The Effect of Structure on Reactivity: Nuclear Substitution of Benzene Derivatives

BY H. F. McDUFFIE, JR.,[1] AND GREGG DOUGHERTY

Introduction

Many attempts have been made to correlate the structure of substituted benzenes with their reactivity. Hammett[2] has compiled lists of substituent constants which accurately measure the effect of a meta or para substituent on the reactivity of various benzene derivatives. Ri and Eyring[3] have lately correlated the rates of nitration in all positions of benzene derivatives with the dipole moments of these compounds.

In order to obtain additional experimental data on the effects of structure on the rates of nuclear substitution, the Friedel–Crafts reaction of acetyl chloride with benzene derivatives in the presence of anhydrous aluminum chloride has been utilized. There were several reasons for the choice of this reaction.

1. The reaction proceeds smoothly at ordinary temperatures to give the expected products in good yields and without the formation of undesirable or unpredictable by-products.

2. The entrance of one acetyl group into an aromatic ring inactivates the molecule for further substitution by acetyl groups under the conditions studied.

3. The relative reactivities of two benzene derivatives can be determined by the use of competitive measurements on a mixture of the two.

The technique of competitive reactions enables one to know that the two members of the reacting pair of benzene derivatives are at all times under the same conditions of temperature, concentration of reactants, and concentration of catalyst. Briefly, it is the reaction of a limited amount of acetyl chloride with an excess amount of a mixture of the two benzene derivatives which are being tested. Since both substances can react with the acetyl chloride, they will do so in proportion to their respective reactivities and concentrations. The use of known starting concentrations and the analysis of the products of the reaction makes it possible to determine the relative rates of reaction of the two substances being studied.

(1) Present address: Department of Biochemistry, Cornell University Medical College, New York, N. Y.

(2) L. P. Hammett, "Physical Organic Chemistry," Chapter VII, McGraw-Hill Book Company, Inc., New York, N. Y., 1940.

(3) T. Ri and H. Eyring, J. Chem. Phys., 8, 433 (1940).

Experimental

The general method of carrying out the reaction was as follows. Anhydrous aluminum chloride was placed in a one-liter three-neck flask fitted with a condenser and dropping funnel, a mercury- or oil-sealed stirrer, and a thermometer which extended to the bottom of the flask. One mole of each of the two benzene derivatives to be studied was placed in the flask, and acetyl chloride was added through the dropping funnel over a period of one-half an hour. The temperature of the reaction mixture was kept to $\pm 1.0°$, by the use of an external ice–water-bath. A tube was attached to the top of the condenser to lead the evolved hydrogen chloride into the hood chamber. After the addition was complete, the mixture was stirred at the reaction temperature for two hours and then hydrolyzed. Several methods of hydrolysis were tried during the course of the experiments, and all gave satisfactory results. The method finally adopted was to add 200 cc. of petroleum ether (30°/60° or 60°/75° b. p.) to the reaction mixture and then to add 200–250 cc. of water slowly with stirring and external cooling. The first hundred cc. of water was added dropwise, but the second hundred cc. was added all at once. The resulting two-layer mixture was placed in a liquid–liquid extractor and extracted with petroleum ether. This extract, containing the unreacted benzene derivatives, ketone products, and petroleum ether, was then fractionated through a column 75 × 1.2 cm., filled with helical packing and containing about 12–15 theoretical plates, and the amounts of unreacted benzene derivatives were carefully determined. The fractionation was discontinued after the recovery of all the unreacted starting aromatics, and the undistilled ketone mixtures were collected and weighed. Consistency in weights of recovered ketones from duplicate reactions was taken to indicate consistency in the total amount of reaction which had taken place.

Fractionation of the ketone mixtures would also indicate the relative reactivity of the benzene derivatives involved, but this was not attempted because of the difficulty of any quantitative separation of such ketone mixtures.

Table I summarizes the experimental data which have been collected for various pairs of benzene derivatives.

Discussion

In order to determine the relative reactivities of all the benzene derivatives studied, the above data were interpreted by means of the following derivation.[4]

If A_0, B_0 and C_0 are the initial amounts of A, B and the acylating agent (whatever it may be), and A and B are the actual quantities remaining after a time t, then at any moment

$$-dA/dt = k_a A [A + B - (A_0 + B_0) + C_0]$$
$$-dB/dt = k_b B [A + B - (A_0 + B_0) + C_0]$$

(4) C. K. Ingold and F. R. Shaw, J. Chem. Soc., 2919 (1927).

TABLE I

Number	Component A	Component B
I	Toluene	Benzene
IIIa	o-Chlorotoluene	Chlorobenzene (B and A AlCl₃)[a]
IIIb	o-Chlorotoluene	Chlorobenzene (Merck AlCl₃)[a]
IVa	Benzene	o-Chlorotoluene (B and A AlCl₃)[a]
IVb	Benzene	o-Chlorotoluene (Merck AlCl₃)[a]
VI	Chlorobenzene	p-Chlorotoluene
VII	Chlorobenzene	Bromobenzene
IX	m-Xylene	Toluene
X	Mesitylene	Toluene[b]

Number	I	IIIa	IIIb	IVa	IVb	VI	VII	IX	X
AlCl₃ (moles)	1.0	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.35
CH₃COCl (moles)	0.8	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.30
Temperature	10	11	11	10	10	16	15	0.0	0.0
No. runs	5	4	3	4	3	9	4	3	1
Moles A_f	0.188	0.550	0.436	0.564	0.465	0.564	0.597	0.419	0.190
Avg. deviation (moles)	.012	.029	.003	.017	.010	.009	.016	.010	...
Moles B_f	.883	.907	.908	.887	.813	.778	.678	.892	.443
Avg. dev.	.010	.015	.005	.008	.019	.015	.021	.010	...
Avg. ketone wt., g	99	80	97	62	75	86	101	89	48
Log A_f/LogB_f	13.3	6.2	8.58	4.7	3.7	2.27	1.3	7.54	2.04

[a] The type of AlCl₃ used had a pronounced effect on the extent of reaction, but the results with each type were consistent within themselves. [b] In this experiment only half moles of the toluene and mesitylene were used.

These equations assume that the reactions are bimolecular and irreversible. On simultaneous integration they give

$$k_a/k_b = (\log A_f - \log A_0)/(\log B_f - \log B_0)$$

where A_f and B_f are the ultimate values of A and B. It is understood that all amounts mentioned are in moles. Since in all our work we have kept $A_0 = B_0 = 1.0$ mole, we can omit $\log A_0 = 0.0$ from the above expression leaving for our expression which determines the relative reactivities of A and B the equation

$$(\log A_f)/(\log B_f) = k_a/k_b$$

This then is the equation by which the experimental data were converted into the following table (Table II) of relative reactivities of the substances studied. Since each benzene derivative was allowed to react in competition with a more active and a less active one in separate experiments, we can use the various relationships so determined to build up a self-consistent scale of reactivities, in which all of the substances are interrelated.

TABLE II

Substance	k_{acyl}	Log K acylation	log K nitration	Log k_p	σ
p-Chlorotoluene	1.0	0.00			
Bromobenzene	1.77	0.248	−1.01	−0.77	+0.232
Chlorobenzene	2.3	0.362	−0.91	−0.91	+0.227
o-Chlorotoluene	19.8	1.297			
Benzene	73.1	1.864	+0.778	+0.778	0.00
Toluene	972	2.988	+1.78		−1.7
Mesitylene	1984	3.297			
m-Xylene	7330	3.865			

Taking the least active member of the series, p-chlorotoluene, as having unit reactivity, we arrive at the following scale of relative reactivities for the other substances: (k_{acyl} is understood to be the rate, relative to p-chlorotoluene).

In order to correlate these rates with other measurements of the variation of reactivity with change in structure, we first examined the data of Holleman[5] and of Ingold and his collaborators[6] dealing with rates of nitration of benzene derivatives and percentages of ortho, meta, and para isomers formed in nitration. Since acetyl chloride is said[7] to give only para derivatives (and presumably slight amounts of meta) of monosubstituted benzene derivatives, and since Fisher-Hirschfelder models of the ortho ketones show considerable restriction of free rotation of the CH₃CO– group about the C–C bond linking it to the benzene ring, we have only included the rates of the substitution in the meta and para positions. Thus $2k_{meta} + k_{para} = k_{nitration}$. The logarithms of these k's are also found in Table II, and we have plotted log $k_{acylation}$ against log $k_{nitration}$ in Fig. 1, for all the monosubstituted derivatives studied. The excellent straight-line agreement over the wide range of activity covered indicates

(5) A. F. Holleman, Chem. Rev., 1, 187 (1924).

(6) Ingold, Lapworth, Rothstein and Ward, J. Chem. Soc., 1959 (1931); Bird and Ingold, ibid., 918 (1938); Ingold and Smith, ibid., 905 (1938); Bedford and Ingold, ibid., 929 (1938); Ingold and Shaw, ibid., 2918 (1927).
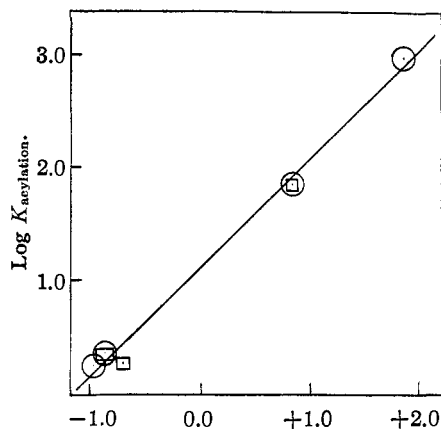
(7) "Organic Syntheses," Coll. Vol. I, p. 105.

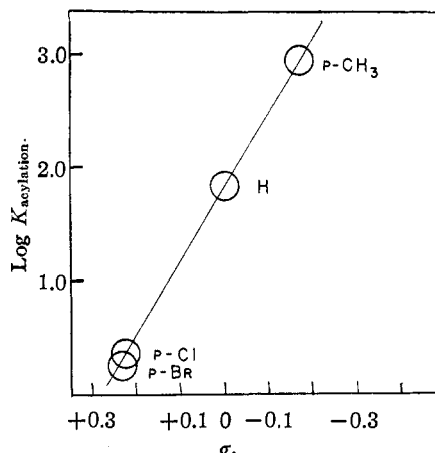Fig. 1.—⊙, Log $K_{nitration}$; ▣, log $K\mu$.

Fig. 2.

that the type of reaction is the same in both cases (*i. e.*, the attack of a NO_2^+ or a CH_3CO^+, with the CH_3CO^+ in the form of an addition compound with aluminum chloride, and that the influence of the substituent is the same for both reactions.

Another set of data with which the acylation data could be compared was the table of "substituent constants" presented by Hammett.[2] These substituent constants are supposed to measure accurately the effect of a substituent upon any process occurring in a position para or meta to the substituent. Since the amount of meta substitution is negligible compared with that of para substitution, we have plotted log $k_{acylation}$ against σ, the substituent constant, for all of our monosubstituted benzene derivatives in Fig. 2. Again, the excellent agreement obtained indicates that the effect of the substituent in the case of acylation is the same as its effect in the many reactions discussed by Hammett.

Both the comparison with nitration rates and with the substituent constants represent correlations of experimental data with experimental data from another source. In order to correlate our relative rates with some non-chemical function of the structure we utilized the data of Ri and Eyring[3] which deal with the calculation of dipole moments, from nitration rates. These workers also made the reverse calculation and used the experimentally determined values of dipole moments to determine the charge distribution within the benzene ring. From this calculated charge distribution they calculated the rates of reaction in the different positions relative to the substituent present. As with the nitration data we have

made up rates by taking only the meta and para values. Thus $k = 2k_{meta} + k_{para}$. These rates listed in Table II are plotted against the rates for acylation in Fig. 1. Because of the limitations of the method of calculation, we were only able to obtain values for benzene, chlorobenzene, and bromobenzene. Of these values, the bromobenzene and chlorobenzene are in the wrong order of activity, but they are very close together. They are seen to fall very close to the line drawn for nitration, and this confirms the general view of the reaction advanced by Ri and Eyring.

Summary

Experimental data on the relative reactivities of various mono-, di- and tri-substituted benzene derivatives have been obtained through the use of competition measurements involving the Friedel–Crafts reaction of acetyl chloride with aromatic compounds. ·

The data obtained for monosubstituted benzene derivatives correlate well with the available data for nitration, the substituent constants presented by Hammett, and the rates calculated from the dipole moments of the monosubstituted benzenes.

This correlation further confirms the ionic mechanism of the reaction (and indeed of all nuclear substitutions of aromatic compounds) and demonstrates that the influence of substituents on the reactivity of benzene derivatives is the same as in other nuclear substitutions and side-chain processes.