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MECHANISM STUDY OF THE PROTOPHILIC SUBSTITUTION OF HYDROGEN IN AROMATIC COMPOUNDS BY MEANS OF HYDROGEN ISOTOPE EXCHANGE WITH LIQUID AMMONIA

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Abstract—The mechanisms of hydrogen isotope exchange between aromatic compounds and KNH_2 in liquid NH_3 and of metalation reactions are discussed. Both types of reactions manifest similar correlations and are united under the group of protophilic hydrogen substitutions. Their rate depends upon the acidity of the CH-bonds, the limiting step being the stretching or rupture of such bonds in the transition state of reaction between the hydrogen atom and a base (NH_2^- ion, carbanion of the organo-alkali compound). The CH-bond acidity of benzene derivatives is determined to a considerable extent by the inductive effect of the substituent. This is seen by the orientation in metalation reactions and by the direct proportionality between the partial rate factors (p.r.f.) of deutero-exchange in the *ortho*-position and Taft's polar substituent constants σ_I. The p.r.f's of deutero-exchange with bases and with acids proceeding by the electrophilic substitution mechanism have been compared. Depending upon the reactant and the reaction mechanism, donor or acceptor properties may predominate in the same substituents (OC_6H_5, OCH_3, $NC_6H_5(CH_3)$, $N(CH_3)_2$) the two properties being interrelated. The alkyl group is an electronic donor in deutero-exchange of a substance with acid or with base. The difference in mechanisms of these reactions, and the predominance of a conjugative effect in the one case, and of an inductive effect in the other, greatly influences deutero-exchange in polymethylbenzenes. The experimental rate constants are close in value to those calculated from the p.r.f's for toluene on the basis of the additivity principle.

THERE is much in common between certain groups of isotope exchange reactions and the chemical substitution of hydrogen in organic compounds. Ingold[1] was the first to indicate the similarity existing between hydrogen isotope exchange in aromatic compounds, proceeding with the participation of acids and electrophilic substitution of hydrogen (halogenation, nitration etc.).

The generic unity of the relationships displayed by these reactions was still further brought to the fore by Melander, Gold, Satchell, Mackore, Oláh, Eaborn *et al.*,* and by the systematic investigations of deutero-exchange reactions in liquid halohydrides

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* For references to the literature see reviews[2–6].

[1] C. K. Ingold, C. G. Raisin and C. L. Wilson, *Nature, Lond.* **134**, 734 (1934); *J. Chem. Soc.* 1637 (1936)

[2] L. C. S. Melander, *The Use of Nuclides in the Determination of Organic Reaction Mechanism.* University of Notre Dame Press (1955).

[3] V. Gold and D. P. N. Satchell, *Quart. Revs.* **9**, 51 (1955).

[4] A. I. Brodskiĭ, *Khimija Izotopov* (*The Chemistry of Isotopes*) Moskva, Izd. AN SSSR (1950).

[5] S. Z. Roginskiĭ, *Teoreticheskie Osnovy Izotopnykh Metodov Izucheniya Khimicheskikh Reaktsiĭ* (*Fundamental Principles of Isotope Methods of Studying Chemical Reactions*) Moskva, Izd. AN SSSR (1956).

[6] A. I. Shatenshtein, [a] *Izotopnyĭ Obmen i Zameshchenie Vodoroda v Organicheskikh Soedineniyakh v Cvete Teorii Kislot i Osnovaniĭ* (*Hydrogen Isotope Exchange and Substitution in Organic Compounds in Light of the Acid–Base Theory*) Moskva, Izd. AN SSSR (1960); [b] *Uspekhi Khim.* **21**, 914 (1952); **24**, 377 (1955); **28**, 3 (1959); [c] *Ukrain. Khim. Zh.* **22**, 3 (1956).

(HF, HBr, HI) carried out in our laboratory from 1951 onwards.[7] Evidence of the intimate connection between the mechanisms of this group of isotope and chemical reactions may also be found in the fact that they obey Brown's selectivity relation.[8,9]

The mechanism of the acid-catalysed exchange of hydrogen in aromatic compounds is still not entirely clear. Melander and Olson[10] as a result of the accepted mechanism for electrophilic substitution of hydrogen, proposed a two-stage scheme for the exchange reaction. In the first stage a proton of the acid adds to the deuterium- (or tritium)-link. A σ-complex is thus formed, with atoms of the light and heavy hydrogen isotopes bound to the same carbon. The rupture of the bond with the isotope atom initially in the molecule takes place in the transition state of which the structure is close to that of the σ-complex. In contrast to these authors Gold and Satchell[11] believe that the proton adds to the aromatic molecule with the formation of an intermediate π-complex in which the bonds with the two isotope atoms are unsymmetric. The rate determining step is the exchange of places between the isotopes, following which a hydrogen ion bound to the aromatic ring as a whole is rapidly eliminated.

In the present report a discussion is presented of the mechanism of hydrogen exchange in aromatic compounds with strong bases and of metalation reactions united under the group of protophilic substitution reactions of hydrogen.

Metalation was discovered by Shorygin. The reaction may be expressed by the equation $RH + R_1Me \rightleftarrows RMe + R_1H$ (for example, $C_6H_5CH_3 + C_6H_5K \rightleftarrows C_6H_5CH_2K + C_6H_6$). The similarity between metalation and hydrogen isotope exchange of hydrocarbons with liquid deutero-ammonia and with potassium amide in liquid deutero-ammonia was first noted in a paper from our laboratory published in 1950. On this, and in subsequent works,[12,13] it was shown that the more easily replaceable hydrogen atoms of a compound are the same both on substitution by alkaline metals and by deuterium. Such are for instance the hydrogen atoms of the aliphatic CH-bonds in phenylated alkanes or the allyl hydrogens of olefins, etc. Substances arranged in accordance with the relative ease of replacement of the most easily substituted hydrogen atoms by metals or by deuterium, will assume the same sequence in both cases; for example, indene ($4 \cdot 10^1$) > fluorene ($2 \cdot 10^{-2}$) > triphenylmethane ($2 \cdot 10^{-7}$) > diphenylmethane ($7 \cdot 10^{-9}$). The numbers in the parentheses refer to the rate constants (sec^{-1}) of deutero-exchange with liquid ND_3 measured at 120° or

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[7] A. I. Shatenshtein, Ya. M. Varshavskii, V. R. Kalinachenko, K. I. Zhdanova, P. P. Alikhanov, A.V Vedeneev *et al.*, *Dokl. AN SSSR* **85,** 157 (1952); **91,** 577 (1953); **95,** 297 (1954); **102,** 779 (1955); **133,** 1117 (1960); *Zh. Obshch. Khim.* **26,** 1666 (1956); **28,** 2638 (1958)· **29,** 849 (1959); **30,** 999 (1960); **31,** 250, 1432 (1961). *Zh. Fizich. Khim.* **30,** 1140, 1647, 2093, 2098 (1956); 1377 (1957); **34,** 587 (1960).

[8] A. I. Shatenshtein, *Synopsis of Report at the VIII Mendeleev Congress on General and Applied Chemistry Sbornik.* (Collection of Synopses) No. 12, p. 43. Moskva (1958); *Izd. AN SSSR. Zh. Fizich. ĭ Khim.* **34,** 594 (1960).

[9] L. M. Stock and H. W. Brown, *J. Amer. Chem. Soc.* **81,** 3323 (1959); **82,** 1942 (1960).

[10] L. Melander and S. Olson, *Acta Chem. Scand.* **10,** 879 (1956); *Ark. Kemi* **14,** 85 (1959).

[11] V. Gold, R. W. Lembert and D. P. N. Satchell, *J. Chem. Soc.* 2461 (1960).

[12] A. I. Shatenshtein, Yu. P. Vyrskiĭ, E. A. Izrailevich, N. M. Dykhno, L. N. Vasil'eva, E. N. Zvyagintseva *et al.*, *Dokl. AN SSSR.* **70,** 1029 (1950); **79,** 479 (1951); **85,** 381 (1952); **94,** 923 (1954); **95,** 115 (1954); **117,** 852 (1957); **124,** 146 (1959); *Zh. Fizich. ĭ Khim.* **25,** 1206 (1951); **28,** 3, 11, 14, 193 (1954); **32,** 2711 (1958); *Zh. Obshch. ĭ Khim.* **28,** 2939 (1958); *Izvestiya AN SSSR, Otd. Khim. Nauk*, 104 (1958); 1805 (1959).

[13] A. I. Shatenshtein, Yu. I. Ranneva, E. A. Izrailevich, A. V. Vedeneev *et al.*, *Zh. Obsh. ĭ Khim.* **28,** 2644 (1958); **30,** 583 (1960); **31,** 1423 (1961). *Zh. Fizich. ĭ Khim.* **34,** 587 (1960).

recalculated for this temperature. Another example is toluene ($1{\cdot}4 \,.\, 10^{-3}$) > ethylbenzene ($2 \cdot 10^{-4}$) > isopropylbenzene ($4 \cdot 10^{-5}$). The values refer to the rate constants of exchange of the alkyl α-hydrogen with 0·02 N potassium amide solution in liquid deutero-ammonia at 10° (metalation cf.[15]).

In the papers cited[12,13] data is presented on the reactivities of numerous organic compounds and the regularities of deuterium exchange with strong bases are established.

In the course of studies on hydrogen isotope exchange carried out in our laboratory with non-aqueous solvents-acids[7] and bases (liquid ammonia[12,13], anhydrous hydrazine, anhydrous ethylenediamine and anhydrous ethanolamine[16]) the concept of hydrocarbons as bases and acids was firmly grounded and the theory was developed of the acid–base character of heterolytic hydrogen exchange reactions.[6]* The definitions of acids and bases were modified to conform with the general change in views on protolytic reactions: a *base* being an electron-donating reactant, possessing affinity for a proton and an *acid*, an electron-accepting reactant, the hydrogen of which participates in equilibrium reaction with bases. The acid combines with the base through a hydrogen bond or yields it a proton.

We considered that the similarity between deutero-exchange with potassium amide in liquid ammonia and metalation can be explained by the fact that both reactions proceed according to the acid–base mechanism, the substrate being the acid and the reactant the base. Such an assumption is in accord with the views of Conant and Wheland[14] who regard metalation as displacement of an acid from its salt by a stronger acid, but contradicted by Morton.[18] The latter maintains that metalation of aromatic compounds takes place as a result of electrophilic attack of the cation of the organo-alkali compound on a carbon atom with increased electron density. Morton bases his views on the fact that *o,p*-orienting substituents (for instance OCH_3, $N(CH_3)_2$ etc.) direct the metalation in the ortho-position. However, a number of facts are revealed which cannot be reconciled with Morton's theory. Roberts and Curtin[19] have shown that in the metalation of $C_6H_5CF_3$ the *ortho* isomer is formed in good yield, although the CF_3 group orientates 100 per cent *meta* in the electrophilic substitution of hydrogen in the benzene ring. Morton's hypothesis also disagrees with the experimental results of Gilman[20] on the metalation of 2-methoxynaphthalene and the findings of Gronowitz[21] with thiophene derivatives.

Roberts[19] and Wittig[22] explain the discrepancies by pointing out that, even if at first sight metalation reactions seem to obey the rules of electrophilic substitution, the actual mechanisms of both reactions are different. When the aromatic ring possesses a substituent, such as a methoxy group, electrophilic substitution of hydrogen is due mainly to conjugation of the p-electrons of the oxygen atom with the π-electrons of

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* New methods of preparing deuterated compounds resulted from the study of deutero-exchange with acids and bases. The compounds have been employed in I.R. and U.V. spectral work.[17]

[14] J. B. Conant and G. W. Wheland, *J. Amer. Chem. Soc.* **54**, 1212 (1932).

[15] D. Bryce-Smith, *J. Chem. Soc.* 1079 (1954).

[16] A. I. Shatenshtein and E. A. Yakovleva, *Dokl. AN SSSR* **105**, 1024 (1956); *Zh. Obshch. i Khim.* **28**, 1714 (1958).

[17] A. I. Shatenshtein, E. A. Izrailevich, V. R. Kalinachenko, G. S. Landsberg, A. F. Prikhot'ko *et al.*, *Optika i Spektroskopiya* **1**, 34 (1956); **5**, 113 (1958); *Zh. Fizich. i Khim.* **32**, 146 (1958).

[18] A. A. Morton, *Chem. Rev.* **35**, 1 (1944); *J. Amer. Chem. Soc.* **69**, 969 (1947).

[19] J. D. Roberts and D. J. Curtin, *J. Amer. Chem. Soc.* **68**, 1658 (1946).

[20] H. Gilman and T. H. Cook, *J. Amer. Chem. Soc.* **62**, 2813 (1940).

[21] S. Gronowitz, *Ark. Kemi* **7**, 361 (1954).

[22] G. Wittig, *Naturwiss.* **30**, 698 (1942); *Angew. Chem.* **66**, 10 (1954); **69**, 245 (1957).

the aromatic ring. This results in increased electron density at the *ortho* and *para* carbon atoms so that they can bind an electrophilic agent. In metalation reactions, however, the inductive displacement of σ-electrons comes to the fore. This displacement is due to the electron affinity of oxygen, the hydrogen atoms of the CH-bond becoming more positively charged than in the case of non-substituted benzene and as a result their protonization by base and substitution by alkali metal is facilitated. This process takes place most easily in the *ortho* position, because the inductive effect is rapidly attenuated with removal of the CH-bond from the substituent. The electron-donating alkyl group, displacing the electrons towards the ring, exerts a directly opposite effect. As Bryce-Smith[15] has shown t.-butylbenzene metalates slower than benzene and the *para*-isomer is obtained in greatest yield, i.e. the hydrogen furthest removed from the substituent undergoes the most rapid substitution.

The basic difference between the mechanisms of electrophilic substitution and of metalation lies in the fact that in the latter process the reactant does not react with the carbon atom of the ring nor with the ring π-electron system as a whole, but with the hydrogen atom of the CH-bond. Bryce-Smith[15] regards metalation as a protophilic hydrogen substitution reaction in order to stress that the underlying cause is protonization of a hydrogen atom of the CH-bond by a strong base such as is the anion of the organo-alkali compound. The substance undergoing metalation under these circumstances plays the part of the acid.

In favour of the assumption of the stretching or rupture of the CH-bond in the transition state as the rate-limiting step of the reaction is the existence of a positive kinetic effect. Bryce-Smith *et al.*[23] found that deutero-benzene and deutero-toluene are metalated 1/2 and 1/5 as fast as the isotopically unsubstituted counterparts. According to Gronowitz and Halvarson[24] protium in a thiophene molecule is substituted six times faster by an alkali metal than tritium.

The existing contradictions between the treatments of metalation and of hydrogen exchange in liquid ammonia are resolved by the aforementioned works. The results of kinetic measurements of hydrogen isotope exchange in ammonia solutions summarized below extend our knowledge of the correlations and mechanisms of protophilic hydrogen substitution.

In our laboratory[25] kinetic studies have been made of deuterium- or tritium-exchange of fluorene and methyl-β-naphthyl ketone with liquid ammonia. In the first compound the heavy hydrogen isotopes were in the methylene group and in the second deuterium or tritium was incorporated in the methyl group. The following mean rate constants of exchange of deuterium and tritium with protium were obtained:

Substance	$k_D \cdot 10^5$	$k_T \cdot 10^5$	k_D/k_T
Fluorene	$16 \pm 0{\cdot}1$	$8{\cdot}3 \pm 0{\cdot}1$	1·9
Ketone	$8{\cdot}0 \pm 0{\cdot}1$	$3{\cdot}7 \pm 0{\cdot}2$	2·2

Aliphatically* bound deuterium exchanges with protium twice as fast as does tritium.

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* Experiment with aromatically bound deuterium and tritium are now under way.

[23] D. Bryce-Smith, V. Gold and D. P. N. Satchell, *J. Chem. Soc.* 2743 (1954).

[24] S. Gronowitz and K. Halvarson. *Ark. Kemi* **8**, 343 (1955).

[25] F. S. Yakushin, A. I. Shatenshtein, E. A. Yakovleva and Yu. G. Dubinskii. *Zh. Fizich. i Khim.* **33**, 2820 (1959); *Kinetika i Kataliz* **1**, 489 (1960).

Recently, Streitwieser[26] found $k_D/k_T = 3{\cdot}0 \pm 0{\cdot}3$ for the isotopic exchange of heavy isotopes in the methylene group of ethylbenzene. The reaction was catalysed by lithium cyclohexylamide dissolved in cyclohexylamine ($T_{\text{exp}} = 49{\cdot}9°$). In the same communication there is reference to analogous measurements by Langworthy, according to which for substitution of deuterium and tritium in the methyl group of toluene $k_D/k_T = 2{\cdot}75$ and $2{\cdot}98$.

Data on the k_D/k_T ratio published up till now is in agreement with the results of theoretical calculations[10,27,28] showing that at room temperature the C—D bond should break about 2–3 times faster than the C—T bond. The theoretical treatment is in the nature of an approximation and does not take into account the possibility of dissimilar polarization of the bonds in the transition state. At any rate the results obtained from studies of the kinetic isotope effect both during metalation and during deutero-exchange with bases in general agree with each other and confirm the similarity of the mechanisms of these reactions.

TABLE 1. PARTIAL RATE FACTORS OF DEUTERO-EXCHANGE WITH SOLUTION OF KNH_2 IN LIQUID AMMOINA

Substituent	pK_i	σ_I	lg f_{ortho}	f_{ortho}	f_{meta}	f_{para}
F	2·66	0·52	6·0	10^6	10^3	10^2
CF_3	3·07	0·41	5·0	10^5	10^4	10^4
C_6H_5O	3·12	0·38	4·3	$2 . 10^4$	$5 . 10^1$	4
CH_3O	3·53	0·25	2·7	$5 . 10^2$	1	$5 . 10^{-1}$
$C_6H_5(CH_3)N$	—	—	1·5	33	2·9	1·3
C_6H_5	4·31	0·1	0·7	4·7	3·3	2·9
$(CH_3)_2N$	—	0·1	0·2	1·4	$2 . 10^{-1}$	$7 . 10^{-2}$
H	4·76	0·00	0·0	1	1	1
CH_3	4·88	−0·05	−0·7	$2 . 10^{-1}$	$4 . 10^{-1}$	$4 . 10^{-1}$

A series of investigations[13] has been devoted to determining the partial rate factors of unequal deuterium atoms in aromatic compounds. The partial rate factor (p.r.f.) is the ratio of the rate constant of deuterium atom exchange in a given position of a benzene derivative molecule to that of deuterium exchange in benzene carried out under the same conditions. The p.r.f. values of deutero-exchange in C_6H_5F and $C_6H_5CF_3$ have calculated from Roberts' data.[29]

The p.r.f.'s for exchange of deuterium initially incorporated in the *ortho*, *meta* and *para* positions of benzene derivatives, with KNH_2 in liquid NH_3 solution (f_{ortho}, f_{meta}, f_{para}) are presented in Table 1. p$K_i = -\lg K_i$, where K_i is the ionization constant of the substituted acetic acids with the same substituents as in the benzene ring.[30] σ_I are Taft's polar substitution constants which this author[31] deduced for reactions (including the ionization of carboxylic acids) the equilibrium or rate of which are determined exclusively by the inductive effect of the substituent.

If values of f_{ortho} are plotted against pK_i a straight line is obtained (Fig. 1). A

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[26] A. Streitwieser and D. E. van Sickle, *J. Amer. Chem. Soc.* **82**, 1513 (1960).

[27] J. Biegeleisen, *Science* **110**, 14 (1949).

[28] H. Zollinger, *Angew. Chem.* **70**, 204 (1958).

[29] G. E. Hall, R. Piccolini and J. D. Roberts, *J. Amer. Chem. Soc.* **77**, 4540 (1955).

[30] E. A. Braude and F. C. Nachod, *Determination of Organic Structures by Physical Methods* p. 577. New York (1955).

[31] R. Taft, *J. Amer. Chem. Soc.* **79**, 1045 (1957); **80**, 2436 (1958).

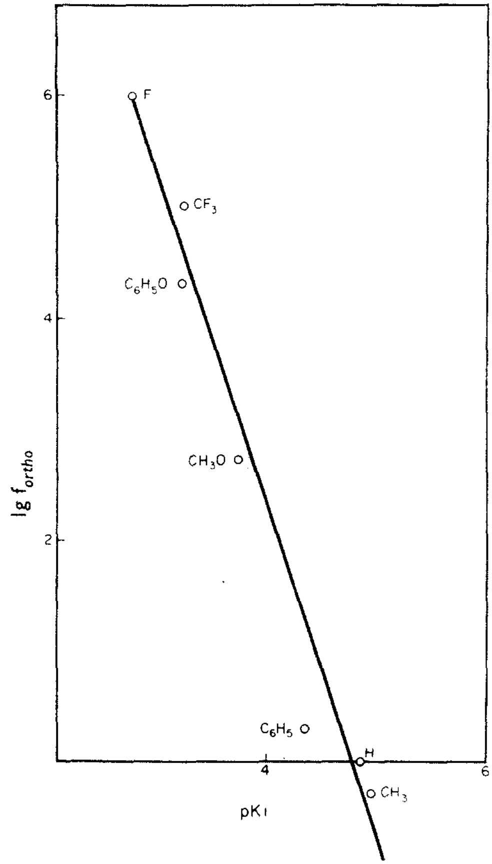

FIG. 1. A dependence between f_{ortho} and K_i.

linear dependence is also observed between f_{ortho} and σ_I (Fig. 2).* Hence the inductive effect of a substituent in the benzene ring plays an important part in deutero-exchange between aromatic compounds and bases and the rate of the isotope exchange is determined by the relative acidity of the CH-bond, as in the case of metalation. If the substituent is an electron-acceptor, $f_{ortho} > 1$. With increase in electronegativity of the substituent the acidity of its nearest CH-bond will increase and hence there will be an increase in the f_{ortho} value. On the contrary, if there is an electron donor substituent in the ring $f_{ortho} < 1$, the effect of the substituent on the mobility of the hydrogen atom weakens as it is removed from the latter, i.e. from *ortho* to *meta* to *para*.

If the substituents are arranged in the order of diminishing f_{ortho} values they will

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* The data therefore obey Hammett–Taft's rule:

$$\lg f_{ortho} = \lg \frac{k_{ortho}}{k_{C_6H_6}} = \rho\sigma_I = 11\sigma_I$$

[32] D. P. N. Satchell, *J. Chem. Soc.* 3911 (1956).

[33] M. J. S. Dewar and D. S. Urch, *J. Chem. Soc.* 3079 (1958).

[34] A. I. Shatenshtein, E. N. Zvyagintseva and Z. N. Ovchinnikova, *Zh. Obshch. i Khim.* **31**, 1432 (1961).

[35] E. N. Yurigina, P. P. Alkhanov, E. A. Izrailevich, P. N. Manochkina and A. I. Shatenshtein, *Zh. Fizich. i Khim.* **34**, 587 (1960).

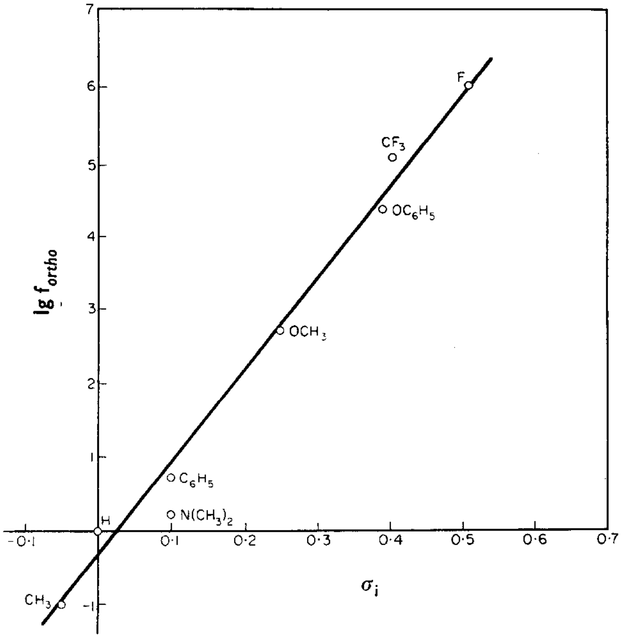

FIG. 2. A dependence between f_{ortho} and σ_I.

TABLE 2. COMPARISON OF PARTIAL RATE FACTORS OF PROTOPHILIC AND ELECTROPHILIC SUBSTITUTION OF HYDROGEN[8,13]

Substituent	Reactant	f_{ortho}	f_{meta}	f_{para}
OC_6H_5	$NH_3 + KNH_2$	20000	50	4
OC_6H_5	$CF_3COOH(40°)$*	[1·5 . 10^{-5}]	—	[4·6 . 10^{-5}]
OC_6H_5	nitration	117	—	234
OCH_3	$NH_3 + KNH_2$	5000	1†	0·5
OCH_3	$H_2SO_4(8{\cdot}5M)$[32]	23000	0·25‡	55000
OCH_3	Cromination[9]	8·7 . 10^7	2	1·1 . 10^{10}
$N(CH_3)C_6H_5$	$NH_3 + KNH_2$	33	2·9	1·3
$N(CH_3)C_6H_5$	$CH_3COOH(90°)$*	[2·3 . 10^{-5}]	—	[1·8 . 10^{-5}]
$N(CH_3)C_6H_5$	nitration[33]	831000	—	575000
$N(CH_3)_2$	$NH_3 + KNH_2$	1·4	0·2	0·07
$N(CH_3)_2$	CH_3COOH (90°)[34]	[2·2 . 10^{-4}]	—	[1·7 . 10^{-4}]
C_6H_5	$NH_3 + KNH_2$	4·7	3·3	2·9
C_6H_5	HBr[35]	500	0·4	3000
CH_3	$NH_3 + KNH_2$§	0·23	0·45	0·41
CH_3	HBr[35]	1000	5	4000
CH_3	Cromination[9]	600	5·5	2420

The bracketed values are for the rate constants of deutero-exchange (sec^{-1}).

* According to Yu. I. Ranneva.

† According to.[29]

‡ Exchange with 10·4M $HClO_4$ solution.

§ According to E. A. Izrailevich.

form a sequence (F > C_6H_5O > CH_3O > $N(CH_3)_2$ > CH_3) which was qualitatively established in studies on metalation reactions.[15,22] Values of p.r.f. have been obtained[15] so far only for the metalation of isopropylbenzene by ethylpotassium (f_{ortho} = 0·1, f_{meta} = 0·4, f_{para} = 0·5). They are close to the values for toluene given in Table 1.

The different substituent effects in the protophilic and electrophilic substitution of hydrogen in virtue of the different mechanisms of these reactions may be clearly seen from a comparison of the p.r.f.'s of deuterium exchange of the same compounds with acid and with base. Tables 2 and 3 show that *meta*-atoms exchange with a base at a rate approaching that of *para*-atoms, whereas exchange of *meta*-atoms with acid takes place either at rates several orders of magnitude less than those for the *para*-position, or it is too small to be measured at all. *Ortho-* and *para*-atoms of all the substances under consideration exchange at comparatively similar rates, whereas in deutero-exchange with bases f_{ortho}/f_{para} may vary by a factor of 8000 for various cases, the ratio gradually decreasing in value if nitrogen takes the place of oxygen in the substituent and finally heteroatoms more negative than carbon are excluded altogether.

TABLE 3. PARTIAL RATE FACTORS OF DEUTERO-EXCHANGE WITH BASES AND ACIDS, REFERRED TO f_{para}

Substituent	Base			Acid		
	ortho	*meta*	*para*	*ortho*	*meta*	*para*
OC_6H_5	5000	12	1	0·3	—	1
OCH_3	1000	2	1	0·4	$5\,.\,10^{-6}$	1
$NC_6H_5(CH_3)$	19	2·2	1	1·3	—	1
$N(CH_3)_2$	18	3	1	1·2	—	1
C_6H_5	1·7	1·1	1	0·2	$1\,.\,10^{-1}$	1
CH_3	0·6	1	1	0·3	$1\,.\,10^{-3}$	1

The substituents shown in Tables 2 and 3 are electron-donors in reactions with acid and manifest electron-acceptor properties in reactions with base. The CH_3-group is an exception. It remains electron-donating in both cases, but, because the conjugative effect is predominant in electrophilic substitution and the inductive effect in protophilic substitution, completely changes the substitution rate ratios of *ortho*, *meta* and *para* hydrogen atoms.

The concept of the relativity of the chemical function: the same substance may frequently react both as donor and as acceptor of electrons (or protons), i.e. as a reducing or as an oxidizing agent (as a base or as an acid) is now firmly established

TABLE 4. QUANTITIES CHARACTERIZING THE ELECTRON-DONOR AND ELECTRON-ACCEPTOR PROPERTIES OF SUBSTITUENTS

Substituent	μ	δ_{para}	$\Delta\lambda_1$	$\Delta\lambda_2$	σ_{para}	k_{ratio}
NO_2	−4·01	0·42	3	103	0·778	$2\cdot10^{-6}$
$N(CH_3)_2$	1·61	−0·50	101	10	−0·600	$5\cdot10^{18}$
OCH_3	1·28	−0·23	40	−5	−0·268	$1\cdot10^{9}$
OC_6H_5	—	—	—	—	−0·028	$1\cdot10^{7}$

in modern chemistry. Obviously, this generalization formulated for reactants also holds for the substituents in compounds.

A mutual relation exists between the oxidative and reductive powers of a substance just as between its acidic and basic functions. The electron-donor and electron-acceptor properties of substituents are also interrelated; the stronger one of these properties is manifested, the weaker is the other.

In Table 4 is presented data on the electron-donor properties of $N(CH_3)_2$, OCH_3 and OC_6H_5 groups. Comparison of these values with reference to the nitro-group, one of the most powerful electronegative substituents, shows that the electron-donor properties diminish in the following order: $N(CH_3)_2 > OCH_3 > OC_6H_5$. The following designations have been adopted in Table 4: μ—the dipole moment of the aromatic compounds with the substituents indicated.[30]* δ_{para}—the value of the "chemical shift", as determined by means of nuclear magnetic resonance measurements, which gives an idea of the relative electron density of the *para*-carbon atom of the aromatic ring.[36] $\Delta\lambda_1$ and $\Delta\lambda_2$ are the shifts of absorption bands in the electronic spectra on incorporation of the second substituent in the *para*-position in nitrobenzene and dimethylaniline, respectively.[37] The shifts are the greater the difference between the electron-donor (electron-acceptor) properties of the substituents in the compound.

TABLE 5. LOGARITHMS OF PARTIAL RATE FACTORS OF BROMINATION AND OF DEUTERO-EXCHANGE WITH BASES

Reaction	Substituents			
	$N(CH_3)_2$	OCH_3	OC_6H_5	F
Bromination	19·5	9·8	7·9	0·8
Deutero-exchange	0·2	2·7	4·3	6·0

σ_{para}—Hammett's constants which allow a quantitative estimation to be made of the effect of the substituent on the reactivity of the side group in the *para* position.[38] k_{ratio}—approximate value of the ratio of the rate constant of bromination of a benzene derivative with a given substituent to that of bromination of benzene.[39]

The rate of electrophilic substitution of hydrogen increases with increasing electron-donating properties of the substituents. Thus, dimethylaniline is brominated at a rate 9 orders of magnitude greater than anisole and 11 orders of magnitude greater than diphenyl ether, whereas nitrobenzene is brominated 24 orders of magnitude slower than dimethylaniline.[39]

The inverse dependence between the electron-donor and electron-acceptor properties of the same substituents may be seen on comparing the f_{para} values for bromination[40] and the f_{ortho} values for deutero-exchange with potassium amide in liquid ammonia (Table 5).†

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* On page 395.

† The fact that f_{para} was taken for the first reaction and f_{ortho} for the second does not influence in any way the results inasmuch as in electrophilic substitution reactions f_{para} and f_{ortho} are usually of the same order of magnitude (see Table 3).

[36] P. L. Corio and B. P. Dailay, *J. Amer. Chem. Soc.* **78**, 3044 (1956).

[37] P. P. Shorygin *Zh. Fizich. i Khim.* **33**, 1477 (1959).

[38] H. H. Jaffe, *Chem. Rev.* **53**, 222 (1953).

[39] R. W. Robertson, P. B. D. de la Mare and B. E. Swedlund, *J. Chem. Soc.* 782 (1953).

[40] P. B. D. de la Mare and J. H. Ridd, *Aromatic Substitution. Nitration and Halogenation* p. 140. London (1959).

A comparison of the data for OCH_3 and OC_6H_5 groups showed that the replacement of CH_3 by C_6H_5 intensifies the electron-acceptor properties and weakens the electron-donor properties of the substituent as a whole. Evidently the same relation should be manifested on comparing the rates of deutero-exchange with acid (CH_3COOH) and with base ($NH_3 + KNH_2$) on the part of dimethylaniline and methyldiphenylamine. Acetic acid was chosen because it forms with dimethylaniline and especially with methyldiphenylamine a molecular compound rather than a salt owing to which there is no significant disturbance of the conjugation of the lone electron pair of the substituent nitrogen with the π-electrons of the benzene ring and the rate constants give, in general, a correct notion of the reactivity of the *ortho-* and *para*-positions of the amine molecules.[32]

The above assumption has been confirmed by measurements of the author in collaboration with Ranneva. Let the values of the rate constants of *para*-deuterium atoms in a dimethylaniline molecule with acid and with base both be set equal to unity. This leads to the results presented in Table 6.

TABLE 6. COMPARISON OF THE RATES OF DEUTERO-EXCHANGE IN METHYLDIPHENYLAMINE AND DIMETHYLANILINE WITH BASE AND ACID

Reactant	$C_6H_5N(CH_3)C_6H_5$		$C_6H_5N(CH_3)_2$	
	ortho	*para*	*ortho*	*para*
Base	470	19	20	1·0
Acid	0·13	0·11	1·2	1·0

Hence, if we assume that the *para*-deuterium atom of dimethylaniline exchanges at the same rate, independent of the reactant the *ortho*-deuterium of methyldiphenylamine will exchange 3600 times faster with base than with acid.

It has already been stated that the methyl group in toluene is an electron-donor, in deuterium exchange with both acid and base, but owing to the different mechanisms of these reactions the p.r.f. values are greater than unity on deutero-exchange with acid and less than unity on exchange with base (Table 7).

TABLE 7. PARTIAL RATE FACTORS OF DEUTERO-EXCHANGE IN TOLUENE WITH ACID AND WITH BASE

Reactant	f_{ortho}	f_{meta}	f_{para}
HBr[35]	1000	5	4000

of exchange with a solution of potassium amide in liquid ammonia, if the same value be assigned to the rates of both reactions in benzene.*

In the present paper, a general notion of the mechanism of protophilic hydrogen substitution in aromatic compounds has been described and compared with electrophilic substitution reactions. The mechanism may doubtlessly be much more involved than that described above. In the first place the inductive effect, while of importance in the protophilic substitution of hydrogen, is not the only determinating factor. This follows, for example, from the absence of correlation between the f_{para} values and the parameters depending only upon the inductive effect *per se*, (Table 1 and Fig. 3).

compounds the runs were made at 70°, with durene at 30° and with mesitylene at 0°). The rates of deutero-exchange are referred to the rate constants for benzene, arbitrarily taken to be 6 (cf.[6a], p. 333). The experimental values are in good agreement with the values for the p.r.f.'s of deutero-exchange in toluene calculated on the basis

TABLE 8. COMPARISON OF DEUTERO-EXCHANGE IN BENZENE AND IN METHYLBENZENE WITH BASE AND WITH ACID

Substance	Base		Acid	
	found	calculated	found	calculated
Benzene	6	6	6	6
Toluene	1·75	1·75	$9{\cdot}34 . 10^2$	$9{\cdot}34 . 10^2$
p-Xylene	$6{\cdot}0 . 10^{-1}$	$4{\cdot}0 . 10^{-1}$	$5{\cdot}10 . 10^3$	$3{\cdot}84 . 10^3$
Mesitylene	$9{\cdot}0 . 10^{-2}$	$6{\cdot}2 . 10^{-2}$	$5{\cdot}70 . 10^7$	$8{\cdot}08 . 10^7$
Durene	$2{\cdot}2 . 10^{-2}$	$2{\cdot}0 . 10^{-2}$	$1{\cdot}67 . 10^6$	$1{\cdot}85 . 10^6$

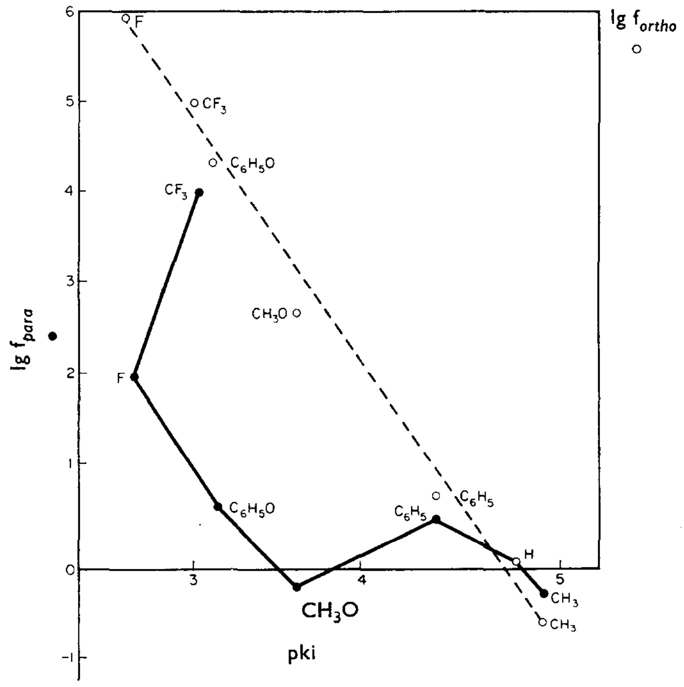

FIG. 3. A dependence between f_{para} and K_i.

of additivity of the differences in free energies of activation of hydrogen substitution in benzene and in each of the positions of the polysubstituted aromatic ring.[40–43]

Consecutive methylation of benzene lowers the rate of deutero-exchange with bases and sharply increases the reaction rate with acids. The relative rate of deutro-exchange with CF_3COOH in mesitylene is 9 orders of magnitude greater than the rate

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[42] F. E. Condon, *J. Amer. Chem. Soc.* **70**, 1936 (1948).
[43] H. C. Brown *et al*, *J. Amer. Chem. Soc.* **74**, 2310 (1955). **79**, 1421, 5175 (1957); **80**, 2296, 6439 (1958).

of exchange with a solution of potassium amide in liquid ammonia, if the same value be assigned to the rates of both reactions in benzene.*

In the present paper, a general notion of the mechanism of protophilic hydrogen substitution in aromatic compounds has been described and compared with electrophilic substitution reactions. The mechanism may doubtlessly be much more involved than that described above. In the first place the inductive effect, while of importance in the protophilic substitution of hydrogen, is not the only determinating factor. This follows, for example, from the absence of correlation between the f_{para} values and the parameters depending only upon the inductive effect *per se*, (Table 1 and Fig. 3). A possible explanation of this should be sought in the assumption that the relative acidity of the CH-hydrogen depends upon the participation in the electronic density distribution not only π- but also σ-electrons. This is the interpretation advanced by Barnes and Bush[44] of the phenomena observed in the metalation of 1,7-dimethoxynaphtalene. Secondly, the cation effect on reactions with participation of base anions must not be neglected. This counter-ion effect may often be considerable.[45–47] It is this effect that may be responsible for example for the unequal coordinating power of cations participating in the formation of cyclic structures in the transition state.

Doubtless considerable further study will have to be carried out before we shall be in a position to describe in all its details the mechanism of the diverse reactions of protophilic substitution of hydrogen.

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* It can be shown by calculation that the difference in relative rates of deutero-exchange in the pentamethylbenzene ring with liquid hydrogen bromide and potassium amide solution in liquid ammonia should attain a value of 12 orders of magnitude.

[44] P. A. Barnes and W. M. Bush, *J. Amer. Chem. Soc.* **81,** 4705 (1959).

[45] A. A. Morton and E. J. Lanfer, *J. Org. Chem.* **23,** 1636, 1639 (1958).

[46] H. D. Zook and W. L. Gumby, *J. Amer. Chem. Soc.* **82,** 1386 (1960).

[47] R. M. Schram and G. E. Langlois, *J. Amer. Chem. Soc.* **82,** 4912 (1960).