362. *Direct Introduction of Deuterium into the Aromatic Nucleus. Part I. Qualitative Comparison of the Efficiencies of Some Acidic Deuterating Agents and of the Influence of Some Aromatic Substituents.*

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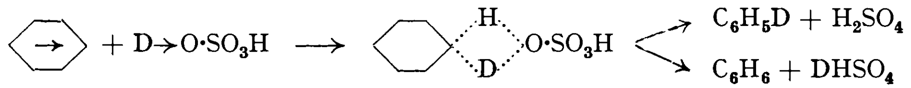
The logical commencement of the researches to be described in this series has already been published, first as a brief note (*Nature*, 1934, **134**, 734), and then somewhat more fully in connexion with our work on the stereochemistry of benzene (this vol., p. 915). It consisted in showing that sulphuric acid containing deuterium can be used in order to introduce this isotope into the benzene molecule.

Consideration of the electronic classification and general chemical behaviour of the two participants in this exchange reaction led us to the view (*Nature*, 1934, **134**, 847) that it was probably identical in mechanism with ordinary electrophilic substitutions; we formulated it thus:



The implications of this hypothesis have not yet been discussed in any detail, although we have given reasons for our disbelief in other suggested mechanisms (*loc. cit.*; this vol., p. 917). The work now to be described is largely based on a consideration of the theoretical requirements of the mechanism advanced.

The most critical group of requirements is that the deuteration of the substitution products of benzene by acidic reagents such as sulphuric acid should follow the known rules for orientation and velocity in electrophilic aromatic substitutions (Ingold, *Rec. trav. chim.*, 1929, **48**, 797). To take a few examples, the substituents ·SO_3H and ·NO_2 should strongly retard deuteration, but in the event of its occurrence should direct it to the *m*-positions; the groups ·Cl and ·Br should retard deuteration, but direct it to the *o*- and *p*-positions; ·Me should accelerate deuteration, moderately for the *o*- and *p*-positions but only slightly for the *m*-positions; ·OMe should considerably accelerate deuteration in the *o*- and *p*-positions and slightly retard it in the *m*-positions; ·NMe_2 should strongly accelerate deuteration, but only in the *o*- and *p*-positions; and ·$\overset{-}{O}$ should do the same more strongly still. Reference to the paper cited will show that many definite predictions could be made.

A second group of theoretical requirements relates to the relative efficiencies of different deuterating agents: for any given benzene derivative the deuterating efficiencies of different acid reagents should increase with the hydrion-donating * power of the reagent. For

* We reserve the term hydrion to connote a hydrogen nucleus no matter whether it is a proton or a deuteron; the ion $H_3\overset{+}{O}$ is called the hydroxonium ion.

instance, the series $H_2SO_4 > H_3\overset{+}{O} > HOAc > H_2O$ represents hydrion-donating power, as one can easily see by considering which of any two neighbouring members would preferentially transfer a hydrion to some suitably chosen weak base. Our hypothesis requires that, if the entities formulated contain deuterium, the above series will represent their deuterating efficiencies.

This paper records part of a preliminary survey of the experimental enquiries suggested by these two sets of deductions. The survey will be extended and followed by more detailed investigations of those parts of the field which promise to repay fuller study. Our object hitherto, however, has been to discover whether the broad qualitative relationships fit in with the mechanistic picture we have advanced. We consider below the following aromatic substituents and deuterating agents :

Substituents ....$\cdot SO_3H$, $(\cdot H)$, $\cdot OMe$, $\cdot NMe_2$, $\cdot\overset{-}{O}$
Reagents......................H_2SO_4, H_2SeO_4, (HNO_3), $H_3\overset{+}{O}$, HOPh, H_2O

The results are first described, and then summarised in the form of comparative statements about the substituents and deuterating agents.

Results.

Benzene.—Hydrogen exchange occurs with sulphuric acid, and less readily with selenic acid. A selection of results is given in Table I, the headings of which are self-explanatory. The figures show that, with sulphuric acid of 62 mols.% concentration, deuteration nearly reaches equilibrium in the course of one day at room temperature. Two experiments are included in which equilibrium was fully attained, and the results illustrate our finding that the deuterium partition-ratio * is approximately unity. As already reported, sulphonation in general accompanies deuteration, but the former reaction is the more effectively suppressed by the addition of water. With selenic acid of 65 mols. % concentration as reagent, deuteration is still far from its equilibrium value after 6 days at room temperature. With nitric acid of various concentrations, either without a solvent or in the presence of sufficient acetic acid to render the mixture with benzene homogeneous, no deuteration could be observed although nitration took place ; it seems impossible to cause deuteration to precede nitration. Aqueous hydrochloric acid does not deuterate benzene.

TABLE I.

Atoms H in acid per mol. of C_6H_6.	Concn. of aq. acid (mols. % H_2SO_4 or H_2SeO_4).	Time at room temp. (hours).	Benzene sulphonated (%).	Excess density (p.p.m.) of		
				H_2O in H_2O+xSO_3 (SeO_3).		H_2O from C_6H_6.
				Initl.	Final (diff.).	
Sulphuric acid						
6	62·3	3	20	2165	2082	83
6	62·3	24	20	2165	1215	950
6	57·4	24	4	1215	1014	201
6	42·4	24	0	2165	2157	8
6	16·5	120	0	2165	2165	0
18	62·6	108	50	2193	1613	1741
18	54·9	108	10	2183	1616	1698
Selenic acid.						
1	64·8	144	—	2300	1960	340
1	57·2	216	—	1600	1500	100

Benzenesulphonic Acid.—We have already published observations (this vol., p. 917) showing that benzenesulphonic acid undergoes no perceptible deuteration with sulphuric acid under conditions in which the deuteration of benzene proceeds to equilibrium.

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* The " partition-ratio " is the proportion at equilibrium of deuterium in the exchangeable hydrogen of the organic compound, divided by the proportion in the exchangeable hydrogen of the reagent. In the limit of low deuterium concentrations, this is evidently the same as the " equivalent equilibrium constant " which has elsewhere been defined as the deuterium/protium ratio in the exchangeable hydrogen of the organic compound divided by the corresponding ratio for the exchangeable hydrogen of the reagent.

Anisole.—Results for the deuteration of anisole with sulphuric acid are given in Table II, the headings of which explain themselves except that of the last column. The figures under this heading represent the statistical average number of positions in the anisole molecule which we calculate to have undergone exchange under the assumption of equilibria governed for each position by a deuterium partition-ratio of unity.* This ratio has been shown to be nearly unity in the case of benzene, and therefore it must be nearly unity for the nuclear positions of anisole, since it is determined essentially by vibration frequencies which are not much influenced by the substituent. Our results show that the exchange reaction with anisole proceeds at first very rapidly, but only with respect to three positions; when this rapid reaction has ceased, deuteration continues, but very much more slowly. We assume that the rapidly exchanged atoms are those of the *o*- and *p*-positions, whilst the slowly substituted ones are those of the *m*-positions; the rate relations are then as we should expect from the theory of the substitution. Orientation experiments on such products of directed deuteration are being carried out and will be discussed in another connexion. Aqueous hydrochloric acid, which has no effect on benzene, slowly deuterates anisole. The results showing this are included in Table III for comparison with corresponding data relating to dimethylaniline. Anisole is not deuterated by neutral water, and even **1** : **3** : 5-trimethoxybenzene was unaffected by heating with " heavy " water for several weeks at 100°.

TABLE II.

Deuteration of Anisole with Sulphuric Acid.

Concn. of initial aqueous acid = 54·5 mols. %. Excess density of H_2O in initial $H_2O + xSO_3$ = 2343 p.p.m.

Atoms H in acid per mol. of PhOMe.	Time at room temp. (hours).	Anisole sulphonated (%).	Excess density (p.p.m.) of H_2O in $H_2O + xSO_3$ (final, by diff.).	Excess density (p.p.m.) of H_2O from combustion of PhOMe.	Statistical exchange number.
3·93	6	6	1370	478	2·8
4·07	84	30	1334	514	3·1
3·95	168	>30	1239	546	3·5

Dimethylaniline.—This substance has been deuterated by means of aqueous hydrochloric acid under the conditions specified in Table III. Salt formation occurs, with the result that, of the two reacting entities, which we assume to be the hydroxonium ion and the free dimethylaniline base, one is always present in necessarily low concentration. This being taken into account, it is apparent from the figures of Table III that the exchange reaction between dimethylaniline and hydroxonium ion has a greater specific rate than the corresponding reaction of anisole. The observed rate of reaction of dimethylaniline appears to have the same sort of magnitude no matter whether the hydrochloric acid is in small stoicheiometric deficit or in considerable excess with respect to the base, and this is what we should expect from the operation of the mass law for a reaction between the

TABLE III.

Deuteration of Anisole and Dimethylaniline with Aqueous Hydrochloric Acid.

Excess density of H_2O corresponding to total H in initial $xHCl + yH_2O$ = 2165 p.p.m.

R in C_6H_5R.	Time at room temp. (days).	G.-mols. HCl.	G.-mols. H_2O.	G.-mols. C_6H_5R.	Excess density of combustion water (p.p.m.).
OMe	5	0·20	0·90	0·50	3
	11	0·20	1·01	0·28	20
NMe_2	9	0·20	0·90	0·24	26
	48	0·20	0·90	0·24	160
	7	0·20	2·67	0·08	17

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* We may define " statistical exchange number " in a more general way as the number of hydrogen atoms calculated to have undergone exchange under the assumption that an equilibrium is established which is governed by an " equivalent equilibrium constant " of unity (see footnote p. 1638). In the limit of low deuterium concentrations the definition in the text is equivalent.

free base and hydroxonium ions. The low concentrations of free acid which are effective in the exchange make it impossible to suppose that un-ionised hydrogen chloride is concerned, and we know that the exchange is not to be attributed to the action of water molecules on the base, special experiments having shown that this reaction is quite inappreciable.

Phenol.—This substance rapidly exchanges one hydrogen atom, presumably that of the hydroxyl group, with water alone; the deuterium partition-ratio is about 1·08. The reaction has previously been observed by Harada and Titani (*Bull. Chem. Soc. Japan*, 1935, **10**, 554; 1936, **11**, 465), who obtained almost the same partition-ratio (1·07 ± 0·05). It should be said that, as this exchange is rapid, no method of separating the phenol for isotopic analysis can be guaranteed not to disturb the deuterium distribution. The Japanese authors used extraction with carbon tetrachloride. We employed distillation or extraction with ether alternatively, in the belief that the error due to the latter method would be different from, and probably much less than, that of the former, so that by comparing the results one could estimate the seriousness of the disturbance. It does not appear to be serious in the case of phenol, since the results agreed closely, as is shown in the first two lines of Table IV.*

We have further observed that in the presence of alkali three more hydrogen atoms, presumably those of the *o*- and *p*-positions, become exchangeable, although more slowly. Calculated over all four exchangeable atoms, the deuterium partition-ratio is close to unity. These statements are illustrated in the last three lines of Table IV.

TABLE IV.

Deuteration of Phenol by Means of Water and Aqueous Alkali.

		Mols.				Excess density (p.p.m.) of			
						H_2O in H_2O+xNa_2O.			
Time (days).	Temp.	PhOH.	H_2O.	NaOH.	Method of separation.	Initial.	Final (diff.).	H_2O from PhOH.	Statistical exchange number.
0·6	25°	0·281	0·552	—	D	2165	1705	301	1·06
20	25	0·271	0·554	—	E	2165	1710	310	1·09
14	50—60	0·289	0·554	0·128	E	1941	1268	480	2·3 †
30 + 7	100 25	0·223	0·553	0·148	E	1910	1093	766	4·2
44 + 10	100 25	0·263	0·554	0·143	E	1916	1053	685	3·9

Note : D = Distillation. E = Extraction with ether.

† Not in equilibrium.

In our first consideration of the question of which entities could be concerned in the nuclear deuteration, we set down the four possibilities (1) $H_2O + PhOH$, (2) $\overset{-}{O}H + PhOH$, (3) $H_2O + Ph\overset{-}{O}$, (4) $\overset{-}{O}H + Ph\overset{-}{O}$, and expected to establish the correctness of (3). Mechanism (1) was excluded by the fact that alkali was necessary for the nuclear exchange. In order to distinguish (4) from (2) and (3) we carried out two experiments with reagents in the approximate proportions PhOH + 2NaOH and PhOH + 3NaOH. On passing from the first of these to the second, [PhOH] is halved, [$Ph\overset{-}{O}$] remains stationary, and [$\overset{-}{O}H$] is doubled, so that for mechanisms (2) and (3) the speed should remain unchanged whilst for (4) it should be doubled. Actually, it was appreciably reduced, and this led us to a fifth possibility, which we ought to have foreseen would be the most important, *viz.*, (5) $PhOH + Ph\overset{-}{O}$.

The characteristic feature of this mechanism is that the speed of deuteration should pass through a sharp maximum when the reagents are in the proportion PhOH + $\frac{1}{2}$NaOH.

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* If only one hydrogen atom is exchangeable, the statistical exchange number is the same as the deuterium partition-ratio in the limit of low deuterium concentration; if *n* atoms are exchangeable the exchange number is *n* times the partition-ratio in the same limit.

The results in Table V show that there is indeed a strong maximum somewhere in this neighbourhood.

In explanation of the table it must be noted that, as we were concerned only with nuclear deuteration, we wished to avoid the complications arising from the introduction of deuterium into the side group; therefore, the phenol was isolated as anisole by methylating it with methyl sulphate under standard conditions; the excess densities recorded in col. 8 are those of the water of combustion of the anisole thus formed, and the very small correction ($<$ 6 p.p.m.) necessary to allow for the deuteration which occurs during methylation has been applied. From these excess densities we can calculate those of water corresponding to the hydrogen in the three exchangeable nuclear positions, and these values are in col. 9.

It seemed necessary to have some aid to the comparison of these values, although, as a kinetic analysis of a trideuteration, which must consist of several simultaneous chains each of three consecutive reactions, is obviously out of the question, any numerical device designed to assist a comparison of rates must necessarily be arbitrary. Some of the experiments enable us to calculate the deuterium partition-ratio for the three exchangeable nuclear positions taken collectively; these ratios are in col. 12. From the mean of these partition-ratios (0·90) we can calculate the excess density of water corresponding to the hydrogen which would be in the three exchangeable positions in each case at infinite time. These figures are in col. 10, and comparison with the numbers in col. 9 indicates the extent to which the reaction has proceeded at the times stated. As these times are not always the same, and we do not know the precise rate law, we have where possible calculated a rate " constant " on the arbitrary assumption that the rate law approximates to the exponential form which it would have if the process were a single-stage one. These " constants " are in col. 11; it will be understood that they are intended for qualitative comparison only, and have no precise chemical meaning.

TABLE V.

Rate of Deuteration of Phenol at 100° *by Means of Aqueous Sodium Hydroxide.*

G.-mols.			Ratio NaOH PhOH.	Time, t (hrs.).	Excess density (p.p.m.) in H_2O from H in :					Rate " constant " (10^{-3}, hrs.$^{-1}$).	Deuterium partition ratio.
					All reactants less NaOPh.			Exchangeable nuclear H.			
PhOH.	H_2O.	NaOH.			Initial.	Final (diff.).	PhOMe.	At t.	$t = \infty$ (calc.).		
0·169	4·14	0·303	1·79	96	2048	2029	123	328	1758	2·15	—
0·154	4·14	0·437	2·82	96	2021	2010	77	205	1745	1·30	—
0·161	4·14	0·220	1·37	96	2070	2035	236	629	1781	4·54	—
0·161	4·11	0·162	1·00	96	2083	1981	678	1808	—	—	0·91
0·163	4·14	0·077	0·47	96	2105	2003	682	1815	—	—	0·91
0·168	4·14	0·171	1·02	18	2080	2029	326	869	1784	37·1	—
0·168	4·14	0·040	0·24	24	2112	2006	670	1787	—	$>$100	0·89
0·170	3·41	0·000	0·00	22	2113	2112	4	11	1791	0·28	—
										(Mean)	0·90

One other conclusion may be drawn from the figures, *viz.*, that, accompanying reaction (5) $(\mathrm{PhOH}+\mathrm{Ph}\bar{\mathrm{O}})$, there is a much slower reaction, which we presume to be (3) $(\mathrm{H_2O}+\mathrm{Ph}\bar{\mathrm{O}})$. If mechanism (5) operated alone, the speed of deuteration should fall practically to zero in the presence of slightly more than 1 equiv. of sodium hydroxide; actually, it falls to a small finite value, which only slowly diminishes as the relative amount of sodium hydroxide is increased. This residual rate we take to be due essentially to mechanism (3); and here we are guided by theory, as there is nothing in the observations which excludes mechanism (2). The slow diminution referred to shows that mechanism (4) is absent, since this reaction would require an increase.

The predominance of reaction (5) should have been anticipated from our general theory, which requires the most rapid reaction to be between the most electrophilic (in this case acidic) deuterating agent and the most nucleophilic aromatic compound; evidently phenol (containing PhOD) is the most acidic deuterating agent present in the system, whilst the phenoxide ion is certainly the most nucleophilic aromatic compound.

Discussion.

The results described in the foregoing section may be summarised in the following scheme, which represents the relative deuterating efficiencies of reagents, and the behaviour of aromatic substituents in retarding or facilitating deuteration :

$$\begin{array}{lll}
\text{PhH} & H_2SO_4 > H_3\overset{+}{O},\ H_2O & \\
 & H_2SO_4 > H_2SeO_4\ (>HNO_3) & \text{With } H_2SO_4:\ \cdot SO_3H < \cdot H < \cdot OMe \\
\text{PhOMe} & H_2SO_4 > H_3\overset{+}{O} > H_2O & \\
 & & \text{With } H_3\overset{+}{O}:\ \cdot OMe < \cdot NMe_2 \\
\text{PhNMe}_2 & H_3\overset{+}{O} > H_2O & \\
 & & \text{With } H_2O:\ \cdot NMe_2 < \cdot \overset{-}{O} \\
\text{Ph}\overset{-}{O} & PhOH > H_2O > \overset{-}{O}H &
\end{array}$$

The position of nitric acid in the scheme is uncertain from an experimental point of view. Theoretically we expect it to fall below sulphuric acid and above the hydroxonium ion in the deuterating efficiency series; but deuteration with the three reagents mentioned is sought or observed against different backgrounds—sulphonation in one case, nitration in another, and no competing reaction in the third—and this makes it impossible to base on the absence of any observed deuteration with nitric acid a definite conclusion regarding the relation of its deuterating efficiency to that of the other reagents.

By making the probable, although unproved, assumption that the deuterating efficiency of the hydroxonium ion is greater than that of phenol ($H_3\overset{+}{O} > PhOH$), we can digest the above summary still further as follows :

$$\begin{array}{ll}
\text{Aromatic substituents ......} & \cdot\overset{-}{O} > \cdot NMe_2 > \cdot OMe > \cdot H > \cdot SO_3H \\
\text{Deuterating agents ....} & H_2SO_4 > H_2SeO_4 > H_3\overset{+}{O} > PhOH > H_2O > \overset{-}{O}H
\end{array}$$

These series agree well with what we should expect from our conception of the deuteration as an electrophilic aromatic substitution of the ordinary type—the only essentially special feature being that the reagent attacks through hydrogen, *i.e.*, that its electrophilic functions are in this particular case acidic functions.

EXPERIMENTAL.

Preparation of Materials.—The substitutions were usually carried out with reagents the hydrogen of which contained about 2 atoms % of deuterium. As it was unnecessary, indeed undesirable, that the reagents should be anhydrous, they were usually made by adding a small amount of commercial 20% or 99% deuterium oxide to the ordinary " light " reagent; this applies to sulphuric, selenic, and nitric acids. Aqueous deuterium chloride was prepared from thionyl chloride and 2% deuterium water; the sulphur dioxide was removed by heating. The same 2% deuterium water was used for the neutral and alkaline aqueous reagents.

Hydrogen Exchange.—When two liquid phases were present, the mixtures were simply shaken together in sealed flasks under approximately standard mechanical conditions for the times stated and at room temperature, usually 17—20°. An exception was made when nitric acid was used, since, owing to the liability of the mixtures to evolve gases, it was found preferable to employ stationary flasks with mercury-sealed stirrers. When only one liquid phase was present, the reactions were carried out in stationary sealed flasks placed in thermostats.

Isolation.—The methods were conventional, and the only case requiring special remark is that of phenol. As specified in the introduction, the methods used were distillation, extraction with ether (after neutralisation of sodium hydroxide, where necessary, with carbon dioxide), and methylation. In experiments in which the last method was employed, mixtures of phenol (about 15 g.), 2% heavy water (about 75 c.c.), and sodium hydroxide were enclosed in sealed flasks at room temperature, trial experiments having shown that no nuclear exchange occurs under these conditions in several hours. After being heated at 100° for the requisite time, each flask was cooled in ice-water. The quantity of added sodium hydroxide was then made up to about 14 g., and 20 c.c. of methyl sulphate were immediately introduced; the methylation, facilitated by vigorous shaking, was completed below 50°. The anisole was then isolated and purified by customary methods, and burnt. Blank experiments showed that, with phenol containing no deuterium in the nucleus, this method of isolation introduced sufficient deuterium to make the density of the combustion water from the anisole 6 p.p.m. too high; so that, as a correction for the error due to deuteration during isolation, we have taken a proportion of 6 p.p.m. determined by how far the replaceable hydrogen in the nucleus of the phenol is out of equilibrium with the solvent. This correction has been applied to the figures in col. 8 of Table V.

Isotopic Analysis.—The materials were burnt on red-hot copper oxide in quantity sufficient to yield about 4 c.c. of combustion water. The more volatile compounds were carried into the combustion tube by means of a stream of nitrogen, or air, or air mixed with oxygen. The less volatile compounds were delivered dropwise through a capillary tube into the combustion tube. The combustion water, collected from the drawn-out combustion tube at − 78°, was purified by non-ebullient distillation from silver oxide in an evacuated all-glass still. Its density was determined with a 3-c.c. pyknometer to an accuracy of about 1 p.p.m.

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