[CONTRIBUTION FROM THE DEPARTMENT OF INDUSTRIAL CHEMISTRY, THE FACULTY OF Engineering, Kyoto University]

THE ACCELERATIVE ORTHO EFFECT. I. THE ORIENTATION IN THE AROMATIC NUCLEOPHILIC SUBSTITUTIONS

YOSHIRO OGATA AND MASARU TSUCHIDA

Received April 5, 1955

It is well known that an *ortho* substituent in an aromatic substitution reaction often exhibits a retarding effect on the substitution velocity and in general this is attributed to the so-called steric hindrance or steric inhibition of resonance. There are, however, several examples in which the *ortho* substituent accelerates the reaction. It is of interest to note that this phenomenon of rate inversion due to orientation exists in the case of nucleophilic substitutions on halobenzene derivatives (1); *i.e.*, it seems that nucleophilic reagents may be classified into two groups with respect to their position of most favorable attack. Thus with *o*- and *p*-nitrohalobenzenes [chloronitrobenzene (2–11), bromonitrobenzene (2), (4), (8, 10), (12), (13), and iodonitrobenzene (4), (10), (13)] the *o*-compound reacts faster than the *p*-isomer with uncharged nucleophilic reagents (*e.g.*, hydroxide and alkoxide ion) the reverse is true [chloronitrobenzene (4), (14–17) and bromoitrobenzene (2), (18)]. The same phenomenon was observed with halobenzonitriles (7) and with 3,4,6-trichloronitrobenzene (19).

The studies described in this article were undertaken for the purpose of demonstrating it in the existing literature and to add some new data related to it by carrying out experiments with other substituted halobenzenes, and especially to explain these phenomena on the basis of the atomic charge distribution pattern assumed for each activated complex.

Since there has been no data on the rate comparison between o- and p-halo derivatives of benzophenone, methyl phenyl sulfone, and acetophenone, the authors measured the rates of reaction of these compounds with piperidine (an uncharged reagent) and sodium ethoxide or hydroxide (charged reagents). The results are listed in Table I.

The table shows the preference of *ortho* substitution with the uncharged reagent and the preference of *para* attack with negatively charged reagents, the only exception being the *p*-bromophenyl methyl sulfone which reacted with sodium ethoxide slower than the *o*-isomer, as does *p*-chlorophenyl methyl sulfone (16).

There are two reports which are opposed to this generalization. Campbell, Anderson, and Gilmore (20) have reported that p-bromonitrobenzene reacted with piperidine faster than its o-isomer. Our experiment, however, shows the reverse result, which is also consistent with the recent Chapman-Parker-Soanes' result (8) obtained in a 99.8% ethanolic solution and also Brieux-Deulofeus' data in benzene (11). Another communication (4) reporting that o-bromonitrobenzene reacts with sodium ethoxide more readily than the p-isomer does not seem to be correct, since the inevitable formation of azo-compound occurs under these conditions and the reaction leading to this compound should consume

OGATA AND TSUCHIDA

Attacking Reagent		Piperidine				NaOC2H5	NaOH
Reaction ter	mp. and time	165° 25 hrs.	175° 22 hrs.	165° 21 hrs.	70°	81°	75° 7 hrs.
Initial	Substrate	0.09	0.09	0.09	0.09	0.0015	0.001
Conc'n M.	Reagent	1.3	1.3	1.3	1.3	0.54	0.3
Substituent	Reaction rate	C.P.ª	C.P.	C.P.	R.C. ^b	R.C.	C.P.
o-COCH₃		84.0	90.8			$4.4 imes 10^{-6}$	
$p\operatorname{-COCH}_3$		26.1	34.9			$35 imes10^{-6}$	
$o-\mathrm{SO}_2\mathrm{CH}_3$		93.3	94.8			96×10^{-6}	
$p-\mathrm{SO}_2\mathrm{CH}_3$		75.3	79.9	-	<u> </u>	$6.1 imes 10^{-6}$	
o-COC ₆ H ₅		-		25.8			0.6
$p\operatorname{-COC}_6\mathrm{H}_5$				4.3	—		2.4
$o-NO_2$		-			40.1×10^{-6}	$1.3 imes 10^{-4c}$	
p-NO ₂					$8.4 imes10^{-6}$	$7.4 imes10^{-4c}$	

TABLE I Reaction Rates or Percentages of o- and p-Substituted Bromobenzenes with Nucleophilic Reagents

^a C.P. represents conversion percentage.

^b R.C. represents second-order rate constant in 1./(mole. sec.).

• The reaction temperature is 60°.

alkoxide and organic bromide. The authors recognized that at an early stage of the reaction, the rate of bromide ion formation from p-bromonitrobenzene was greater than that of the *o*-isomer, but that it decreased with time and the rate became even slower than that of the *o*-isomer.

Recently, Hawthorne (21) suggested an explanation for this inversion of orientation on the basis of plots of the probable positions of the activated complex along the reaction coördinate obtained from the consideration of relative equilibrium data. He assumes the same free energy content for the o- and p-amine transition states and concludes that the difference in the free energies of activation for o- and p-substitutions would be due to the difference in ground state free energies of the two sets of reactants. It is true that an o-halonitrobenzene will have a higher energy content than the p-isomer owing to the repulsive force between substituents in o-position, but their energy contents in the transition state do not seem equal.

In the amine (or ammonia) substitution, the attacking agent donates its two electrons for bond formation and is positively charged in the transition state; the electrostatic attraction between this positively charged nitrogen and negative poles of the substituent will surely contribute to the lowering of the energy level of the activated complex, while in the transition state of the alkoxide reaction, no interaction save a coulombic repulsion is conceivable between the substituent and the reactant, which together with steric hindrance will make the *para*

,

.

transition state stable to such an extent as to surpass the energy difference in the ground states.

The authors attempted to correlate the electrostatic interaction of the atomic charges in the assumed transition state with the rate of substitution such as Price (22) and Sixma (23) have done with electrophilic substitutions. Price (22) has assumed that the atomic charge induced in the benzene ring by a substituent is concentrated on atom C_1 in most benzene derivatives. However, the dipole moments calculated on this basis are not in accord with the true values and we have distributed the charge to the *o*- and *p*-carbon atoms (no charge on C_1 , C_3 , and C_5), in order to obtain agreement of the dipole moment and bond moment data tabulated by Price (24).

As an example, the reaction between o- and p-chloronitrobenzenes and ammonia will be discussed rather precisely. The molecular model for chloronitrobenzene was derived from Stosick's data of tetranitromethane (25) and Huse-Powell's data of picryl iodide (26), *i.e.*, C—N_(Nitro) distance: 1.35 Å and O—N—O angle: 120°. The C—N_(Ammonia) distance was assumed to be elongated in the activated complex 10% (27) over the usual covalent bond distance, 1.47 Å (27). The transition state for the nucleophilic aromatic substitution is assumed to be quinoidal with the plane which involves the old C—Cl and new C—N bonds perpendicular to the plane of benzene nucleus (28). The atomic distances necessary for calculation were evaluated graphically.

The electrostatic attraction energy between charges +e and -e' at distance r is expressed as $ee'/\epsilon r$, where ϵ is the dielectric constant. Thus if one electronic charge is 4.77×10^{-10} e.s.u., the Avogadro number 6.062×10^{23} , and 1 cal. corresponds to 4.185×10^7 ergs, the energy of interaction between the atomic charges on the nitro group and the positive charge on the *ortho* amine nitrogen will approximately be (attraction is indicated by a plus sign)

$$\Delta E_{o} = \frac{4.77 \times 10^{-29} \times 6.062 \times 10^{23}}{10^{-8} \times 4.185 \times 10^{11} \epsilon} \left[2.025 \left(\frac{1}{2.73} + \frac{1}{4.00} \right) - \frac{3.476}{2.88} \right]$$
$$= 2.83/\epsilon \text{ k cal/mole}$$

On the other hand, the interaction between the atomic charges introduced on benzene carbons *ortho* and *para* to the chlorine atom may be calculated according to Price's calculation (22)

$$\Delta E_{\sigma}' = \frac{\left(1.59 - \frac{0.574}{3}\right) \times 6.062 \times 10^{23}}{4.185 \epsilon} \left[\left\{ -2.025 \left(\frac{1}{4.08} + \frac{1}{4.66}\right) + \frac{3.476}{3.67} \right\} 2 - 2 \right] \\ \times \frac{2.025}{2.20} + \frac{3.476}{1.35} = 15.53/\epsilon \text{ k cal./mole}$$

and hence $\Delta E_o + \Delta E_o' = 18.36/\epsilon$ k cal./mole. In the same way, for the substitution of *m*- and *p*-chloronitrobenzene with ammonia, the decrease of energy will be

$$\Delta E_m + \Delta E_{m'} = (1.26 + 4.75)/\epsilon = 6.01/\epsilon \text{ k cal./mole}$$

$$\Delta E_p + \Delta E_{p'} = (1.43 + 15.53)/\epsilon = 16.96/\epsilon \text{ k cal./mole}$$

Therefore, if ϵ remains constant, the value of electrostatic interaction is in the order, o > p > m, and in accord with the experimental results. However, since the energy contents of o- and p-chloronitrobenzene do not seem to be equal, the electrostatic interactions between the chlorine atom and the nitro group in the *ortho* and the *para* positions were compared. In the molecular model for o-chloronitrobenzene, the nitro group was assumed for convenience to be coplanar with the benzene ring (29). Thus the energy difference between o- and p-compounds in their initial states is

$$\Delta E_{\sigma-p}^{\prime\prime} = \frac{0.97 \times 6.062 \times 10^{23}}{4.185 \epsilon} \left[\left\{ -2.025 \left(\frac{1}{2.45} + \frac{1}{4.19} \right) + \frac{3.476}{2.98} \right\} - \left\{ -2.025 \left(\frac{2}{6.58} \right) + \frac{3.476}{5.90} \right\} \right] = 0.21/\epsilon \text{ k cal./mole}$$

and the *o*-compound is seen to be of higher energy content, but this energy difference in the original state may be neglected in comparison with that in the transition state.

Since the observed rate increase in going from the p- to the o-position is mainly due to an increase of entropy of activation (9), the electrostatic attraction above will make its main contribution to the desolvation of reactants in the transition state; this desolvation will increase the entropy of activation, and accelerate the reaction (30). In order to coincide with the experimental value of entropy of activation (9), the value of ϵ should be 3-5.

Similar calculations for halogenated acetophenone, benzophenone, and bromophenyl methyl sulfone again demonstrate the preference of *ortho* substitution as shown in Table II. Here also each initial energy level of the *o*-compound will be higher than that of the corresponding *p*-isomer, and at least does not reverse the tendency for preferential *o*-substitution. Even if the relative rates of *o*-, *m*-, and *p*-substitution are rational, the unusually low values of Δ E's calculated for sulfones does not agree with experiment. The sulfone is also abnormal in that it does not allow *o*-*p* inversion. These facts may be attributed to the peculiarity of the sulfur atom which may utilize a d-orbital for activation and hence to the small change in the group geometry between the initial and activated states (31).

The transition-state energy decrease is probably not due to hydrogen bonding,

TABLE II

INTERATOMIC	Electrostatic	INTERACTIO	ON ENERG	IES (ΔE	$+ \Delta E'$	in kg.	cal./mole	AT
TI	HE TRANSITION	STATE FOR	Ammonia	REACTION	N (Attra	ction -	-)	

Holo devia	Substitution position				
	0	m	Þ		
Nitrobenzene Acetophenone Benzophenone Phenyl methyl sulfone	18.36 15.4 14.0 12.8	$6.01 \\ 7.0 \\ 4.2 \\ -3.5$	$ 16.96 \\ 12.6 \\ 5.8 \\ -1.2 $		

1634

for no appreciable change in the rate was observed with deuterated piperidine (21).

EXPERIMENTAL

Materials. o- and p-Bromonitrobenzenes were prepared from the corresponding nitroanilines by the Sandmeyer reaction and were recrystallized from methanol (32). The o-compound melted at 43° and the p-isomer at 127.5°. p-Bromoacetophenone was prepared from bromobenzene and acetic anhydride by the usual Friedel-Crafts reaction (33), m.p. 50°. o-Bromoacetophenone was synthesized from o-bromonitrobenzene via the reduction, the Sandmeyer nitrile synthesis, and by the Grignard reaction on the bromobenzonitrile so produced (34), b.p. 118-119° (16 mm.). p-Bromobenzophenone was obtained by the condensation of bromobenzene with benzoyl chloride and melted at 82° (35). The o-isomer was prepared from anthranilic acid by way of o-bromobenzoic acid and then the Friedel-Crafts condensation of its chloride with benzene, m.p. 41.5° (36). p-Bromophenyl methyl sulfone was synthesized by the reaction of methyl iodide and p-bromobenzenesulfinic acid obtained from a bromobenzene-sulfur dioxide condensation, m.p. 103° (37). The o-isomer was obtained similarly from o-sulfinic acid prepared by the condensation of diazotized o-bromoaniline with sulfur dioxide, m.p. 108.5°. A new compound.

Anal. Calc'd for C7H7BrO2S: C, 35.76; H, 3.00; Br, 33.98.

Found: C, 35.86; H, 3.38; Br, 33.75.

General procedure for rate measurements. (A). The reaction with piperidine. In a thickwalled glass tube of ca. 25 ml. capacity were introduced xylene (10 ml.) and weighed amounts of the bromide and piperidine. These tubes were sealed and completely immersed in an oilbath. After appropriate periods of time, the reaction product was extracted with dilute nitric acid and the quantity of bromide was measured by the Volhard procedure, *i.e.*, after adding an excess aqueous solution of silver nitrate, it was titrated with thiocyanate using ferric salt as an indicator.

(B) The reaction with sodium ethoxide. In a flask equipped with a reflux condenser, was placed a solution of sodium ethoxide in absolute alcohol. After the flask was thermostatted, a known quantity of a sample was introduced into it. Aliquots were taken out at regular time intervals by a long pipet, and the bromide ion content was measured as described in (A). The second-order rate constants were calculated by means of the usual method.

Since o- and p-bromobenzophenones are labile to reduction with alcoholate, the authors employed in this case sodium hydroxide in an aqueous acetone solution, and estimated only a conversion percentage.

An attempted rate measurement for o- and p-bromophenyltrimethylammonium iodide was unsuccessful, since they gave dimethylaniline with piperidine.

Acknowledgments. The authors wish to express their gratitude to Prof. R. Oda and Dr. M. Okano for their advice in performing these experiments, and to the referee for his helpful suggestions.

SUMMARY

The rates of the nucleophilic substitutions at o- and p-positions have been compared between the *ortho* and the *para* isomers of bromoacetophenones, bromobenzophenones, and bromophenyl methyl sulfones etc. When ethoxide ion was used as a reagent, the p-isomer reacted faster except in the case of the sulfone, while with piperidine as a reagent the o-isomer was more reactive. The existing literature as well as our own experiments described above confirmed the preference of *ortho* substitution with uncharged reagents (*e.g.*, ammonia and amine) and *para* substitution with negatively charged reagents (alcoholate and hydroxide) on nitro-, cyan-, sulfon-, acetyl-, and halogen-substituted halobenzenes. This acceleration to the *ortho* substitution with the uncharged reagent (positively charged in its activated complex) will be due mainly to the coulombic attraction between oppositely charged atoms in the activated complex. The electrostatic energies in the transition states of o-, m-, and p-substitutions with ammonia were calculated by means of the atomic charge distribution pattern, and the order of these values was shown to be in accord with the experimental orientation.

Yoshida, Kyoto, Japan

REFERENCES

- OGATA AND TSUCHIDA, J. Chem. Soc. Japan, 74, 1000 (1953). A similar idea was presented by Bunnett and Morath at the 126th National Meeting of the American Chemical Society, New York, N. Y., September 1954.
- (2) NAGORNOW, Chem. Zentr., I, 886 (1898).
- (3) DEMOOY, Rec. trav. chim., 35, 5 (1916).
- (4) FRANZEN AND BOCHHACKER, Ber., 53, 1175 (1920).
- (5) BREWIN AND TURNER, J. Chem. Soc., 332 (1928).
- (6) VOROZHTZOV AND KOBELEV, Chem. Abstr., 33, 4114, 8580 (1939).
- (7) SPITZER AND WHELAND, J. Am. Chem. Soc., 62, 2995 (1940).
- (8) CHAPMAN, PARKER, AND SOANES, Chemistry & Industry, 148 (1951).
- (9) CHAPMAN, PARKER, AND SOANES, J. Chem. Soc., 2109 (1954).
- (10) BRIEUX AND DEULOFEU, Chem. Abstr., 46, 11125 (1952).
- (11) BRIEUX AND DEULOFEU, J. Chem. Soc., 2519 (1954).
- (12) MENSCHUTKIN, Ber., 30, 2967 (1897).
- (13) PERNA, Chem. Zentr., I, 1127 (1903).
- (14) DE BRUYN, Rec. trav. chim., 9, 200 (1890).
- (15) DE MOOY, Rec. trav. chim., 35, 26, 517 (1916).
- (16) TODD AND SHRINER, J. Am. Chem. Soc., 56, 1382 (1934).
- (17) RIKLIS, Chem. Abstr., 40, 6952 (1946); 42, 2497 (1948).
- (18) RHEINLANDER, J. Chem. Soc., 3099 (1923).
- (19) The uncharged reagents attack the chlorine at the 6-position, while the negatively charged reagents substitute at the 4-position. BEILSTEIN AND KURBATOW, Ann. 196, 211 (1879); LE FEVRE AND TURNER, J. Chem. Soc., 1113 (1927); HOLLEMAN AND VAN HAEFTEN, Rec. trav. chim., 40, 67 (1921).
- (20) CAMPBELL, ANDERSON, AND GILMORE, J. Chem. Soc., 446 (1940).
- (21) HAWTHORNE, J. Am. Chem. Soc., 76, 6358 (1954).
- (22) PRICE, J. Am. Chem. Soc., 73, 5833 (1951).
- (23) SIXMA, Rec. trav. chim., 72, 273, 538, 543 (1953).
- (24) PRICE, Chem. Revs., 29, 37 (1941).
- (25) STOSICK, J. Am. Chem. Soc., 61, 1127 (1939).
- (26) HUSE AND POWELL, J. Chem. Soc., 1398 (1940).
- (27) RI AND EYRING, J. Chem. Phys., 8, 433 (1940).
- (28) BUNNETT AND ZAHLER, Chem. Revs., 49, 273 (1951).
- (29) FRANCEL, J. Am. Chem. Soc., 74, 1265 (1952).
- (30) FROST AND PEARSON, Kinetics and Mechanism, John Wiley & Sons, New York, N. Y., 1953, p. 132.
- (31) KLOSTERZIEL AND BACKER, Rec. trav. chim., 72, 185 (1953).
- (32) JÄGER, Z. anorg. Chem., 101, 120 (1917).
- (33) ADAMS AND NOLLER, Org. Syntheses, Coll. Vol. I, 2nd Ed., 109 (1941).
- (34) BORSCHE AND SCRIBA, Ann., 541, 285 (1939).
- (35) CONE AND LONG, J. Am. Chem. Soc., 28, 520 (1906).
- (36) KOOPAL, Rec. trav. chim., 34, 153 (1915).
- (37) BUNNETT AND LEVITT, J. Am. Chem. Soc., 70, 2778 (1948).