the ratio of the acidity constants of the intermediate; $K^{\rm H}_{\rm ArXH^+}/\bar{K}^{\rm D}_{\rm ArXD^+} = 3{\cdot}9$. This value assumes $q = 0{\cdot}85$; with $q = 1$, the corresponding ratio is $3{\cdot}3_5$. Either ratio seems reasonable in view of our limited understanding of these isotope effects on acid dissociation constants.

This complete analysis utilises data on very dilute solutions of perchloric acid but the absence of any perceptible trend in the leaving-atom isotope effect (Table 1) as the acid concentration is varied by a factor of over 300 (and the rate by a factor of over 1000) argues against a change of mechanism at least up to 2M-perchloric acid.

In absolute magnitude the values of r, s, $r_{\rm A}$, and $s_{\rm A}$ are remarkably large. The isotope effect for hydrogen transfer to the aromatic substrate is smaller for the stronger acid (H_3O^+) as expected (*i.e.*, $s < s_{\rm A}$). The value of r is close to the calculated maximum isotope effect for C–H bond rupture in a methylene group.[8] Large structural changes in the base which accepts the proton transferred from the intermediate must therefore lead to a smaller value of this isotope effect,[25] irrespective of whether the base is stronger than water (as in the present case, on going from water to the acetate ion) or weaker. These considerations explain the experimentally found order $r > r_{\rm A}$, which is opposed to an earlier generalisation [19] linking isotope effect and base strength in proton transfer. A similar point has been raised by Dr. A. J. Kresge regarding the variation of r with structure of the aromatic substrate.[26]

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[24] McDougall and Long, *J. Phys. Chem.*, 1962, **66**, 429.

[25] Westheimer, *Chem. Rev.*, 1961, **61**, 265; Bigeleisen, Symposium on Isotope Mass Effects in Chemistry and Biology, I.A.E.A., Vienna, 1963; *Pure and Appl. Chem.*, 1964, **8**, 217.

[26] Kresge, discussion remarks, Symposium on Isotope Mass Effects in Chemistry and Biology, I.A.E.A., Vienna, 1963; *Pure and Appl. Chem.*, 1964, **8**, 517.