The Hydrogen Isotope Effect in the Metallation of Benzene and Toluene.

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In the metallation of deuterobenzene and α-deuterotoluene by ethylpotassium, protium is replaced by potassium more rapidly than is deuterium. The respective rate ratios, k_D/k_H, are 0·50 ± 0·10 and 0·22 ± 0·05. Part, but probably not all, of the difference between the ratios may be attributed to the use of a higher temperature for the former reaction. The observed selectivity supports the " protophilic " mechanism for metallation reactions of this type (Bryce-Smith, *J.*, 1954, 1079).

Whenever the breaking of the bond attached to a hydrogen atom plays a part in determining the rate of its replacement, the velocity is expected to be greater when that hydrogen atom is one of protium, than when it is one of deuterium. The rate of replacement of deuterium (k_D) divided by that of protium (k_H) is known as the isotopic rate ratio for the particular reaction.

When a compound containing a known distribution of the two isotopes among its molecules is attacked by a deficit of a substituting reagent, determination of the deuterium abundance of the product enables the value of k_D/k_H to be calculated, as is shown below.

These considerations have been the basis of the present work, the aim of which has been to test the validity of the protophilic mechanism for aromatic metallation, evidence for which has recently been advanced by one of us (Bryce-Smith, *loc. cit.*).

Both side-chain and nuclear metallation have been studied by means of the following reaction (Bryce-Smith, *loc. cit.*; Bryce-Smith and Turner, *J.*, 1953, 861) :

$$(1)\ \mathrm{PhH} + \mathrm{EtK} = \mathrm{PhK} + \mathrm{C_2H_6};\ \mathrm{PhK} + \mathrm{CO_2} \longrightarrow \mathrm{Ph{\cdot}CO_2K}$$

$$(2)\ \mathrm{PhMe} + \mathrm{EtK} \longrightarrow \mathrm{Ph{\cdot}CH_2K} + \mathrm{C_2H_6};\ \mathrm{Ph{\cdot}CH_2K} + \mathrm{CO_2} \longrightarrow \mathrm{Ph{\cdot}CH_2{\cdot}CO_2K}$$

EXPERIMENTAL

Isotope Analysis.—A sample of organic compound, sufficient to provide about 0·35 ml. of water, was burnt according to standard semimicro-procedure. The water was condensed, at −80°, in a trap which could be sealed off from the combustion train. It was purified by repeated distillation essentially as by Keston, Rittenberg, and Schoenheimer (*J. Biol. Chem.*, 1937, **122**, 227). The isotopic composition of the water was measured by the density-gradient tube method (Linderstrøm-Lang, *Compt. rend. Lab. Carlsberg, Sér. chim.*, 1936, **21**, 315). Whenever it was necessary to bring the density of the water within the range of a gradient tube, the original material was diluted, before combustion, with a suitable proportion of the " light " compound.

From the level of reproducibility of analyses at different degrees of dilution, duplicate experiments, and other tests of " memory " and accuracy, it is estimated that the atom percentages of deuterium quoted are reliable within ±0·1% for values of about 20% and somewhat more accurate at lower percentages.

Deuterium oxide, containing 99·7% of D_2O by wt., was used in the following experiments.

Preparation of [α-$^2H_1$]*Toluene.*—The product from the reaction of ethereal benzylmagnesium chloride with deuterium oxide (cf. Choppin and Smith, *J. Amer. Chem. Soc.*, 1948, **70**, 577) was treated with solid carbon dioxide to destroy excess of the Grignard reagent. Crude deuterotoluene, b. p. 110°, was obtained in 60% yield by fractional distillation, contact with mineral acids being avoided in order to run no risk of isotope exchange (Found : D, 11·72. Calc. for C_7H_7D : D, 12·50 atoms %). A portion of the product was oxidised by alkaline permanganate. The resulting benzoic acid contained D, 0·20 atom %. This indicated the presence of nuclear deuterium in the toluene, but it is uncertain whether this arose from a rearrangement during the hydrolysis (cf. Coleman and Forrester, *ibid.*, 1936, **58**, 27) or from the presence of nuclear isomers in the specimen of benzyl chloride which was used (cf. Melander, *Arkiv Kemi*, 1950, **2**, 261). Turkevich, McKenzie, Friedman, and Sporr (*J. Amer. Chem. Soc.*, 1949, **71**, 4045) showed that no dideuterium compounds are formed in the reaction concerned. Accordingly the present product had the following composition : C_7H_8, 6·2; $C_6H_4D{\cdot}CH_3$, 1·2; $C_6H_5{\cdot}CH_2D$, 92·6 mole %.

Preparation of Deuterobenzene ([$^2H_1$]*Benzene*).—The Grignard procedure described by Weldon and Wilson (*J.*, 1946, 235) was modified in order to avoid working with solvent-free phenylmagnesium bromide. A solution of phenylmagnesium bromide was prepared by the addition (30 min., stirring) of a solution of bromobenzene (125 g., 0·8 mole) in di-*n*-butyl ether (200 ml., dry, peroxide-free) to a heated suspension of magnesium (20 g., 0·82 g.-atom) in the same solvent (50 ml.) under anhydrous conditions. Reaction commenced almost immediately at 140° and stirring was continued at this temperature (15 min.). Material of b. p. <149° was removed at once by distillation through a 20-cm. Fenske column, *ca.* 15 ml. of benzene being obtained. Deuterium oxide (16·4 g., 0·82 mole) was added (2 hr., stirring) to the solution at 60° and after the mixture had been kept overnight at room temperature, crude deuterobenzene (29·5 g.) was obtained by distillation through the column. Further fractional distillation, followed by fractional freezing, gave a product of m. p. 5·5° (22·5 g.) (Found : D, 15·30. Calc. for C_6H_5D : D, 16·67 atoms %). On the assumption (cf. Weldon and Wilson, *loc. cit.*) that molecules containing more than one deuterium atom were absent, the composition of the material (benzene A) was : C_6H_6, 8·0; C_6H_5D, 92·0 mole %.

Mixed Deuterobenzenes ([^{2}H]*Benzene*).—The method of Ingold, Raisin, and Wilson (*J.*, 1936, 915) was used. Benzene (90 ml.) was shaken at room temperature for 150 hr. with deuterosulphuric acid (18 g.) which was stronger than monohydrate. Exchange equilibrium should have been reached under these conditions. Analysis of the product gave *D*, 7·8 atoms %. On the assumption that the distribution of deuterium atoms is random, the material (benzene B) had the following composition : C_6H_6, 62·8; C_6H_5D, 29·2; $C_6H_4D_2$, 6·8; $C_6H_3D_3$, 1·06; $C_6H_2D_4$, 0·13; C_6HD_5, 0·01 moles %. C_6D_6, negligible.

Metallation Experiments.—The general procedure described by Bryce-Smith and Turner (*loc. cit.*) was used.

(a) *Benzene.* A solution of ethyl-lithium (0·43 mole) in the deuterobenzene (20 ml.) was stirred at 75° with potassium (3·5 g., 0·09 g.-atom) until gas evolution had become negligible

(2·5 hr.). The dark brown product was cooled and poured on solid carbon dioxide in ether. Alkali metals were destroyed by the cautious addition of aqueous *tert.*-butyl alcohol. Dicarboxylic acids were removed from the product by virtue of their insolubility in chloroform. Benzoic acid (2·35 g.; m. p. 117—119°) was obtained by evaporation of the chloroform. After recrystallisation from water it melted at 121·5°. The acid obtained by metallation of benzene A was found to contain 13·8 atoms % of deuterium and that from benzene B to contain 6·41 atoms %.

(b) *Toluene.* An alloy of potassium (5 g.) and sodium (1 g.) was added to the stable solution of ethyl-lithium (0·07 mole) in the deuterotoluene (33 g.) at 20°. The mixture was stirred at this temperature until the evolution of gas had become negligible (125 hr.). Reaction with solid carbon dioxide in ether gave phenylacetic acid (m. p. 66°; 3·5 g.) which after a single recrystallisation from light petroleum (b. p. 40—80°) melted at 76·7°. This acid was found to contain 10·4 atoms % of deuterium.

DISCUSSION

It is convenient to express the experimental results in terms of the isotopic rate ratios to which they correspond.

Calculation of k_D/k_H.—When a deficit of reagent is used, as in the experiments described, the isotopic abundance of the reaction product is a function, not only of k_D/k_H and the isotopic abundance of the starting material, but also of the distribution of the two isotopes among the molecules of the starting material. In the calculations it has been assumed that the amount of reagent consumed was negligible compared with the amount of benzene or toluene present, so that the isotopic composition of the hydrocarbon was effectively constant. The principle of the calculation for a mixture of isotopically different benzene molecules is as follows. If h and d are proportional to the reactivities of positions carrying protium and deuterium atoms respectively, *i.e.*, proportional to k_H and k_D, then n_0 molecules of C_6H_6 will yield $6hn_0$ molecules of $C_6H_5{\cdot}CO_2H$, while n_1 molecules of C_6H_5D yield $5hn_1$ molecules of $C_6H_4D{\cdot}CO_2H$ and dn_1 molecules of $C_6H_5{\cdot}CO_2H$, and n_2 molecules of $C_6H_4D_2$ yield $4hn_2$ molecules of $C_6H_3D_2{\cdot}CO_2H$ and $2dn_2$ molecules of $C_6H_4D{\cdot}CO_2H$, etc. In this way the known isotopic composition of the product may be obtained in terms of the known values of n_0, n_1, n_2, etc., for the starting material and of h and d. Hence d/h ($= k_D/k_H$) may be calculated, or, reversing the calculation, the atom percentage of deuterium to be expected in the product can be found for a variety of assumed values for k_D/k_H.

TABLE 1. *Variation with* k_D/k_H *of the atom percentage of deuterium to be expected in the product.*

	Atom % expected in product		
k_D/k_H	Benzene A	Benzene B	Toluene
0·00	$15{\cdot}1_0$	6·36	$11{\cdot}3_9$
0·20	$14{\cdot}5_7$	—	$10{\cdot}4_6$
0·25	$14{\cdot}4_4$	—	$10{\cdot}2_4$
0·333	$14{\cdot}2_3$	—	$9{\cdot}9_0$
0·40	$14{\cdot}0_8$	—	$9{\cdot}7_0$
0·50	$13{\cdot}8_5$	6·41	$9{\cdot}3_1$
1·00	$12{\cdot}7_8$	6·47	$7{\cdot}8_7$

Found: Benzene A, 13·8 ± 0·09; Benzene B, 6·41 ± 0·03; Toluene, 10·4 ± 0·09 atom %.

Table 1 illustrates, in the case of benzene, the effect of altering the isotopic distribution in the starting material and shows that, on consideration of the experimental error, the identification of the rate ratio is more clear-cut when one species greatly predominates, the presence of others restricting the range of atom percentages that can be expected in the product. The experimental values indicate that for benzene $k_D/k_H = 0{\cdot}50 \pm 0{\cdot}10$ and that for toluene $k_D/k_H = 0{\cdot}22 \pm 0{\cdot}05$. In both cases, therefore, metallation involves a definite isotope effect. The isotopic rate ratios obtained are of the same order as those found by other workers for reactions involving hydrogen abstraction (see, *e.g.*, review by Bonhoeffer, *Trans. Faraday Soc.*, 1938, **34**, 252). Of particular interest also in relation to the present work is that of Melander (*loc. cit.*; Berglund-Larsson and Melander, *Arkiv Kemi*, 1953, **6**, 219) who has used tritium to study the mechanism of electrophilic aromatic substitution.

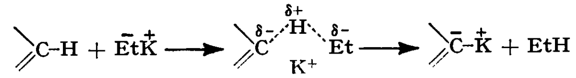
In general, correlations should exist between the measured value of k_D/k_H on the one hand, and the force constant of the broken bond, the strength of the accepting base, the temperature, and, to a smaller extent, the nature of the solvent, on the other. The first two items help to determine the important zero-point energy differences, and the temperature controls the magnitude of the factor arising from these differences and also that arising from the possible incidence of quantum-mechanical tunnelling. Finally the value of k_D/k_H will also depend upon the relative importance of the rôle which the breaking of the hydrogen linkage plays in determining the overall rate.

Work in this field up till now has not been systematic or precise enough to allow definite conclusions to be drawn about the relative importance of these various factors. At present, therefore, comparison of two isotopic rate ratios does not always afford unequivocal deductions.

In the present work, apart from the inevitable change in solvent and any difference between the force constants of side-chain and nuclear hydrogen bonds, the reaction with benzene was carried out, for reasons of experimental convenience, at a temperature 55° higher than that with toluene. If the isotopic rate ratio is attributed entirely to the difference in heat of activation occasioned by the differences in zero-point energy between isotopic compounds, then the differences in heats of activation corresponding to the observed ratios for benzene and for toluene are about 480 and 890 cals. respectively. The larger of these values is too small to account for the change in the ratio k_D/k_H from 0·22 to 0·50 for a rise in temperature of 55°. However, temperature effects of a greater magnitude than this have previously been reported for the ionisation of 2-*o*-carboxybenzylindan-1-one (Wilson, *J.*, 1936, 1550) where k_D/k_H changed from 0·23 to 0·33 for a rise in temperature of only 20°. Although Wilson did not consider his data to be incompatible with the sole operation of the zero-point energy effect on the activation energies, nevertheless, it seems possible that in his experiments and in the present work the quantum-mechanical tunnel effect is making itself felt, so that the two values, 0·50 and 0·22, need not in fact imply any fundamental difference between the two reactions.

However this may be, it is clear that the loss of hydrogen is of kinetic significance and, to be acceptable, any mechanism for metallation must account for this. The mechanism recently supported by one of us (Bryce-Smith, *loc. cit.*) passes the test.

Isomer ratios, partial rate factors, and other considerations in connection with the metallation of alkylbenzenes led to the following reaction scheme for the replacement of a nuclear hydrogen atom :



In the present case, that of potassium, the metal alkyl is considered to behave as an ion pair, any effect due to the metal being electrostatic. The reaction scheme for the other alkali metals is thought to be broadly similar, though not necessarily identical in all details. The same is probably true for side-chain in relation to nuclear substitution, both reactions being essentially protophilic in character. The hydrogen atom is accordingly removed as a proton and hence benzene, toluene, and other hydrocarbons to which the mechanism applies are logically described as acids in this reaction (Bryce-Smith, *loc. cit.*). Acidic behaviour in the methyl group of toluene is a concept which is not wholly foreign. It should be especially well developed if a nitro-group is also present in the ring as is shown by the base-catalysed condensation of nitrotoluenes with benzaldehyde. Toluene itself appears to behave as an acid in its reaction with cæsium, forming the salt benzylcæsium and evolving hydrogen (de Postis, *Compt. rend.*, 1946, **222**, 398). The suggestion that the nuclear hydrogen atoms of an aromatic compound can, in suitable circumstances, behave in an acidic fashion may, perhaps, not find ready acceptance. Here again, however, it is possible to strengthen their acidity with electron-withdrawing substituents and the acidity of the hydrogen atoms in trinitrobenzene is revealed by the observation that this compound will undergo hydrogen-isotope exchange with ethanol only in the presence of alkali (Kharasch, Brown, and McNab, *J. Org. Chem.*, **1937**, **2**, 36).

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