[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF NORTH CAROLINA]

The *ortho: para* Ratio in Activation of Aromatic Nucleophilic Substitution by the Nitro Group[1]

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o-Chloronitrobenzene reacts with piperidine faster than its *para* isomer does. The *ortho:para* ratio of rates decreases as the solvent becomes more polar, changing from 80 in xylene to 1.4 in 1% dioxane:99% water. The change in ratio is largely caused by an increase in rate in the *para* series; in the *ortho* series there is little change in rate, energy of activation or entropy of activation. These results indicate that the *ortho* transition state requires less solvation than one would expect for a zwitterionic species. Interpretation: Direct electrostatic interaction of the neighboring positive and negative poles acts as a sort of "built-in" solvation, decreasing the need for participation of solvent molecules in the transition complex.

Although the ratio of *ortho-* to *para* substitution, in *electrophilic* aromatic substitution reactions, has been a subject of active discussion for at least thirty years,[2] chemists have paid relatively little attention to the corresponding phenomenon in *nucleophilic* aromatic substitutions. Certain steric effects on the *ortho: para* ratio in nucleophilic substitutions were recognized, from published experimental data, by Bunnett and Zahler.[3,4] More recently, Miller[5] and Chapman[6] and their associates have contributed additional pertinent information. Also, Hawthorne[7] has discussed factors governing the *ortho: para* ratio in activation by the nitro group.

The *ortho:para* ratio in activation by the nitro group varies in a complex way, as follows[8]: (a) In reactions of 2,4-dihalonitrobenzenes with nucleophilic reagents of all sorts, the 2-halogen atom is preferentially replaced[9]; thus *ortho* activation predominates. (b) The *para* isomers of halonitrobenzenes and dinitrobenzenes react more rapidly than the *ortho* isomers with sodium alkoxides[5a,8,21,22] and with sodium thiophenoxide[23]; thus *para* activation predominates. (c) *o*-Halonitrobenzenes react more rapidly than their *para* isomers with amines[7,8,24,25]; thus once more *ortho* activation is dominant. The present work is directed toward an untangling of these complexities.

In our experiments, we have determined rate coefficients for the reactions of *o*- and *p*-chloronitrobenzene with piperidine in three solvents: 93% ethanol, 75% methanol and 1% dioxane. From the rate coefficients, we have calculated energies and entropies of activation, and *ortho:para* rate ratios in the various solvents. Our data are summarized in Table IV; this table includes values for three additional solvents (99.8% ethanol, benzene and xylene) taken from publications of other workers.

Experimental

Reactants and Products.—*o*- and *p*-chloronitrobenzenes were commercial samples recrystallized. Matheson Practical piperidine was dried over sodium hydroxide and fractionally distilled, the fraction b.p. 105.8–107° being used. *o*-Nitrophenylpiperidine, m.p. 77–78° (lit.[26] 81°), and *p*-nitrophenylpiperidine, m.p. 103–104° (lit.[26] 105.5°), were prepared as authentic samples by heating the corresponding chloronitrobenzenes with excess piperidine, and recrystallizing the products from 95% ethanol to constant melting point. These nitrophenylpiperidines also were isolated from the reactions of piperidine with the corresponding chloronitrobenzenes in all three solvents at 102° under the conditions used for the rate studies, and identified by their melting points.

Solvents.—Commercial "95%" ethanol was redistilled and was found, by determination of its density, to contain 93% ethanol by weight. 75% methanol was prepared by combining three parts by weight of pure methanol[27a] with one part by weight of distilled water. 50% dioxane was

(1) Presented in part to the New York Meeting of the American Chemical Society, September, 1954.

(2) For a recent discussion, see C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p. 256.

(3) J. F. Bunnett and R. E. Zahler, *Chem. Revs.*, **49**, 322 (1951).

(4) These effects were also predicted from theory by J. Miller, *Revs. Pure Applied Chem. (Aust.)*, **1**, 171 (1951).

(5) (a) J. Miller and V. A. Williams, *J. Chem. Soc.*, 1475 (1953); (b) THIS JOURNAL, **76**, 5482 (1954).

(6) R. R. Bishop, E. A. S. Cavell and N. B. Chapman, *J. Chem. Soc.*, 437 (1952).

(7) M. F. Hawthorne, THIS JOURNAL, **76**, 6358 (1954).

(8) This summary is adapted from Bunnett and Zahler (ref. 3, p. 312), with some revisions.

(9) This behavior has been observed in the reaction of 2,4-difluoronitrobenzene with sodium methoxide,[10] in the reactions of 2,4-dichloronitrobenzene with ammonia,[11,12] with ethanolamine,[13] with sodium hydroxide in ethanol,[11] with sodium methoxide,[14] with sodium methylmercaptide,[15] with sodium thiophenoxide[16] and with phenyl benzenethiolsulfonate,[16] and in the reaction of 2,4-dibromonitrobenzene with ammonia.[17] Closely related is the preferential displacement of the 2-chlorine atom in the reactions of 2,4,6-trichloronitrobenzene with sodium methoxide[18] and with sodium thio-*p*-cresoxide,[19] and in the reactions of 2,3,4-trichloronitrobenzene with alcoholic ammonia[20] and with sodium methoxide.[18] In the following cases such behavior has been assigned on the basis of analogy with the above, without proper proof of product structure: the reaction of 2,4-dichloronitrobenzene with diethylamine,[14] the reaction of 2,4,6-trichloronitrobenzene with ammonia,[18] and the reaction of 2,4,6-tribromonitrobenzene with piperidine.[19]

(10) F. Swarts, *Rec. trav. chim.*, **35**, 154 (1915); see also H. H. Hodgson and J. Nixon, *J. Chem. Soc.*, 1879 (1928), in connection with the structure of the product.

(11) F. Beilstein and A. Kurbatow, *Ann.*, **182**, 94 (1876).

(12) H. J. den Hertog and C. Jouwersma, *Rec. trav. chim.*, **72**, 44 (1953).

(13) C. B. Kremer and A. Bendich, THIS JOURNAL, **61**, 2658 (1939).

(14) A. F. Holleman, W. J. de Mooy and J. ter Weel, *Rec. trav. chim.*, **35**, 1 (1915).

(15) H. H. Hodgson and F. W. Handley, *J. Soc. Chem. Ind.*, **46**, 435-T (1927).

(16) G. Leandri and A. Tundo, *Ann. Chim.*, **44**, 271 (1954).

(17) W. Körner, *Gazz. chim. ital.*, **4**, 363 (1874).

(18) H. H. Hodgson and W. A. Batty, *J. Chem. Soc.*, 1433 (1934); see also H. H. Hodgson and J. S. Wignall, *ibid.*, 2216 (1927).

(19) J. D. Loudon, *ibid.*, 1525 (1940).

(20) F. Beilstein and A. Kurbatow, *Ann.*, **192**, 235 (1878).

(21) C. W. L. Bevan and G. C. Bye, *J. Chem. Soc.*, 3091 (1954).

(22) However, C. W. L. Bevan, *ibid.*, 2340 (1951); 655 (1953), found that *o*-fluoronitrobenzene reacts faster than its *para* isomer with sodium ethoxide.

(23) R. F. Snipes has found that *p*-chloronitrobenzene reacts faster than its *ortho* isomer with sodium thiophenoxide in 60% dioxane (unpublished work in this Laboratory).

(24) N. B. Chapman, R. E. Parker and P. W. Soanes, *J. Chem. Soc.*, 2109 (1954).

(25) J. A. Brieux and V. Deulofeu, *Anales Assoc. Quim. Argentina*, **9**, 189 (1951).

(26) E. Lellman and E. Geller, *Ber.*, **21**, 2281 (1888).

(27) (a) J. F. Bunnett, H. Moe and D. Knutson, THIS JOURNAL, **76**, 3936 (1954); (b) G. W. Beste and L. P. Hammett, *ibid.*, **62**, 2481 (1940).

prepared by combining equal weights of distilled water and purified dioxane.[27b] In preparing "1% dioxane" reaction solutions, one volume of a solution of a chloronitrobenzene in 50% dioxane was combined with an aqueous solution of piperidine and then diluted to fifty volumes with distilled water. The small percentage of dioxane was necessary to dissolve the chloronitrobenzenes in sufficient concentration for the rate studies.

Rate Measurements.—Both *o*- and *p*-nitrophenylpiperidine absorb strongly in the range between 400 and 470 mμ, whereas piperidine and *o*- and *p*-chloronitrobenzene have negligible absorption in this region. It therefore was convenient to follow the reaction by spectrophotometric measurements. Our general procedure was as follows: Aliquots of a reaction solution (containing a chloronitrobenzene and piperidine in one of the three solvents) were sealed in ampoules and the ampoules were immersed, all at once, in a thermostat. After the thermostat had returned to temperature, an ampoule was removed and chilled, and subsequently other samples were removed, all times being recorded. The thermostats were constant to ±0.15°. Soon after being removed from the thermostat, each ampoule was opened and its contents carefully transferred to a volumetric flask, which was then filled to the mark with "quenching solution" (made by diluting 150 cc. of 0.1 *N* sulfuric acid in water to 1000 cc. with 95% ethanol). The optical density of the resulting quenched solution was measured by means of a Beckman model B spectrophotometer. Independently, a "theoretical infinity solution" was prepared, containing the appropriate nitrophenylpiperidine in the concentration expected at the completion of reaction. Measurement of the optical density of an aliquot of this solution quenched in the usual manner served to relate optical density to product concentration. It was shown that Beer's law was obeyed in these systems, and that the optical density was not changed by modest variations in the acidity of the quenching solution.

The reaction solutions in 93% ethanol and 75% methanol were approximately 0.015 *M* in aryl chloride and 0.030 *M* in piperidine. Rate coefficients were calculated from the expression $2kt = 1/(a - x) + C$, appropriate for a second order reaction. In 93% ethanol, the reactions were followed to about 65% of completion in the case of *p*-chloronitrobenzene, and to about 75% in the case of the *ortho* isomer. Plots of $1/(a - x)$ *vs.* t were linear in this range, except that a slight tendency for the rate coefficient to drift downward above 55% reaction was noticeable in the case of the *para* isomer reacting at 119.7°. In 75% methanol, the reactions were followed to about 75% of completion. Plots of $1/(a - x)$ *vs.* t had scarcely any curvature at *ca.* 102° but considerable curvature at *ca.* 119.7°. The data for a representative run showing considerable curvature are displayed in Table I. In such cases, rate coefficients were based only on data from the first 50–60% of reaction.

We believe the curvature arises from the incursion of a side reaction of alcoholysis or hydrolysis. Piperidine interacts with these solvents to form alkoxide and hydroxide ions which may then react with the chloronitrobenzenes to form nitrophenyl ethers or nitrophenols. This complication was discussed by Bunnett and Zahler[28] and has been considered at length by Chapman and co-workers.[24,29] The fact that the complication is more serious in 75% methanol (in which the basic dissociation constant of piperidine is higher) and in the reactions of *p*-chloronitrobenzene (which reacts more rapidly with alkoxide ions) is in accord with this interpretation.[30]

The reaction solutions in 1% dioxane were approximately 7.4×10^{-4} *M* in aryl chloride and 0.030 *M* in piperidine; these concentrations were chosen because of the low solubility of the chloronitrobenzenes in this solvent, and were designed to furnish pseudo first-order kinetics. It was found in all runs that plots of optical density *vs.* time rose to a maximum about 90% of the optical density expected for quantitative conversion into nitrophenylpiperidines, and then slowly drifted downward. This indicated a subsequent reaction destroying the nitrophenylpiperidines. It was observed independently that a solution of piperidine in very dilute dioxane does attack both *o*- and *p*-nitrophenylpiperidines, converting them to products having lower extinction coefficients in acid media.

TABLE I

REACTION OF *p*-CHLORONITROBENZENE WITH PIPERIDINE IN 75% METHANOL AT 119.6°

Initial concentrations (at 26°): *p*-$C_6H_4ClNO_2$, 0.0150 *M*. $C_5H_{10}NH$, 0.0300 *M*

Time, hr.	O.D. (460 mμ)	$1/(a - x)$	$2k$, l. mole^{-1} hr.$^{-1}$
0.00	0.003	66.8	...
3.50	.066	70.1	0.943
49.50	.550	111.8	.909
53.08	.575	115.4	.916
101.00	.782	156.6	.889
125.17	.839	173.6	.853
164.75	.920	205.4	.841
190.92	.963	227.6	.842

A quenched aliquot of the "theoretical infinity solution" had O.D. 1.362 at 460 mμ. The average of the first four values of "$2k$," 0.914 l. mole^{-1} hr.$^{-1}$, was taken to represent the rate of this reaction. This value was then halved and corrected for solvent expansion.

The data from runs in 1% dioxane could not, however, be successfully interpreted in terms of an assumption of two consecutive first-order reactions,[31] A → B → C. It was necessary also to take account of a concurrent, competing first-order reaction

$$\begin{array}{ccccc} & & \xrightarrow{k_1} & & \\ A & & \longrightarrow & & D \\ & \xrightarrow{k_2} & & \xrightarrow{k_3} & \\ A & \longrightarrow & B & \longrightarrow & C \end{array}$$

In this scheme, A is a chloronitrobenzene and B a nitrophenylpiperidine. Letting a and b represent the concentrations of A and B at any time, and following Frost and Pearson,[31] we derived an expression giving b as a function of a_0, t, and the rate coefficients k_1, k_2 and k_3

$$da/dt = -(k_1 + k_2)a$$

Integrating $$a = a_0 e^{-(k_1 + k_2)t}$$

$$db/dt = k_2 a - k_3 b = k_2 a_0 e^{-(k_1 + k_2)t} - k_3 b$$

Upon integration, this gives (if $b_0 = 0$, as it does in our case)

$$b = \frac{a_0 k_2}{k_3 - (k_1 + k_2)} [e^{-(k_1 + k_2)t} - e^{-k_3 t}]$$

In applying this equation, we chose values of k_1, k_2 and k_3, calculated a value of b for each time that a sample was removed, and compared the calculated with the experimental values of b. If a satisfactory fit was not obtained, a new set of k values was chosen and a new set of b values calculated. This process was continued until a satisfactory fit was obtained; in most cases, two or three sets of k values had to be tried for each run. These calculations were tedious, but rewarding in that they did furnish a successful interpretation of the experimental data. A representative fit of calculated and found b values is displayed in Table II. In Table III we list values of k_1, k_2 and k_3 for all runs in 1% dioxane.

Presumably C and D in the above reaction scheme are the same substance, namely, a nitrophenol produced, respectively, by hydrolysis of the nitrophenylpiperidine and the chloronitrobenzene present in the reaction mixture. We obtained positive indications of the presence of nitrophenols amongst the products from the action of piperidine on the two chloronitrobenzenes in 1% dioxane at 100°.

***o*-Nitrophenol from *o*-Chloronitrobenzene.**—A mixture of 1.45 g. of *o*-chloronitrobenzene, 30.6 g. of piperidine, 90 cc. of purified dioxane and 8900 cc. of distilled water was refluxed for 48 hours. A portion of the resulting mixture was acidified with enough hydrochloric acid to destroy the color

(28) Reference 3, p. 344.

(29) E. A. S. Cavell and N. B. Chapman, *J. Chem. Soc.*, 3392 (1953).

(30) Very recently, Dr. T. Okamoto isolated, by elution chromatography, a small amount of pure *p*-nitroanisole as a product from the reaction of *p*-chloronitrobenzene with piperidine in 75% methanol at 102°. This product was identified by its melting point (54–56°) and by comparison of its infrared spectrum with that of authentic *p*-nitroanisole.

(31) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," John Wiley and Sons, Inc., New York, N. Y., 1953, p. 153.

of the nitrophenylpiperidine, steam was passed through, and about 15 cc. of steam distillate was collected. The odor of *o*-nitrophenol was detected. The steam distillate was nearly colorless and in the spectrophotometer showed steadily diminishing absorption as the wave length was increased above 350 mμ. Upon being made alkaline with sodium hydroxide, the solution became yellow and showed an absorption maximum at 410–420 mμ, the intensity of absorption at the maximum being 12 times as great in the basic medium. We confirmed that *o*-nitrophenol shows qualitatively this sort of change in absorption spectrum with change from acidic to alkaline medium.

TABLE II

REACTION OF *p*-CHLORONITROBENZENE WITH PIPERIDINE IN 1% DIOXANE AT 119.9°

Initial concentrations (at 24°): *p*-$C_6H_4ClNO_2$, 7.42×10^{-4} *M*; $C_5H_{10}NH$, 3.00×10^{-2} *M*. Theoretical O.D.$_\infty$ = 0.704 (at 400 mμ). Rate coefficients chosen for this solution: k_1, 0.0112 hr.$^{-1}$; k_2, 0.147 hr.$^{-1}$; k_3, 0.00155 hr.$^{-1}$; *b* is expressed in units of optical density.

Time, hr.	*b* (calcd.)	*b* (obsd.)
0.80	0.078	0.076
1.30	.122	.122
2.67	.225	.230
4.42	.328	.331
7.53	.452	.451
16.35	.595	.591
41.68	.618	.621
49.20	.612	.611
65.00	.597	.597

p-Nitrophenol from *p*-Chloronitrobenzene.—A similar reaction mixture, containing *p*-chloronitrobenzene, was refluxed for 97 hours. A portion of the resulting mixture was made strongly acid and extracted with ether. The ether extracts were extracted with dilute sodium hydroxide. The sodium hydroxide extracts were acidified and extracted with ether. Finally the ether extracts were again extracted with dilute sodium hydroxide. One aliquot of the resulting aqueous layer was diluted directly to 25 cc., while another aliquot was acidified and then diluted to 25 cc. The acidic solution was colorless and showed negligible absorption above 380 mμ, while the basic solution was yellow and had a strong absorption maximum at 400 mμ. We confirmed that *p*-nitrophenol shows qualitatively this sort of change in absorption spectrum as the *p*H is changed. It should be noted that only an acidic substance would come through the series of extractions we performed.

The method of calculation of the *k* values in Table III was such as to allow very little latitude in the choice of k_2 values in order for a satisfactory fit to result. On the other hand, considerable changes in k_1 and k_3 values could be made without seriously disturbing the quality of the fit. Therefore the k_1 and k_3 values in Table III should be taken only as representing the order of magnitude of the rates of the respective complicating reactions. In quoting k_1 and k_3 values with several digits, we simply report the numbers that were in fact used in the calculations.

TABLE III

REACTIONS OF *o*- AND *p*-CHLORONITROBENZENE WITH PIPERIDINE IN 1% DIOXANE

Isomer	Temp., °C.	$[C_5H_{10}NH]_0$[a]	k_1, hr.$^{-1}$[b]	k_2, hr.$^{-1}$[b]	k_3, hr.$^{-1}$[b]
para	102.2	0.0285	0.00443	0.0456	0.00051
	102.2	.0283	.00407	.0456	.000594
	119.3	.0296	.014	.134	.00155
	119.6	.0302	.00899	.116	.00162
	119.9	.0300	.0112	.147	.00155
ortho	102.2	.0295	.00132	.0610	.00074
	102.2	.0297	.00248	.0615	.00074
	119.3	.0297	.0035	.173	.00367
	119.6	.0302	[c]	.178	.00440

[a] At *ca.* 25°. [b] See text for meaning of these symbols. [c] In this case, a satisfactory fit was obtained when the competing reaction was ignored.

In Table III, it is noteworthy that k_1 values are considerably higher, at a given temperature, for the *para* than for the *ortho* isomer. In view of the fact that *p*-chloronitrobenzene reacts faster than its *ortho* isomer with alkoxides, this supports our interpretation of the competing reaction as hydrolysis. On the other hand, k_3 values are higher in the *ortho* series; the significance of this is not obvious.

In calculating rate coefficients for reactions in 93% ethanol and 75% methanol, account was taken of the expansion of these solvents with temperature, the following experimentally determined density ratios being used: for 93% ethanol d_{102}/d_{22} = 0.902, d_{119}/d_{22} = 0.882; for 75% methanol, d_{102}/d_{22} = 0.914, d_{119}/d_{22} = 0.895. The first-order rate coefficients determined in 1% dioxane were converted to second-order rate coefficients by dividing by the piperidine concentration; in reckoning the concentration of molecular piperidine in the reacting solutions, we took account of the expansion of the solvent (density values for water were used) and of the extensive basic dissociation of piperidine (K_b = 1.23×10^{-3}; virtually independent of temperature[32]) in this solvent.

Following are the fully corrected rate coefficients for all runs (all in units of l. mole^{-1} min.$^{-1}$ $\times 10^3$):

In 93% Ethanol.—*o*-Chloronitrobenzene: at 101.5°, 3.88 and 3.88; at 119.6°, 12.2; at 119.8°, 11.1. *p*-Chloronitrobenzene: at 101.45°, 1.69 and 1.64; at 119.6°, 4.33; at 119.8°, 4.25.

In 75% Methanol.—*o*-Chloronitrobenzene: at 101.4°, 5.07; at 102.4°, 5.30; at 119.6°, 15.2; at 119.8°, 15.4. *p*-Chloronitrobenzene: at 101.4°, 2.80; at 102.4°, 3.13; at 119.6°, 8.47; at 119.8°, 8.30.

In 1% Dioxane.—*o*-Chloronitrobenzene: at 102.2°, 44.5 and 44.5; at 119.3°, 126; at 119.6°, 128. *p*-Chloronitrobenzene: at 102.2°, 32.8 and 33.0; at 119.3°, 98.3; at 119.6°, 83.3; at 119.9°, 106.

ΔE, the Arrhenius activation energy, and $\Delta S^{\ddagger}$, the entropy of activation, were calculated by standard equations. In view of the uncertainty in the rate coefficients, ΔE should be considered uncertain by about ±1 kcal. per mole, and $\Delta S^{\ddagger}$ about ±3 cal./deg.

Discussion.—It is profitable to consider the transition states for the reactions we have run. The fact that piperidine and N-deuteropiperidine react at identical rates with both *o*- and *p*-chloronitrobenzene[7] shows that the N–H bond of piperidine is not broken during the rate-determining steps of these reactions. The transition states therefore must have their N–H bonds fully intact,[33] and must be zwitterionic in character, having a partial positive charge on the piperidine nitrogen atom and partial negative charge in the nitro group (if the formation of a metastable tetrahedral intermediate

TABLE IV

REACTIONS OF CHLORONITROBENZENES WITH PIPERIDINE

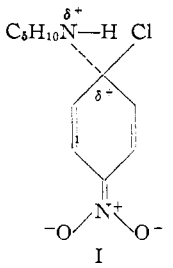
Solvent	Rate coefficient at 102.0°, l. mole^{-1} min.$^{-1}$ $\times 10^3$ *ortho*	Rate coefficient at 102.0°, l. mole^{-1} min.$^{-1}$ $\times 10^3$ *para*	ΔE, kcal. *ortho*	ΔE, kcal. *para*	$\Delta S^{\ddagger}$, cal./deg. *ortho*	$\Delta S^{\ddagger}$, cal./deg. *para*	k_o/k_p at 102°
1% Dioxane	44.0	32.5	17.6	17.9	−28	−28	1.4
75% Methanol	5.20	2.98	17.8	17.2	−32	−35	1.7
93% Ethanol	4.02	1.72	17.7	15.2	−33	−41	2.3
99.8% Ethanol[a]	3.98	1 38	18.1	17.1	−32	−37	2.9
Benzene[b]	5.14	0.11	13.4	13.7	−44	−51	46
Xylene[c]							80[c]

[a] Data from Chapman, Parker and Soanes, ref. 24. [b] Data from Brieux and Deulofeu, ref. 25. [c] Datum from Hawthorne, ref. 7, pertaining to reactions at 116°.

(32) W. F. K. Wynne-Jones and G. Salomon, *Trans. Faraday Soc.*, **34**, 1321 (1938); the temperature dependence of the ion product of water also was considered; *cf.* H. S. Harned and R. A. Robinson, *ibid.*, **36**, 977 (1940).

(33) This conclusion is supported also by a preliminary experiment, in this Laboratory, which indicated that the reaction of piperidine with 1-chloro-2,4-dinitrobenzene in 60% dioxane is not catalyzed by sodium hydroxide.

complex is the slow step) or on the chlorine atom (if the reaction occurs by a one-step, SN2-like mechanism[34]). For reasons previously stated,[35] we favor the intermediate complex mechanism, and depict the two transition states as



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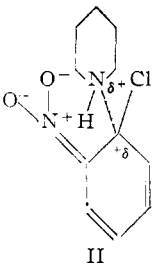

II

It is well known that the rates of reactions involving the formation of extensively ionic transition states from uncharged molecules are strongly solvent dependent. This dependence ordinarily shows the following features[36]: as the solvent becomes more polar, the energy of activation increases slightly, the entropy of activation increases greatly (from large negative to smaller negative values), and the rate increases considerably, owing to domination by the entropy factor. This dependence is explained as a consequence of the increased solvation of the largely ionic transition state as compared to the neutral reactant molecules.

The data (Table IV) for the reaction of *p*-chloronitrobenzene with piperidine show the typical variation with change in solvent. The energy of activation increases from benzene, the least polar solvent for which we have full data, to 1% dioxane, the most polar. The entropy of activation increases greatly, from −51 to −28 cal./deg. And the rate increases nearly 300-fold from the least to the most polar solvent. We can conclude that the *para* transition state is extensively solvated.

The data for the reaction of *o*-chloronitrobenzene with piperidine show a tendency for the same sort of variation with change in solvent, but the variation is much suppressed in the *ortho* series. Particularly because the entropy of activation increases (to smaller negative values) more slowly as the solvent becomes more polar, the rate is remarkably constant, the only considerable change being between 75% methanol and 1% dioxane. As a consequence of the comparative constancy of rate in the *ortho* series, the *ortho:para* ratio changes from 80 in xylene to 1.4 in 1% dioxane.

The fact that the reaction of *o*-chloronitrobenzene with piperidine shows much less than the usual variation in rate, energy of activation and entropy of activation indicates that its transition state II, in spite of its zwitterionic character, is less extensively solvated than the transition state I for the *para* reaction. The reason for this interesting situation becomes evident from examination of the transition state structure II. The sites of positive and negative charge in the zwitterion, the piperidine nitrogen atom and a nitro oxygen atom, are ideally located for direct electrostatic interaction. This mutual electrostatic interaction amounts to a "built-in" solvation, and largely satisfies the tendency of the charged atoms to gather solvent molecules about them.[37]

It is not possible to tell, from our experiments, whether the interaction between positive nitrogen and negative oxygen atoms in the *ortho* transition state II is a direct electrostatic interaction or a matter of hydrogen bonding. Hydrogen bonding has been suggested by Bishop, Cavell and Chapman,[6] but Hawthorne[7] has argued against it on the grounds that N-deuteropiperidine should react at a different rate if hydrogen bonding is significant.

Let us now turn our attention to the general matter of the factors affecting the *ortho:para* ratio in activation of nucleophilic substitution by the nitro group. First, it appears that, all other things being equal, *ortho* substitution is favored. This result has been predicted from quantum-mechanical calculations[38] and may be thought of qualitatively as a consequence of the inductive effect of the nitro group acting more powerfully on neighboring positions.[39] Experimentally, this situation is most nearly represented by the reactions of 2,4-dichloronitrobenzene, in which the 2-chlorine is replaced preferentially by nucleophilic reagents of all sorts.[9,40]

Comparison of the rates of reactions of *o*- and *p*-chloronitrobenzenes with any given reagent is complicated by the fact that the standard free energies of these two aryl halides are unequal and unknown. We shall assume that, owing to steric interactions between the nitro group and chlorine atom in the *ortho* isomer, the *para* isomer has a somewhat lower free energy.[7]

In the transition state for reaction of an *o*-nitrophenyl halide with any nucleophilic reagent, there will be steric interference to the nitro group attaining a coplanar position, and steric compression when and if it does.[41] Because it is critical that the nitro group attain a large degree of double-bondedness to the ring in order to accommodate the negative charge of the pentadienate system, such steric interference with coplanarity will increase markedly the free energy of the *ortho* transition state,[43] as

(34) The one-step mechanism is favored by Chapman.[24,29]

(35) Reference 3, p. 297.

(36) R. G. Pearson, *J. Chem. Phys.*, **20**, 1478 (1952). See also reference 31, p. 127.

(37) This "built-in solvation" effect also could be understood in terms of the one-step, SN2-like mechanism. In the transition state of that mechanism, the piperidine nitrogen atom would carry a partial positive charge, and the oxygens of the nitro group would bear a partial negative charge, owing to the permanently dipolar character of the nitro group. The pairing of positive *vs.* negative charges would be less complete, however, than in the transition state II.

(38) A. L. Green, *J. Chem. Soc.*, 3538 (1954).

(39) The activating effect of the chlorine atom is an instructive analogy. Chlorine, which can only activate through its electron-attracting inductive effect, activates *ortho* much greater than *para* (ref. 3, p. 315).

(40) In most cases, a careful search for the product of replacement of the 4-chlorine was not made. However, den Hertog and Jouwersma[12] isolated a small amount of 4-amino-2-chloronitrobenzene as a by-product from the action of aqueous ammonia on 2,4-dichloronitrobenzene. The action of *ethanolic* ammonia on the same dichloro compound gave only the product of replacement of the 2-chlorine atom, and none of the by-product. This variation of *ortho:para* ratio with change in solvent parallels our observations (Table IV).

(41) This interaction has been discussed by others.[24,42]

(42) A. L. Beckwith, J. Miller and G. D. Leahy, *J. Chem. Soc.*, 3552 (1952).

(43) In some circumstances the steric compression of the *coplanar* nitro group may be less in the transition state than in the starting *o*-nitrophenyl halide.[42] This is of small consequence, however, since the coplanar geometry is essential to the transition state but not to the *o*-nitrophenyl halide molecule.

compared to the free energy of the unhindered *para* transition state. This large increase will overwhelm the (assumed) slightly elevated free energy of the *o*-nitrophenyl halide, causing the *ortho* isomer to react more slowly. This is a powerful effect which more than overcomes the inherent tendency of the nitro group for preferential *ortho* activation. Experimentally, this situation is evident in the reactions of nitrophenyl halides and dinitrobenzenes with alkoxide and thiophenoxide ions; with one exception, all go faster in the *para* series. The exception concerns the reactions of *o*- and *p*-fluoronitrobenzene with sodium ethoxide[22]; in this case, steric interference with coplanarity is small because of the small size of the fluorine atom, and the inherent preferentially *ortho*-activating effect of the nitro group still prevails.[44]

When the reagent is an anion, another effect which no doubt has a bearing on *ortho:para* ratio is electrostatic repulsion in the transition state between the negatively charged oxygen atoms of the nitro group and the still partially negatively charged incoming group.[7] This influence opposes *ortho* substitution, and tends to decrease the *ortho*: *para* ratio. It is not a major effect, for if it were, 2,4-dichloronitrobenzene would undergo considerable replacement of the 4-chlorine by anion reagents. Speaking of 2,4-dichloronitrobenzene, it should be noted that its nitro group is *always* bounded by an *ortho* substituent, and will be sterically hindered in both the *ortho* and *para* transition states; hence our statement that it approaches the situation of "all other things being equal."

In the reactions of *o*- and *p*-nitrophenyl halides with amines, the favorable electrostatic interactions ("built-in solvation") in the *ortho* transition state once more swing the delicate balance of factors back to favoring *ortho* substitution. Here we have an overlay of three effects: first, the inherent preferentially *ortho*-activating effect of the nitro group; second, steric interference with coplanarity in the *ortho* transition state, tending to retard *ortho* substitution; and finally, "built-in solvation" in the *ortho* transition state which restores the predominance of *ortho* substitution.

In the following paper, it is shown that "built-in solvation" plays an important part in determining the *ortho: para* ratio in activation by the carboxylate ($-COO^-$) group.

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(44) It is interesting, however, that *p*-fluoronitrobenzene reacts slightly faster with sodium *methoxide*.[21]

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF NORTH CAROLINA]

The *ortho: para* Ratio in Activation of Aromatic Nucleophilic Substitution by the Carboxylate Group

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The carboxylate group ($-COO^-$) is mildly *para* activating for aromatic nucleophilic substitution. It is *ortho* deactivating for displacement of chlorine by methoxide ion but rather strongly *ortho* activating for displacement of chlorine by piperidine. The *ortho*-activating effect arises from an increase in the entropy of activation. This phenomenon is to be understood as a consequence of "built-in solvation" in the transition state, which decreases the need for participation of solvent molecules in the transition complex.

In the preceding paper[2] we have interpreted successfully the high *ortho: para* rate ratio in the reactions of chloronitrobenzenes with amines, in contrast to the low *ortho:para* ratio in reactions with alkoxides, in terms of a favorable electrostatic interaction between oppositely charged atoms in the transition state of the *o*-aminodechlorination[3] reactions. It is reasonable to expect that such electrostatic interaction should have an important effect on the rates of other reactions. We now report experiments showing the carboxylate[4] group to exert a large activating effect on *o*-piperidinodechlorination.[3] This result also is to be understood in terms of favorable electrostatic interactions in the transition state.

For some time the carboxylate group has been recognized[5-7] as mildly activating toward aromatic nucleophilic substitution in the *para* position. Recently, Miller and Williams[7] showed that the carboxylate group is definitely *deactivating* toward *o*-methoxydechlorination. The contrast between their discovery and ours is striking.

We have determined rate coefficients for the reactions of sodium 4-chloro-3-nitrobenzoate (I) and of sodium 2-chloro-5-nitrobenzoate (II) with piperi-

(1) On leave from the Pharmaceutical Institute, University of Tokyo.

(2) J. F. Bunnett and R. J. Morath, THIS JOURNAL, **77**, 5051 (1955).

(3) This is a systematic name for a substitution reaction. Such names are composed of the parts: the name of the incoming group, the syllable "de," the name of the departing group, and the suffix "ation"; *cf.* J. F. Bunnett, *Chem. Eng. News*, **32**, 4019 (1954); *J. Chem. Soc.*, 4717 (1954).

(4) The group $-COO^-$, resulting from the removal of a proton from a carboxyl group, has variously been called the "carboxylate ion" or the "carboxylate" group, though authors have frequently avoided such names by using the formula of the group instead. We advocate the name, *carboxylate* group, as being simple, sufficient and definite. Analogously, we shall call $-SO_3^-$, resulting from removal of a proton from a sulfo group, the *sulfonate* group.

(5) (a) H. Rouche, *Bull. Acad. roy. Belg., Classe des sciences*, [5] **7**, 534 (1921); *Chem. Zentr.*, **93**, I, 22 (1922). (b) E. Berliner and L. C. Monack, THIS JOURNAL, **74**, 1574 (1952).

(6) J. F. Bunnett and R. E. Zahler, *Chem. Revs.*, **49**, 313 (1951).

(7) J. Miller and V. A. Williams, *J. Chem. Soc.*, 1475 (1953).