ortho Effects on Nucleophilic Aromatic Substitution. The Reactions of 6-R-2-Nitrochlorobenzenes with Piperidine in Benzene

NORMA E. SBARBATI

Laboratorio de Química Orgánica, Facultad de Ciencias Exactas, Universidad de Buenos Aires, Buenos Aires, Argentina

Received March 3, 1965

The rate constants and thermodynamic parameters for the reaction of nine 6-R-2-nitrochlorobenzenes with piperidine in benzene have been determined. The reactions follow the Hammett relationship log $(k_R/k_H) = \sigma\rho$ if the "bulky" substituents, bromine and methyl, are excluded. An approximate van der Waals radius of 1.9 Å. is proposed as the lower limit below which steric effects are negligible, and differences in rate are mainly determined by polar effects. The substituent influence on both enthalpy and entropy of activation is discussed.

The effects of a substituent close to the site of reaction have been discussed by Branch and Calvin.[1] Taft[2] has carried out the separation of polar, steric, and resonance effects, and recently Capon[3] has reviewed the participation of neighboring groups in aliphatic compounds. The terms "*ortho* effect" or "proximity effect"[4,5] have been proposed as better than "steric hindrance" which implies merely the interference due to the bulk of the substituent.

ortho effects on nucleophilic aromatic substitutions have been studied by Berliner, *et al.*,[6] Brady and Cropper,[7] Miller and Williams,[8] and more recently by several workers.[9] Steric inhibition[10] and steric enhancement[11] of the resonance have been also studied.

Many kinetic measurements of the displacement of halogens from 4- and 5-substituted 2-nitrohalobenzenes[12] have been made in order to determine the polar effects of a wide variety of substituents. The reactions of 6-substituted 2-nitrohalobenzenes have been scarcely studied[8,13-15] and there is no systematic survey of the influence of *ortho* substituents on the rate of nucleophilic substitution of *o*-halonitrobenzenes. Miller and his co-workers[16] have studied the reactions of 6-COX-2,4- and 4-COX-2,6-dinitrochlorobenzenes with methoxide ion. In the first system the substituents X are separated by a carbon atom from the *ortho* position and the *ortho* and *para* series are not equally activated.

The present work reports on the reactions of 6-R-2-nitrochlorobenzenes with piperidine in benzene. These results are compared with those obtained previously in this laboratory with 4-R- and 5-R-2-nitrochlorobenzenes.[12]

Experimental Section

Solvents and Reagents.—Piperidine, benzene, and *o*-chloronitrobenzene were purified as described previously.[12]

2,3-Dichloronitrobenzene.—The Theodor Schuchardt product was crystallized from ethanol to constant m.p. 61.5–62.5°.

2-Chloro-3-nitroanisole was prepared by two different methods. (a) From *p*-anisidine, 2,3-dinitro-4-aminoanisole was obtained by Verkade and Witjens' method[17] and diazotized by the procedure of Hodgson and Walker.[18] From the diazonium salt, 2,3-dinitroanisole was obtained using Hodgson and Turner's modification.[19] 2-Amino-3-nitroanisole was prepared by the procedure of Verkade and Witjens[17] and the diazonium solution obtained by Hodgson and Walker's method was treated with cuprous chloride[20] in hydrochloric acid; steam distillation gave 2-chloro-3-nitroanisole, m.p. 93–94° (ethanol). (b) 2-Chloro-3-nitrophenol was prepared from *m*-nitrophenol by van Erp's method[21] and methylated to 2-chloro-3-nitroanisole according to the procedure of Schlieper.[22] The product crystallized from methanol gave m.p. 94–94.5°. A mixture melting point with the product obtained by the first procedure proved that the 2-chloro-3-nitroanisole prepared by method b was isomerically pure and this one was used in the kinetic measurements.

2-Chloro-3-nitrotoluene was prepared from *o*-toluidine by the method of Holleman,[23] b.p. 147–148° (25 mm.), m.p. 23°.

2-Chloro-3-nitrobenzoic Acid.—Oxidation of 2-chloro-3-nitrotoluene was carried out as described by Burton and Kenner[24] and yielded the product of m.p. 183–185° (xylene).

Ethyl-2-chloro-3-nitrobenzoate was prepared from the silver salt as described by Vogel,[25] b.p. 138° (1 mm.)

2-Chloro-1,3-dinitrobenzene.—2,6-Dinitroaniline was prepared and diazotized by Gunstone and Tucker's method.[26] The product of the Sandmeyer reaction was crystallized from glacial acetic acid and then from benzene to constant m.p. 87.5–88°.

2-Chloro-3-nitroaniline.—Reduction of 2-chloro-1,3-dinitrobenzene by Gunstone and Tucker's procedure[26] gave the product of m.p. 96–97° (benzene).

2-Chloro-3-nitrobromobenzene.—2-Chloro-3-nitroaniline diazotized according to Hodgson and Walker's method was poured into cuprous bromide solution[27] and the product crystallized from ethanol, m.p. 59°.

2-Fluoro-1,3-dinitrobenzene[28] was prepared from 2-chloro-1,3-dinitrobenzene by Parker and Read's method,[13] m.p. 60–61°.

(1) G. E. K. Branch and M. Calvin, "The Theory of Organic Chemistry," 2nd Ed., Prentice Hall, Inc., New York, N. Y., 1947, p. 257.
(2) R. W. Taft, "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, Chapter XIII.
(3) B. Capon, *Quart. Rev.* (London), **18**, 45 (1964).
(4) J. F. J. Dippy and R. H. Lewis, *J. Chem. Soc.*, 1426 (1937).
(5) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, pp. 204–207.
(6) E. Berliner, M. Quinn, and P. Edgerton, *J. Am. Chem. Soc.*, **72**, 5305 (1950).
(7) O. L. Brady and F. R. Cropper, *J. Chem. Soc.*, 507 (1950).
(8) J. Miller and V. A. Williams, *ibid.*, 1475 (1953), and previous work.
(9) J. F. Bunnett, *J. Am. Chem. Soc.*, **84**, 3284 (1962); M. Liveris and J. Miller, *J. Chem. Soc.*, 3486 (1963); K. Bowden, A. Buckley, N. B. Chapman, and J. Shorter, *J. Chem. Soc.*, 3380 (1964), and previous work; M. Charton, *J. Am. Chem. Soc.*, **86**, 2033 (1964).
(10) W. C. Spitzer and G. W. Wheland, *ibid.*, **62**, 2995 (1940).
(11) M. J. Kamlet, H. G. Adolph, and J. C. Hoffsommer, *ibid.*, **86**, 4018 (1964).
(12) W. Greizerstein, R. A. Bonelli, and J. A. Brieux, *ibid.*, **84**, 1026 (1962), and the references cited therein.
(13) R. E. Parker and T. O. Read, *J. Chem. Soc.*, 3149 (1962).
(14) P. van Berk, J. O. M. van Langen, P. E. Verkade, and B. M. Wepster, *Rec. trav. chim.*, **75**, 1137 (1956).
(15) P. J. C. Fierens and A. Halleux, *Bull. soc. chim. Belges*, **64**, 696 (1955).
(16) R. L. Heppolette, J. Miller, and V. A. Williams, *J. Am. Chem. Soc.*, **78**, 1975 (1956).
(17) P. E. Verkade and P. H. Witjens, *Rec. trav. chim.*, **65**, 372 (1946).
(18) H. H. Hodgson and J. Walker, *J. Chem. Soc.*, 1620 (1933).
(19) H. H. Hodgson and H. S. Turner, *ibid.*, 748 (1942).
(20) R. N. Keller and H. D. Wycoff, "Inorganic Synthesis," Vol. II, W. C. Fernelius, Ed., McGraw-Hill Book Co., Inc., New York, N. Y., 1946, p. 1; R. W. Meikle, *J. Org. Chem.*, **24**, 278 (1959).
(21) H. van Erp, *J. prakt. Chem.*, **127**, 20 (1930).
(22) F. W. Schlieper, *Chem. Ber.*, **26**, 2465 (1893).
(23) A. F. Holleman, *Rec. trav. chim.*, **27**, 455 (1908).
(24) H. Burton and J. Kenner, *J. Chem. Soc.*, **119**, 1047 (1921).
(25) A. I. Vogel, "A Textbook of Practical Organic Chemistry," 1st Ed., Longmans, Green and Co., London, 1948, p. 376.
(26) F. D. Gunstone and S. H. Tucker, *J. Appl. Chem.* (London), **2**, 204 (1952).
(27) See ref. 25, p. 191.
(28) We are grateful to Mr. R. Caneda for the preparation of this compound.

N-(2,6-Dinitrophenyl)piperidine was prepared by the method described by Bunnett and Morath[29] for N-(*o*- and *p*-nitrophenyl)-piperidine. The product was crystallized from ethanol to constant m.p. 107.5–108°.

N-(2-Chloro-6-nitrophenyl)piperidine.—2,3-Dichloronitrobenzene (1.9 g.) was dissolved in the minor amount of ethanol and refluxed with 10.6 ml. of piperidine during 72 hr. The product was extracted with ethyl ether and washed to neutrality with water. The solvent was evaporated and, after subsequent standing for several days at aproximately 4°, 2.0 g. of a crystalline product was obtained. Crystallization from anhydrous methanol gave a product of m.p. 37.5–38.5°.

Anal. Calcd. for $C_{11}H_{13}ClN_2O_2$: C, 54.9; H, 5.44; Cl, 14.7; N, 11.6. Found: C, 55.1; H, 5.50; Cl, 14.8; N, 11.5.

Kinetic Procedure.—The "slow" reactions ($k_2 \leq 10^{-4}$ M^{-1} sec.$^{-1}$) were followed in the same way as the reactions of 4-R- and 5-R-2-nitrochlorobenzenes[12] by potentiometric titration of the chloride ion. Rate constants were calculated using the expression

$$k_2 = \{2.303/[t(b - 2a)]\} \log [a(b - 2x)/b(a - x)]$$

This technique could not be used for the more reactive compounds: 2,6-dinitrochlorobenzene and ethyl 2-chloro-3-nitrobenzoate. A spectrophotometric technique[29] was used instead. The optical densities of the substituted N-phenylpiperidine produced in the reactions were measured at a convenient wave length, usually 390–410 mμ, with a Beckman DU spectrophotometer. The optical density of a "theoretical-infinity solution" prepared from the pure substituted N-phenylpiperidine agreed satisfactorily with the optical density of the corresponding "infinity" sample.

First-order rate constants, k_ψ, were calculated from the plot of log (O.D.$_{\infty\ \text{expt}}$ − O.D.$_t$) *vs.* t; the slopes divided by the piperidine concentration gave the second-order rate constants, k_2.

Results

The reactions of piperidine with *o*-chloronitrobenzene and with 2,3-dichloronitrobenzene were each carried out at three different initial concentrations and were of first order with respect to each reactant.[30] Since the reactions of the remaining compounds were of second order, it was assumed that they were also of first order with respect to each reactant.

The reaction of 2,3-dichloronitrobenzene was chosen to compare both kinetic procedures, and the results for typical potentiometric (Table I) and spectrophotometric (Table II) runs are given.

TABLE I

REACTION OF 2,3-DICHLORONITROBENZENE WITH PIPERIDINE IN BENZENE AT 75°[a]

Time, min.	x, M	$10^7 k_2$, M^{-1} sec.$^{-1}$
85	0.00765	320
165	0.01480	327
255	0.02075	330
347	0.02665	334
440	0.03150	332
525	0.03520	327
1263	0.05620	329
1365	0.05800	331
		Av. 329 ± 3

[a] Potentiometric titrations. $a = 0.0718$ M, $b = 0.7087$ M.

The reaction of 2,3-dichloronitrobenzene was also carried out at four different initial concentrations of piperidine at 75°. Table III shows that there is not appreciable amine catalysis[31] in this system. We assumed that the remaining compounds behave in the same way. The substrate initial concentration, a, was 0.07 M, except for 2-chloro-3-nitrobenzoic acid, which is slightly soluble in benzene and for which a = 0.03 M, and the two very reactive compounds, 2,6-dinitrochlorobenzene ($a = 4 \times 10^{-4}$ M) and ethyl 2-chloro-3-nitrobenzoate ($a = 10^{-2}$ M). The initial concentration of piperidine, b, was always 0.7 M.

TABLE II

REACTION OF 2,3-DICHLORONITROBENZENE WITH PIPERIDINE IN BENZENE AT 75°[a]

Time, min.	O.D.$_t$
240	0.228
375	0.320
450	0.355
600	0.428
840	0.516
1410	0.635
1530	0.653
1890	0.685

[a] Spectrophotometric method. $a = 3.81 \times 10^{-3}$ M, b = 0.733 M, O.D.$_{\infty,420}$ = 0.730, $10^7 k_\psi = 242$ sec.$^{-1}$, $10^7 k_2 = 330$ M^{-1} sec.$^{-1}$.

TABLE III

REACTION OF 2,3-DICHLORONITROBENZENE WITH PIPERIDINE IN BENZENE AT 75°

a, M	b, M	$10^7 k_2$, M^{-1} sec.$^{-1}$
0.0687	0.343	325
0.0701	0.550	330
0.0718	0.709	329
0.0700	0.996	328
0.0059	0.731	334
0.0038	0.733	330

In every case the reaction was followed up to two half-lives and the rates were determined in duplicate. Data from two tubes removed simultaneously usually did not differ by more than 1%, and the rate constants from independent experiments were within ±2%. The measured rate constants, k_2, and the thermodynamic parameters are given in Table IV. Values of E, calculated by the least-squares method, are accurate to better than ±0.5 kcal./mole, and of ΔS^* to ±1.5 cal. mole^{-1} deg.$^{-1}$. ΔH^*_{75} can be obtained from E by substracting 0.69 kcal./mole.

Discussion

Mechanism of the Reaction.—As part of a work to be reported later we determined the rate constant of the reaction of 2,6-dinitrofluorobenzene with piperidine in benzene at 35° ($k_2 = 0.334$ M^{-1} sec.$^{-1}$). The higher reactivity of the fluoro compound with respect to the chloro compound and the absence of amine catalysis are in favor of a two-step mechanism,[32] in which the decomposition of the intermediate complex, I.C., is not rate determining for these reactions (see Chart I).

The alternative of a simple one-stage mechanism in which there is a small amount of bond stretching in the transition state seems less likely,[33] especially in this nonhydroxylic solvent.[34]

(29) J. F. Bunnett and R. J. Morath, *J. Am. Chem. Soc.*, **77**, 5051 (1955).
(30) K. J. Laidler, "Chemical Kinetics," McGraw-Hill Book Co. Inc., New York, N. Y., 1950, p. 14.
(31) N. E. Sbarbati, T. H. Suarez, and J. A. Brieux, *Chem. Ind.* (London), 1754 (1964).
(32) J. F. Bunnett, *Quart. Rev.* (London), **12**, 1 (1958).
(33) J. Hine, *Ann. Rev. Phys. Chem.*, **11**, 75 (1960).
(34) R. E. Parker and T. O. Read, *J. Chem. Soc.*, 16 (1962).

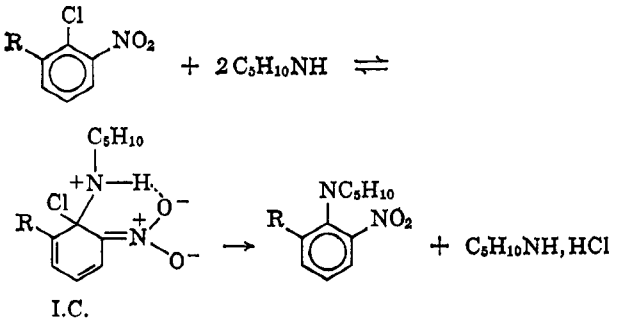
TABLE IV

REACTIONS OF 6-R-2-NITROCHLOROBENZENES WITH PIPERIDINE IN BENZENE[a]

Substituent	$10^7 k_2$, M^{-1} sec.$^{-1}$ 35°	45°	60°	75°	100°	120°	E, kcal. mole^{-1}	ΔS^*_{75}, cal. mole^{-1} deg.$^{-1}$
NO_2	1.29×10^5	1.80×10^5	2.89×10^5	(4.24×10^5)			6.3	49
CO_2Et	1580	2800	5810	(10,200)			10.6	44
CO_2H		624	1520	3510			12.7	40
Cl	15.7	33.7	137	329	1220		12.9	41
Br	617[b]			272	928		12.6	46
H			105	239	903		13.3	44
OCH_3				35.7	130	271	12.3	50
CH_3				1.18	5.69	14.6	15.2	49
NH_2	2.34[b]			0.79	4.25	9.00	14.6	51

[a] Values in parenthesis are extrapolated values. [b] At 90°.

CHART I



I.C.

All the compounds studied are activated by an *o*-nitro group and, therefore, hydrogen bonding[35] and "built-in solvation"[29] may contribute to the stabilization of the transition state and intermediate complex.

As can be expected for the reactions of *ortho* compounds,[36] linear free-energy relationships of the type defined by Leffler[37] and recently criticized by Petersen[38] are not obeyed, but the plot log k_{75} *vs.* log k_{60} of the form proposed by Exner[39] has a slope of 0.958 with a correlation coefficient of 0.999. Although the theoretical meaning of this plot is not very clear, the continuous relationship shown by all the compounds suggest a common mechanism.

The Hammett Equation.—It is known that the empirical relation log $k_R/k_H = \sigma\rho$ established by Hammett[40] generally fails for reactions in which substituents are varied near the reaction center.

Taft[41] has pointed out, however, that the presence of compressed groups is a necessary but not a sufficient condition for the existence of important substituent steric effects upon the reactivity. Certain series having essentially constant steric and resonance factors follow Taft's polar equation log $k_R/k_H = \sigma^*\rho^*$ in which σ^* is a polar substituent constant of the substituent R, relative to the unsubstituted (R = H) compound in the case of reactions of *ortho*-substituted benzene derivatives.

In the series of reactions studied the reactivity order of the substituents (Table IV) is similar to the order shown by the 4-R-2-nitrochlorobenzenes[12] with exceptions for the "bulky" substituents bromine and methyl, which are slower than expected. As the reactivity order nearly follows the order of the polar effects of the substituents the Hammett equation, log $k_R/k_H = \sigma\rho$, was applied. The substituent constants σ_p^* used in the plot (Figure 1) were calculated according to the views of Wepster, *et al.*[42] For each single substituent possessing a mesomeric (M) effect and located at the *para* or, by extension, at the *ortho* position, it can be expected that the importance of the mesomeric interaction is dependent upon the strength of the M effect of the reaction center which, of course, varies from one reaction to another. In order to take into account this effect in the reactions studied, the substituent constants, σ_p^*, were calculated in this way. From the data of the reactions of 5-R-2-nitrochlorobenzenes[12] and using the σ_m values given by McDaniel and Brown[43] (5-R = H, CH_3, Cl, Br, I), a ρ value based on reactions free of mesomeric interaction was obtained. From this ρ value and with the data of the reactions of 4-R-2-nitrochlorobenzenes[12] the σ_p^* constants collected in Table V were calculated. In this way the strength of the mesomeric effect of the reaction center in the substitution of chlorine by piperidine is taken into account. The plot (Figure 1) has a ρ value of +2.65 with a correlation coefficient of 0.991 if data for R = Br and CH_3 are excluded. Upon

TABLE V

SUBSTITUENT CONSTANTS (σ_p^*), RATE RATIOS ($k_{6\text{-R}}/k_{4\text{-R}}$) AT 75°, AND THERMODYNAMIC PARAMETER DIFFERENCES ($\Delta E = E_{6\text{-R}} - E_{4\text{-R}}$, $\Delta\Delta S = \Delta S^*_{6\text{-R}} - \Delta S^*_{4\text{-R}}$) FOR THE REACTIONS OF 6-R- AND 4-R-2-NITROCHLOROBENZENES WITH PIPERIDINE IN BENZENE[a]

Substituent	σ_p^*	k_6/k_4	ΔE	$\Delta\Delta S$
NO_2	+1.21	0.12	−0.2	−4
CO_2Et	+0.67	0.10	+1.2	−1
CO_2H	+0.30	0.60[b]	+0.6[b]	+1[b]
Cl	+0.18	0.29	+1.3	+1
Br	+0.25	0.15	+0.3	−3
H	0.00	1	0.0	0
OCH_3	−0.40	4.5	−3.2	−6
CH_3	−0.25	0.033	+0.7	−5
NH_2	−0.85	1.5	−5.0	−13

[a] Data for 4-R-2-nitrochlorobenzenes from ref. 12; $\Delta S^*_{4\text{-R}}$ was recalculated at 75°. [b] The reaction of 4-chloro-3-nitrobenzoic acid measured with the same conditions that the 2-chloro isomer gave $k_{2,75} = 5410 \times 10^{-7}$ M^{-1} sec.$^{-1}$, E = 12.1 kcal. mole^{-1}, and ΔS^*_{75} = 41 cal. mole^{-1} deg.$^{-1}$.

(35) S. D. Ross and M. Finkelstein, *J. Am. Chem. Soc.*, **85**, 2603 (1963).
(36) See ref. 5, p. 122.
(37) F. E. Leffler, *J. Org. Chem.*, **20**, 1202 (1955).
(38) R. C. Petersen, *J. Org. Chem.*, **29**, 3133 (1964).
(39) O. Exner, *Collection Czech. Chem. Commun.*, **29**, 1094 (1964).
(40) A recent review of the Hammett equation has been published by P. R. Wells, *Chem. Rev.*, **63**, 171 (1963).
(41) R. J. Taft, Jr., *J. Am. Chem. Soc.*, **75**, 4231 (1953).
(42) H. van Bekkum, P. E. Verkade, and B. M. Wepster, *Rec. trav. chim.*, **78**, 815 (1959).
(43) D. H. McDaniel and H. C. Brown, *J. Org. Chem.*, **23**, 420 (1958).

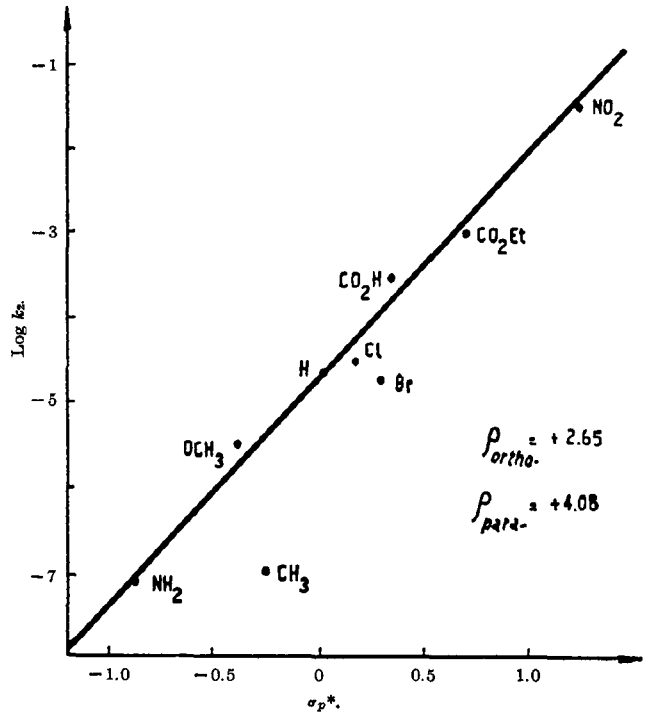


Figure 1.—Plot of log $k_{6\text{-R}}$ at 75° (Table IV) *vs.* σ_p* constants (Table V). Data for the "bulky" substituents, Br and CH_3, have been excluded in the calculation of ρ_{ortho}.

inclusion of these two compounds the correlation coefficient falls to 0.940.

Taft[41] σ_o* values, or other ones more recently evaluated,[44] do not include all the substituents which we studied and, furthermore, the quoted σ constants do not give better correlation coefficients than that obtained with σ_p* constants.

The fact that most of the substituents follows Hammett's equation implies that their effects from the *ortho* positions are mainly polar ones, and that quantitatively they are very close to those exerted from the *para* position. The contribution of steric effects, if present, is less than 15–20%, *i.e.*, within the usual precision of Hammet's equation.

A similar "polar" behavior of *ortho* substituents was observed by Kondo, *et al.*,[45] who obtained a straight line by plotting the infinite dilution shifts, δ_0, of monosubstituted benzoic acids in pyridine *vs.* σ* or σ_p.

The failure of the Hammett equation for methyl and bromine substituents is caused by steric effects, as is shown below. Application of the more complete Taft's equation, $\log k_R/k_H = \sigma^*\rho^* + \delta E_s^2$, that allows for a steric contribution E_s, or of the recently evaluated σ_o constants,[44] does not shift the position of points for 2-chloro-3-nitrotoluene and 2-chloro-3-nitrobromobenzene nearer to the line.

A leveling effect of polar influences from the *ortho* substitution should be noted. The reaction constant ρ is changed from +4.08 to +2.65, on changing from a *para* to a *ortho* substituent.

Substituent Effects on the Enthalpy of Activation.—In these reactions the rate-determining step is the formation of the intermediate complex. *ortho* effects can influence the rate of this step by (1) hindering the entrance of the amine (primary F-strain effect[46]), (2) hindering the coplanarity of the activating *o*-nitro group (secondary steric effect), and (3) there could also be an increase of the inductive effect and a decrease of the resonance effect of a substituent when it is attached to the *ortho* instead of the *para* position.

Effect 1 should be retardative and increase ΔH^*. Piperidine is a relatively large reagent[47] and steric hindrance to its approach will be important when the steric requirements of the *ortho* substituent are large. This is the case for a methyl group; if steric effects are related to the van der Waals radii,[48] the methyl group (van der Waals radius ~2 Å.[49]) is the largest substituent studied, and it shows the greatest deviation from the line (Figure 1). Bromine, which has a similar van der Waals radius, 1.95 Å., also diverges from the line in spite of its different polar effects. This value of ~1.9 Å. seems to be the lower limit below which steric effects are negligible, because the point for chlorine (van der Waals radius 1.80 Å.) is on the line.

Effect 2, should be retardative; decrease of the positive charge density at the reaction center will increase the energy of activation. This effect should be of little importance in this series, because the R substituents are located *meta* to the nitro group.

Effect 3 is very important and it depends on the polar nature of each substituent. Electron-withdrawing substituents will decrease and electron-releasing increase ΔH^*. Polar effects inductively transmitted will be more important from the *ortho* than from the *para* position, while quininoidal resonance will be similar, or lower, if there is steric inhibition of the resonance.[1] When a third substituent is located adjacent to one of two *ortho* groups, the steric compression increases considerably, and coplanarity of the three adjacent groups with the ring is very hindered. In these compounds a decrease of mesomeric effects should be expected.

Substituents NO_2, CO_2Et, and CO_2H which have powerful +M effect show a ratio $k_6/k_4 < 1$ (Table V). Halogens show a similar ratio. This is unexpected on the basis of polar effects alone. Inductive effects of halogens are more important than their mesomeric effects[50] in this type of reaction ($k_{5\text{-R}}/k_{4\text{-R}} > 1$[12]), and halogens should be expected to be more accelerative at the *ortho* positions. Steric effects must be responsible for the decrease in the rate, as is evidenced by the greater decrease with bromine than with chlorine, caused mainly by a decrease in the entropy of activation. The order *o*-Cl > *o*-Br is also probably due to steric effects, rather than to a more powerful inductive (−I) effect of chlorine.

Methoxide and amino substituents retard reaction less from the *ortho* than from the *para* position, as can be expected by their −I+M effects.[8] The large decreases in the entropy of activation on going from a

(44) A. C. Farthing and B. Nam, "Steric Effects in Conjugated Systems," G. W. Gray, Ed., Butterworth and Co. (Publishers) Ltd., London, 1958, p. 131; I. J. Solomon and R. Filler, *J. Am. Chem. Soc.*, **85**, 3492 (1963); M. Charton, *ibid.*, **86**, 2034 (1964).

(45) Y. Kondo, K. Kondo, T. Takemoto, and T. Ikenoue, *Chem. Pharm. Bull.* (Tokyo), **12**, 514 (1964).

(46) D. H. McDaniel and H. C. Brown, *J. Am. Chem. Soc.*, **77**, 3756 (1955).

(47) B. Capon and N. B. Chapman, *J. Chem. Soc.*, 600 (1957).

(48) H. C. Brown, *J. Am. Chem. Soc.*, **75**, 1 (1953).

(49) J. A. A. Ketelaar, "Chemical Constitution," 2nd Ed., Elsevier Publishing Co., New York, N. Y., 1958, p. 201.

(50) J. G. Mather and J. Shorther, *J. Chem. Soc.*, 4744 (1961).

para to an *ortho* position are outweighed by greater decreases in the ΔH^*.

The methyl group should be expected to retard more from the *ortho* than from the *para* position because of its powerful +I effect and, because of its great steric requirements, it exhibits a large *ortho* effect: $k_6/k_4 = 0.033$ due to a greater ΔH^* and a lower ΔS^*. A similar ratio ($k_6/k_4 = 0.037$) is found when bromide is the leaving group.[14]

ortho **Effects and the Entropy of Activation.**—Besides the effects considered there are others which specially affect the entropy of activation. These are hydrogen bonding, built-in solvation, and steric hindrance to motion in the transition state and intermediate complex.

Hydrogen bonding and built-in solvation stabilize the transition state and the intermediate complex. It can be assumed that both effects are mainly associated with the *o*-nitro group which is always present; therefore they are roughly constant through the series.

It can be expected that a bulky substituent near the reaction site, despite its polar nature, will reduce the number of accessible energy levels available to the transition state relative to the initial state. This "bulk" effect will decrease ΔS^*. In all the cases studied the entropy variation ($\Delta\Delta S$, Table V) on going from the *para* to the *ortho* position is negative, when greater than experimental error.

The very low entropy for the reaction of 2-chloro-3-nitroaniline can be explained by an additional effect of electrostatic repulsion in the transition state between the hydrogen atoms of the amino group, and those on the entering nitrogen atom, which is positively charged. (Such repulsions limit the freedom of vibrational and rotational motion.) The same repulsion can exist to a smaller amount in the transition state for the reaction of 2-chloro-3-nitroanisole, but entropy decreases are outweighed by the energy increases owing to the polar effects.

In the case of methyl group an energy increase due to its powerful +I effect is added to the entropy decrease with a consequent large decrease of the rate.

Nitro and bromo groups are "bulky" substituents, and steric hindrance decreases ΔS^*. London forces[51] seem to be unimportant in this type of reaction, because of the low polarizability of the nucleophile.

Acknowledgment.—The author is deeply indebted to Dr. J. A. Brieux, Universidad de Buenos Aires, for having suggested the subject of this work, and to Dr. C. A. Bunton, University of California, for helpful discussions. Thanks are also due to Dr. B. B. de Deferrari for the reported microanalysis.

(51) D. L. Dalrymple, J. D. Reinheimer, D. Barnes, and R. Barker, *J. Org. Chem.*, **29**, 2647 (1964).

Dipolar Addition Reactions of Nitrile Oxides. II.[1] A New Synthesis of Carbodiimides

P. RAJAGOPALAN AND B. G. ADVANI

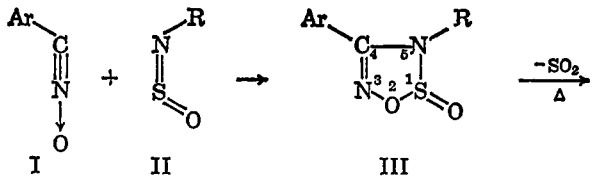
CIBA Research Centre, Goregaon, Bombay 62, India

Received April 13, 1965

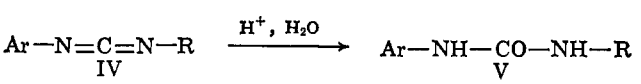
A general method for the preparation of carbodiimides by the pyrolysis of 4,5-disubstituted 1-oxo-1,2,3,5-thiaoxadiazoles is described.

The synthesis of 4,5-diphenyl-1-oxo-1,2,3,5-thiaoxadiazole (IIIa), a representative of a new heterocyclic system, and its pyrolysis to diphenylcarbodiimide (IVa) with the concomitant extrusion of sulfur dioxide were described in a recent communication.[2]

We have examined this reaction in detail to find that the pyrolysis of this novel class of compounds (III) is indeed a general one and that it constitutes a new method for the synthesis of symmetrical and unsymmetrical carbodiimides.



I II III



IV V

Va, Ar = 4-chlorophenyl; R = 4-methoxyphenyl
b, Ar = 4-chlorophenyl; R = 4-methylphenyl
c, Ar = 4-chlorophenyl; R = 4-methylbenzenesulfonyl

The 1-oxo-1,2,3,5-thiaoxadiazoles IIIa–h (Table I) are easily obtained by the dipolar cycloaddition of nitrile oxides (I) to N-sulfinyl compounds (II)[3] and they decompose readily at or just above their melting points yielding the carbodiimides IVa–h (Table II) and sulfur dioxide. This pyrolysis reaction, which is similar to those of 1,5-diaryltetrazoles VI[4] and 3,4-diaryl-Δ^2-1,2,4-oxadiazolin-5-ones VII,[5] differs from them in that, apart from sulfur dioxide, only carbodiimides are formed in this case. Pyrolysis of tetrazoles of the type VI has been reported to yield a mixture of carbodiimides and arimidazoles[4] and that of oxadiazolinones of the type VII arimidazoles[5] only.

The pyrolytic formation of carbodiimides from compounds of the type III was ascribed[2] to the migration of the group initially at the 4 position to an electron-deficient nitrogen arising from the release of sulfur di-

(1) Part I: P. Rajagopalan, *Tetrahedron Letters*, 887 (1964).
(2) P. Rajagopalan and H. U. Daeniker, *Angew. Chem.*, **75**, 91, (1963).
(3) G. Kresze, A. Maschke, R. Albrecht, K. Bederke, H. P. Patzschke, H. Smalla, and A. Trede, *ibid.*, **74**, 135 (1962).
(4) P. A. S. Smith and E. Leon, *J. Am. Chem. Soc.*, **80**, 4647 (1958).
(5) T. Bacchetti and A. Alemagna, *Atti accad. nazl. Lincei, Rend. Classe Sci. fis., mat. nat.*, **22**, 637 (1957); *Chem. Abstr.*, **52**, 15511 (1958).