Dibutyl 1-Butylthio-3,3,3-trichloropropane-1-boronate.—A solution of sodium butyl mercaptide was prepared from 1.21 g. (0.0526 g.-atom) of sodium dissolved in 75 ml. of butanol to which 15 ml. of butyl mercaptan was subsequently added. This solution was added dropwise to 20.0 g. (0.0522 mole) of stirred dibutyl 1-bromo-3,3,3-trichloropropane-1-boronate (1) at room temperature. After 2 hr. the mixture (still slightly alkaline) was treated with 100 ml. of water and 100 ml. of ether, the aqueous phase was extracted with butanol, and the organic phase was washed with four 15-ml. portions of saturated sodium chloride and dried over magnesium sulfate. Distillation through a spinning-band column yielded a forerun containing the butoxy compound **2** (estimated to be about 5% of the crude product by infrared) and 15.5 g. of dibutyl 1-butylthio-3,3,3-trichloropropane-1-boronate, b.p. 100–101° (0.01 mm.); redistilled, n^{24}D 1.4726; strong infrared bands at 6.70, 6.80, 7.3–7.7, 7.96, 8.10, 8.79, 9.30, 9.68, 10.36, 12.1, 13.1, 13.45, and 14.4 μ.

Anal. Calcd. for $C_{15}H_{30}BCl_3O_2S$: C, 46.00; H, 7.72; B, 2.76; Cl, 27.16; S, 8.19. Found: C, 45.85; H, 7.84; B, 2.94; Cl, 27.30; S, 7.99.

Dibutyl 1-Phenyl-3,3,3-trichloropropane-1-boronate.—The butyl B-phenyl-B-(1-bromo-3,3,3-trichloro-1-propyl)-borinate (**3a**),[14] not distilled but identified by infrared, from 11.0 g. of butyl B-phenyl-B-vinylborinate and 30 ml. of bromotrichloromethane was divided into two portions. One portion was treated with 20 ml. of triethylamine in 15 ml. of anhydrous ether, which led to no apparent reaction, followed by 20 ml. of water, which reacted exothermically. Addition of 20 ml. of butanol, acidification with dilute hydrochloric acid, and distillation yielded 7.0 g. of dibutyl 1-phenyl-3,3,3-trichloropropane-1-boronate (**4a**), b.p. 105–115° (0.06 mm.). The other portion of borinic ester was treated with aqueous sodium carbonate and ether until effervescence ceased, then butanol, and distilled to yield 7.2 g. of **4a** (combined yield 80%). Another route to **4a** began with the dropwise addition of 0.20 mole of phenylmagnesium bromide in 100 ml. of ether under nitrogen to 68.8 g. (0.18 mole) of dibutyl 1-bromo-3,3,3-trichloropropane-1-boronate (1) in 200 ml. of ether stirred at −70 to −60°. After 0.5 hr. longer at −70° the mixture was acidified with 10% sulfuric acid, keeping the internal temperature below −30° until acidification was complete. At this point, it was shown in small scale runs by infrared examination that the product was butyl B-phenyl-B-(1-bromo-3,3,3-trichloro-1-propyl)-borinate (**3a**). Addition of 100 ml. of butanol, separation, extraction of the aqueous phase with three 50-ml. portions of butanol, and washing the organic phase with six 50-ml. portions of 5% sodium chloride was followed by shaking with 50 ml. of 5% sodium chloride and increments of solid sodium bicarbonate until effervescence ceased and the aqueous phase remained basic. Distillation yielded 62.2 g. (91%) of **4a**. It was also shown in 0.01-mole runs in ether (30 ml.) and in 1:1 ether–tetrahydrofuran that after 2 hr. at room temperature the solution could be cooled to −70°, acidified with dilute hydrochloric acid, washed with water, and distilled to yield some unreacted 1 and the α-bromoalkylborinic ester **3a**; no butanol was added to the product before distillation and yield of borinic ester was only about 50%, leaving a considerable high boiling residue (presumably borinic anhydride) which could have contained some boronate (**4a**) as the anhydride, but no **4a** was detected by infrared in the distillate. A solution of phenylmagnesium bromide and 1 (0.5 *M* in each) after 4 hr. at room temperature began to deposit a second oily phase, presumably rich in magnesium bromide. After 22 hr., acidification at low temperature, washing with water, distillation of the ether, addition of a few ml. of butanol, and rapid distillation yielded **4a** containing some 1 but no detectable **3a**. The analytical sample of dibutyl 1-phenyl-3,3,3-trichloropropane-1-boronate (**4a**) was prepared by redistillation of the first sample described above through a spinning-band column, b.p. 105–106° (0.02 mm.), n^{24}D 1.4940, n.m.r. spectrum described under "Results"; medium infrared bands at 6.70, 6.86, 7.3–7.7, 7.96, 8.11, 9.32, 9.69, 10.28, 11.66, 12.8, and 14.3 μ.

Anal. Calcd. for $C_{17}H_{26}BCl_3O_2$: C, 53.79; H, 6.90; B, 2.85; Cl, 28.02. Found: C, 53.45; H, 6.76; B, 3.08; Cl, 27.84.

Dibutyl 1-(2,5-Dimethylphenyl)-3,3,3-trichloropropane-1-boronate (4b).—A solution of 0.024 mole of sodium butoxide in 25 ml. of butanol was added dropwise under nitrogen to 10.0 g. (0.242 mole) of butyl B-2,5-dimethylphenyl-B-(1-bromo-3,3,3-trichloro-1-propyl)-borinate (**3b**)[14] with stirring. An exothermic reaction with precipitation of sodium bromide occurred. After 0.5 hr. the solution no longer gave an alkaline reaction with water and phenolphthalein. Treatment with water, ether, and butanol in the usual extraction procedure followed by distillation yielded 8.0 g. (81%) of the boronic ester **4b**; fractionated, b.p. 123–124° (0.02 mm.), n^{25}D 1.4980; weak infrared band at 6.19; strong bands at 6.65, 6.72, 6.85, 7.06, 7.4–7.7, 7.97, 8.11, 9.31, 9.70, 10.28, 12.3, 13.05, and 14.45 μ. Alternately, **4b** was prepared from 0.05 mole of *p*-xylylmagnesium bromide in 30 ml. of tetrahydrofuran and 18.0 g. (0.047 mole) of 1 in 30 ml. of ether. When the reaction mixture was kept cold through the acidification step as described above for the corresponding phenyl compound, the usual extraction procedure (avoiding contact with any base) followed by addition of 10 ml. of butanol and distillation yielded 7.7 g. of unchanged 1 and a second fraction, b.p. 120–135° (0.1 mm.), which appeared to be largely the borinic ester **3b** with a few per cent of boronic ester **4b**. Shaking this material with 15 ml. of ether, 10 ml. of butanol, 20 ml. of water, and enough solid sodium bicarbonate to raise the pH of the aqueous phase to 6–7 yielded 8.2 g. (43%) of the borinic ester **4b** on distillation. A similar procedure except that the solution of xylylmagnesium bromide and 1 was kept at 25° 1.5 hr. before acidification below −40° led directly (without bicarbonate) to the boronic ester **4b**; yield 11.0 g. (57%), free of any detectable amount of borinic ester **3b**.

Anal. Calcd. for $C_{19}H_{30}BCl_3O_2$: C, 56.00; H, 7.41; B, 2.65; Cl, 26.09. Found: C, 56.02; H, 7.58; B, 2.80; Cl, 25.98.

Dibutyl 1-Mesityl-3,3,3-trichloropropane-1-boronate (4c).—Reaction of 1 with mesitylmagnesium bromide under conditions similar to those described for the *p*-xylyl compound above, keeping the reaction mixture cold through the acidification step, led to 7 g. of unchanged 1 and 6 g. of material that was mostly the boronic ester **4c** but contained 10–20% borinic ester **3c**. Treatment with aqueous sodium carbonate and butanol led to pure boronic ester **4c**. A better yield of **4c**, 64%, was obtained when the reaction mixture was allowed to warm to room temperature before acidification; the work-up procedure in this case included washing with aqueous sodium bicarbonate. The analytical sample had b.p. 129–130° (0.04 mm.), n^{23}D 1.5078; medium infrared band at 6.18, strong bands at 6.72, 6.80, 7.06, 7.4–7.7, 7.93, 8.10, 9.31, 9.70, 10.17, 11.70, 13.3, and 14.4 μ.

Anal. Calcd. for $C_{20}H_{32}BCl_3O_2$: C, 56.97; H, 7.65; B, 2.57; Cl, 25.23. Found: C, 56.71; H, 7.64; B, 2.74; Cl, 25.17.

Dibutyl 1,1,1-Trichloropentane-3-boronate (4d).—A solution of 0.038 mole of sodium butoxide in 40 ml. of butanol was added dropwise under nitrogen to 13.10 g. of butyl B-ethyl-B-(1-bromo-3,3,3-trichloro-1-propyl)-borinate (**3d**)[14] with stirring and allowed to stand 1 hr. Treatment with water, ether, and butanol in the usual extraction procedure followed by distillation yielded 11.0 g. (87%) of the boronic ester **4d**. The analytical sample was distilled through a small packed column; b.p. 75–76° (0.06 mm.), n^{24}D 1.4518; strong infrared bands at 6.71, 6.80, 7.03, 7.2, 7.4–7.7, 7.9, 8.09, 8.35, 9.23, 9.56, 10.22, 12.77, and 14.0 μ.

Anal. Calcd. for $C_{13}H_{26}BCl_3O_2$: C, 47.10; H, 7.91; B, 3.27; Cl, 32.10. Found: C, 47.06; H, 7.80; B, 3.40; Cl, 32.27.

[CONTRIBUTION FROM THE RESEARCH CENTER, SPRAGUE ELECTRIC CO., N. ADAMS, MASS.]

Nucleophilic Displacement Reactions in Aromatic Systems. VII. The *ortho*:*para* Ratio in the Reactions of Nitrochlorobenzenes with Piperidine and with 1,4-Diazabicyclo(2.2.2)octane

BY SIDNEY D. ROSS AND MANUEL FINKELSTEIN

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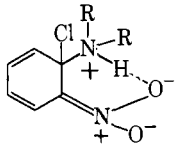
Both *o*- and *p*-nitrochlorobenzene react with two moles of 1,4-diazabicyclo(2.2.2)octane at a rate which is proportional to the product of the amine and chloride concentrations. The product from *p*-nitrochlorobenzene has been shown to be IV. The ratio, k_o/k_p, for the reactions with the above tertiary amine in benzyl alcohol at 150 ± 0.2° was found to be 0.0040. For the reactions with piperidine in the same solvent at 120 ± 0.2° the *ortho*:*para* ratio is 5.6. Values of k_o/k_p greater than one are attributed to hydrogen bonding in the transition state for the reaction with the *ortho*-substituted substrate.

It is well established that *o*-nitrohalobenzenes react with primary and secondary amines more rapidly than do *p*-nitrohalobenzenes. In contrast, those substitutions, which do not at any stage involve the removal of a proton, as in reactions with alkoxides and phenoxides, proceed at a faster rate with *p*-nitrohalobenzenes.

The many observations of this behavior pattern have been reviewed by Bunnett and Morath[1] and, most recently, by Greizerstein and Brieux.[2] The magnitude of the *ortho*:*para* ratio, k_o/k_p, is strongly solvent dependent. For the amine reactions it is largest in nonpolar solvents where k_o/k_p varies from 50–80 and smallest in polar solvents such as alcohol where the ratio is smaller but always greater than unity. For the reaction with alkoxides in alcohols the ratio k_o/k_p is less than one.

Chapman[3] suggested that the faster rate of reaction of *o*-nitrohalobenzenes with primary and secondary amines was attributable to hydrogen-bond formation in the transition state of these reactions as shown in I. Hawthorne[4] rejected this hypothesis, since measure-



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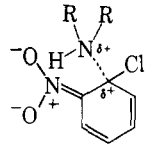


II

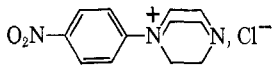
ments of the rates of reaction of both *o*- and *p*-nitrochlorobenzene with piperidine and N-deuteriopiperidine in xylene indicated that there is no observable deuterium isotope effect in these reactions. Bunnett[1] later suggested that direct electrostatic interaction of the neighboring positive and negative poles in the transition state for the *ortho* reaction, II, acts as a sort of "built-in" solvation, decreasing the need for participation of solvent molecules in the transition complex, but noted that his experiments did not permit him to distinguish whether the interaction between positive nitrogen and negative oxygen atoms in II is a direct electrostatic interaction or a matter of hydrogen bonding.

The failure to observe the expected deuterium isotope effect is not a sufficient basis for discarding the Chapman hypothesis. There are at least two cases of nucleophilic aromatic substitutions with amines where there is strong evidence for base catalysis and where, at the same time, deuterium isotope effects are either absent[5] or very small.[6] For the reactions with primary and secondary amines the Chapman and Bunnett proposals are not clearly distinguishable, since the hydrogen bond may have its origin in electrostatic interactions. A differentiation is, however, possible for the reactions with a tertiary amine. When an *o*-nitrohalobenzene reacts with a tertiary amine, the transition state permits direct electrostatic interaction between positive nitrogen and negative oxygen, but there is no possibility of hydrogen-bond formation.

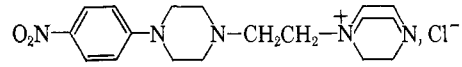
The foregoing considerations have led to the present study in which rates have been measured for the reactions of *o*- and *p*-nitrochlorobenzenes with a secondary amine, piperidine, and a tertiary amine, 1,4-diazabicyclo(2.2.2)octane.

Results

The nitrochlorobenzenes react cleanly with 1,4-diazabicyclo(2.2.2)octane. The product is not the expected quaternary ammonium salt, shown for *p*-nitrochlorobenzene by III, but the salt IV, which results from the interaction of one mole of the chloride



III



IV

with two moles of the tertiary amine. The basis for this assignment of structure will be presented subsequently.

The reactions are second order, first order in the chloride and first order in the amine, and IV is the only product obtained even when the chloride is present in excess. Had there been a prior reaction involving two moles of 1,4-diazabicyclo(2.2.2)octane to give a secondary amine, the over-all reactions would have been third order. In fact, the tertiary amine does not react with itself in the absence of *p*-nitrochlorobenzene under the reaction conditions. The rate-determining step involves a single amine molecule and a chloride molecule, and it is highly probable that the first product formed is III which reacts rapidly with 1,4-diazabicyclo(2.2.2)octane to give IV.

The results of measurements of the rates of reaction of both *o*- and *p*-nitrochlorobenzene with 1,4-diazabicyclo(2.2.2)octane in benzyl alcohol at 150 ± 0.2° are collected in Table I. The average value for the rate constant with *p*-nitrochlorobenzene is 8.3×10^{-5} l. mole^{-1} sec.$^{-1}$. The maximum deviation from this average value is 9.3%, and the average deviation is 3.7%. Within the probable experimental error, the values found may be considered to be constant. There is, however, a trend in the experimental values with the rate constants increasing as the amine concentrations increase. This trend may be due to some competing alcoholysis, and small quantities of benzyloxy-*p*-nitrobenzene were isolated, or it may be due to an undefined source of error, which is proportional to the amine concentration.

TABLE I

RATES OF REACTION OF *o*- AND *p*-NITROCHLOROBENZENE WITH 1,4-DIAZABICYCLO(2.2.2)OCTANE IN BENZYL ALCOHOL AT 150 ± 0.2°

Chloride, mole l.$^{-1}$	Amine, mole l.$^{-1}$	$k_2 \times 10^5$, l. mole^{-1} sec.$^{-1}$
	o-Nitrochlorobenzene	
0.2005	0.0527	0.0320
0.0479	0.2225	0.0324
	p-Nitrochlorobenzene	
0.0476	0.0909	7.71
.0476	.0914	7.74
.0474	.1362	8.01
.0470	.1947	8.03
.0471	.2280	8.41
.0471	.3157	8.89
.1951	.0472	7.94
.3561	.0904	8.27

For purposes of comparison, rates were determined for the reactions of piperidine with both *o*- and *p*-nitrochlorobenzene in the same solvent, benzyl alcohol. These data are compiled in Table II. With both chlorides there is a definite tendency for the observed rate constants to increase as the initial amine concentrations increase. This might be due to experimental error, to a medium effect, to the occurrence of some alcoholysis in this system, or to weak base catalysis by piperidine. In any event the effect is small and not of consequence for present considerations.

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(2) W. Greizerstein and J. A. Brieux, *ibid.*, **84**, 1032 (1962).
(3) R. R. Bishop, E. A. S. Cavell, and N. B. Chapman, *J. Chem. Soc.*, 437 (1952).
(4) M. F. Hawthorne, *J. Am. Chem. Soc.*, **76**, 6358 (1954).
(5) S. D. Ross, M. Finkelstein, and R. C. Petersen, *ibid.*, **81**, 5336 (1959).
(6) H. Zollinger, *Ann. Rev. Phys. Chem.*, **13**, 405 (1962).

TABLE II

RATES OF REACTION OF *o*- AND *p*-NITROCHLOROBENZENE WITH PIPERIDINE IN BENZYL ALCOHOL AT 120 ± 0.2°

Chloride, mole l.$^{-1}$	Amine, mole l.$^{-1}$	$k_2 \times 10^5$, l. mole^{-1} sec.$^{-1}$	Chloride, mole l.$^{-1}$	Amine, mole l.$^{-1}$	$k_2 \times 10^5$, l. mole^{-1} sec.$^{-1}$
——*o*-Nitrochlorobenzene——			——*p*-Nitrochlorobenzene——		
0.0493	0.1852	22.8	0.0489	0.1843	3.93
.0490	.3081	22.5	.0490	.1845	4.00
.0486	.4628	23.7	.0487	.3133	4.06
.0486	.7417	24.0	.0490	.4617	4.00
			.0492	.7419	4.36
			.0490	.7355	4.41

Experimental

Materials.—Reagent grade benzyl alcohol was distilled under nitrogen at 11 mm., and a middle cut, b.p. 93–94°, was used. The purification of piperidine has been described previously.[7] 1,4-Diazabicyclo(2.2.2)octane was obtained from the Houdry Process Corp. and sublimed immediately before use; m.p. 156–157° in a sealed tube. Eastman Kodak Co. White Label *p*-nitrochlorobenzene was crystallized from ethanol; m.p. 83–84°. Eastman Kodak Co. White Label *o*-nitrochlorobenzene was crystallized from methanol; m.p. 35–36°. 2-Hydroxyethylpiperazine was obtained from the Wateree Chemical Co. and used as received.

Rate Measurements.—A determinate solution containing the amine and the halide was prepared at room temperature. Aliquots were withdrawn and sealed in ampoules. The concentrations given in the tables are those at the temperatures of the rate measurements and have been corrected for solvent expansion. The ampoules were placed in a constant temperature bath, withdrawn at appropriate time intervals, and cooled in ice-water. The contents of the ampoules were washed with benzene into a separatory funnel and partitioned between benzene and dilute nitric acid (1:4). The benzene layer was extracted twice with water, and the combined aqueous extracts were analyzed for chloride ion by the Volhard method. In the runs with a high concentration of 1,4-diazabicyclo(2.2.2)octane it was found advantageous to quench the reaction with a benzene–water mixture rather than a benzene-acid mixture and to add Celite before filtering the silver chloride.

Isolation of Products. 1. **N-2-Nitrophenylpiperidine.**—A solution of piperidine (30 ml., 0.303 mole) and *o*-nitrochlorobenzene (6.30 g., 0.04 mole) made up to 400 ml. with benzyl alcohol was kept in a stoppered flask at 120° for 16 hr. The reaction mixture was taken up in benzene (500 ml.), washed twice with water, and dried over magnesium sulfate. The benzene was removed at atmospheric pressure and the benzyl alcohol at 13 mm. The dark residue was crystallized from methanol by cooling in Dry Ice–acetone to give 7.73 g. (94%) of orange crystals, m.p. 76–77° after recrystallization from methanol; previously reported[1] m.p. 77–78°.

2. **N-4-Nitrophenylpiperidine.**—The same procedure was followed using *p*-nitrochlorobenzene and a reaction time of 70 hr. The total yield of crude product was 7.84 g. (95%); m.p. after crystallization first from ethanol and then from methanol, 101–102°; previously reported m.p. 103–104°.

3. **N-*p*-Nitrophenyl-N′-[2-(4-aza-1-azoniabicyclo(2.2.2)-octane)-ethyl]-piperazine Chloride (IV).**—A solution of *p*-nitrochlorobenzene (31.5 g., 0.20 mole) and 1,4-diazabicyclo(2.2.2)-octane (6.47 g., 0.0576 mole) in benzyl alcohol (400 ml.) was kept in a stoppered flask at 150° for 20 hr. The reaction mixture was poured into benzene (1 l.), and this solution was extracted five times with water. Water was removed from the combined extracts under vacuum, and the dark residue was crystallized from isopropyl alcohol. The total crude product, obtained in three crops, weighed 10.0 g. (91%). A sample was crystallized three more times for analysis. It does not melt but decomposes slowly starting at 250°.

Anal. Calcd. for $C_{18}H_{28}N_5O_2Cl$: Cl, 9.29. Found: Cl, 9.09, 9.17.

The above product was also obtained by refluxing a solution of 1,4-diazabicyclo(2.2.2)octane (22.4 g., 0.2 mole) and *p*-nitrochlorobenzene (7.9 g., 0.05 mole) in *n*-propyl alcohol (200 ml.) for 92 hr. The solvent was distilled under vacuum, and the residue was washed with ether, yielding 13.3 g. (70%) of IV. After crystallization from isopropyl alcohol the product was found to contain 9.13% chloride ion by Volhard analysis.

4. **Benzyl-*p*-nitrophenyl Ether.**—A solution of 1,4-diazabicyclo(2.2.2)octane (11.5 g., 0.102 mole) and *p*-nitrochlorobenzene (4.2 g., 0.027 mole) in benzyl alcohol (200 ml.) was kept at 150° for 72 hr. The reaction mixture was added to benzene, and the solution was extracted four times with water. The organic layer was dried over magnesium sulfate, and the benzene and benzyl alcohol were vacuum distilled under nitrogen through a Vigreux column. The dark residue that remained was dissolved in benzene and chromatographed on alumina to give 18.3 mg. (0.3%) of white solid, which after crystallization from methanol did not depress the melting point of authentic benzyl-*p*-nitrophenyl ether; m.p. 104–106°.[8]

Stability of 1,4-Diazabicyclo(2.2.2)octane under the Reaction Conditions.—1,4-Diazabicyclo(2.2.2)octane (5.02 g., 0.045 mole) in benzyl alcohol (47 ml.) was kept at 150–160° for 70 hr. The reaction mixture was diluted with ether, and a solution of *p*-nitrophenol (13 g., 0.093 mole) in ether was added. The crystals obtained, 13.98 g., had m.p. 182–184° and on mixture with authentic bis-*p*-nitrophenolate of 1,4-diazabicyclo(2.2.2)-octane melted at 182–184°.[9] A second crop, 2.38 g., m.p. 180–183°, was obtained after concentration of the mother liquor and addition of ether. The total yield of amine recovered as the bis-*p*-nitrophenolate was 93.6%.

Synthesis of N-*p*-Nitrophenyl-N′-[2-(4-aza-1-azoniabicyclo-(2.2.2)octane)-ethyl]-piperazine Chloride (IV). 1. **1-(2-Hydroxyethyl)-4-*p*-nitrophenylpiperazine Hydrochloride.**—A solution of 1-(2-hydroxyethyl)-piperazine (60 g., 0.462 mole) and *p*-nitrochlorobenzene (31.6 g., 0.201 mole) in acetonitrile (250 ml.) was refluxed 26 hr. Half of the solvent was distilled under vacuum, and the residue was poured into a large volume of weakly alkaline, cold water. The yellow precipitate was filtered, dried, and crystallized from benzene–hexane; yield 32.2 g. (64%), m.p. 100–102°. A solution of this compound (9.2 g., 0.037 mole) in chloroform (50 ml.) was treated dropwise with magnetic stirring with a solution of unpurified thionyl chloride (5 ml.) in chloroform (30 ml.). Ether was added, and the yellow solid obtained was crystallized from methanol; yield 9.2 g. (82%), m.p. 225° dec.

Anal. Calcd. for $C_{12}H_{18}N_3O_3Cl$: Cl, 12.32. Found: Cl, 11.80.

2. **1-(2-Chloroethyl)-4-*p*-nitrophenylpiperazine Hydrochloride.**—1-(2-Hydroxyethyl)-4-*p*-nitrophenylpiperazine hydrochloride (6 g., 0.021 mole) was suspended in warm dimethylformamide (100 ml.). Thionyl chloride (10 ml.) was added dropwise with magnetic stirring. The reaction mixture was poured into a large volume of ether, and the gummy, yellow precipitate obtained was crystallized from methanol–ether; yield 5 g. (78%), m.p. 245–250° dec.

Anal. Calcd. for $C_{12}H_{17}N_3O_2Cl$: ionic Cl, 11.58; total Cl, 23.16. Found: ionic Cl, 11.83; total Cl, 23.40.

3. **Compound IV.**—A solution of the above 2-chloroethylamine hydrochloride (500 mg., 0.00163 mole) and 1,4-diazabicyclo(2.2.2)octane (1.1 g., 0.01 mole) in isopropyl alcohol (12 ml.) was refluxed 18 hr. The solvent was distilled at the water pump, and some of the excess amine was removed by heating the residue under vacuum. The yellow solid obtained was heated for several hours in a sublimation apparatus under vacuum to remove further traces of 1,4-diazabicyclo(2.2.2)octane, and the crude product (844 mg.) was fractionally crystallized from isopropyl alcohol. The yield of pure IV was 301 mg. (48%). This product gave an infrared spectrum identical in all respects with that of the product of the reaction between *p*-nitrochlorobenzene and 1,4-diazabicyclo(2.2.2)octane.

Anal. Calcd. for $C_{18}H_{28}N_5O_2Cl$: Cl, 9.29. Found: Cl, 9.48, 9.08, 9.34.

Discussion

Both *o*- and *p*-nitrochlorobenzene react with 1,4-diazabicyclo(2.2.2)octane at a rate which is proportional to the product of the amine and chloride concentrations. The integrated rate expression for this reaction is given by 1, where a is the amine concentration

$$kt = \frac{2.3026}{a - 2b} \log \frac{b}{a} \cdot \frac{a - 2x}{b - x} \qquad (1)$$

and b the halide concentration. The 2's enter the expression because two moles of the amine are consumed for every mole of the chloride. Individual runs give linear plots with a termolecular equation,[10] but the derived rate constants vary widely with changing initial concentrations.

(7) S. D. Ross and M. Finkelstein, *J. Am. Chem. Soc.*, **79**, 6547 (1957).

(8) G. Kumpf, *Ann.*, **224**, 123 (1884).

(9) O. Hromatka, *Ber.*, **75B**, 1302 (1942).

(10) The integrated, termolecular rate equation is

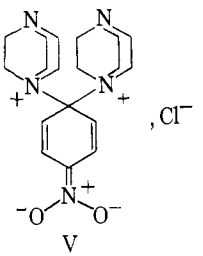
$$\frac{1}{(2b - a)}\left[\frac{1}{(a - 2x)} + \frac{2.3026}{2b - a} \log \frac{a - 2x}{b - x}\right] = k_3 t + \frac{1}{(2b - a)}\left[\frac{1}{a} + \frac{2.3026}{(2b - a)} \log \frac{a}{b}\right]$$

The rate-determining step thus involves one chloride molecule and one amine molecule and forms an intermediate which then reacts rapidly with a second molecule of 1,4-diazabicyclo(2.2.2)octane to give the isolated product. This final product contains all of the atoms originally present in both the chloride molecule and two amine molecules.

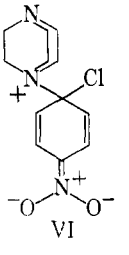
In studying the structures of these products, attention has been focused entirely on the product obtained with *p*-nitrochlorobenzene since the *ortho* isomer reacts at an extremely slow rate with 1,4-diazabicyclo(2.2.2)octane. The following three structures have been given consideration:

1. A donor-acceptor complex between III and a molecule of 1,4-diazabicyclo(2.2.2)octane. The amine is an electron donor, and the cation of III has both a nitro group and the positively charged nitrogen to make it an effective acceptor.

2. The structure V, which is of the type obtained by Jackson and Boos[11] on treating picryl chloride with



V



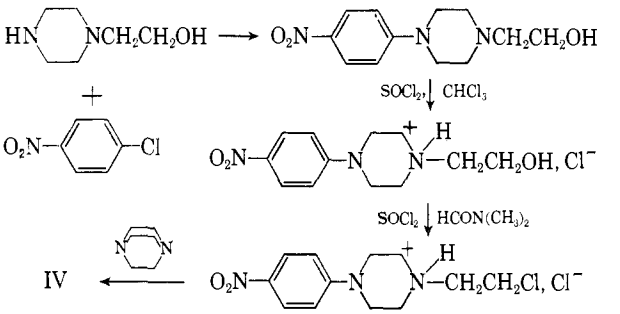
VI

sodium methoxide and by Meisenheimer[12] from the reaction of *s*-trinitroanisole with potassium ethoxide. Although V is somewhat improbable because of the accumulation of fixed charges on the cation, it would conceivably arise by addition of the amine to *p*-nitrochlorobenzene to give VI, which could then react with a second amine molecule to form V.

3. The structure IV, which would result from a nucleophilic attack by 1,4-diazabicyclo(2.2.2)octane on a bicyclic ring carbon adjacent to the positively charged nitrogen in III. This type of ring-opening reaction is analogous to that observed in the acid-catalyzed polymerization of 1,4-diazabicyclo(2.2.2)octane.[13] In the present instance the gain in resonance energy due to interaction of the nitro group and the amino group attached to the 4-position of the aromatic ring in IV may make a significant contribution to the driving force for this reaction and account for the facility with which it occurs.

The product obtained from *p*-nitrochlorobenzene and 1,4-diazabicyclo(2.2.2)octane is a yellow salt which decomposes above 250° without melting. Dilute aqueous solutions of the salt are weakly basic or neutral, but in concentrated acid two molecules of hydrogen chloride are added. Its absorption spectrum in ethanol shows two maxima, one at 230 mμ (ε 7800) and one at 375 mμ (ε 16,000). This spectrum is to be compared with that of *p*-nitrodimethylaniline, which also gives two maxima, one at 232 mμ (ε 9500), and one at 390 mμ (ε 20,000), and of N-*p*-nitrophenylpiperidine, which shows maxima at 235 mμ (ε 8600) and at 392 mμ (ε 19,600). Conversion of the salt to the dihydrochloride does not significantly alter its spectrum. Maxima for the dihydrochloride are observed at 230 mμ (ε 8500) and at 375 mμ (ε 17,300). By contrast, *p*-nitrotrimethylanilinium chloride, prepared as described by Zaki and Fahim,[14] shows a single maximum at 246 mμ (ε 10,000).

These spectroscopic results point to an amino group rather than an ammonium group in the position *para* to the nitro group and are consistent with structure IV. The spectrum of the dihydrochloride is not altered appreciably, since the protonation occurs on the two amino nitrogens other than the one *para* to the nitro group. Since no suitable model compound on the basis of which to predict the spectrum of V was available, it was deemed desirable to synthesize IV. This was accomplished by the sequence of known reactions shown below and clearly demonstrates that IV is the correct structure.



As can be seen from Table I, 1,4-diazabicyclo(2.2.2)-octane reacts with *o*-nitrochlorobenzene at a rate which is very much slower than the rate at which it reacts with *p*-nitrochlorobenzene. In benzyl alcohol at 150 ± 0.2° the ratio k_o/k_p is only 0.0040. The reactions with piperidine in the same solvent at 120 ± 0.2° present a very different behavior pattern. Here, it is *o*-nitrochlorobenzene which reacts more rapidly, and the ratio k_o/k_p is equal to 5.6.

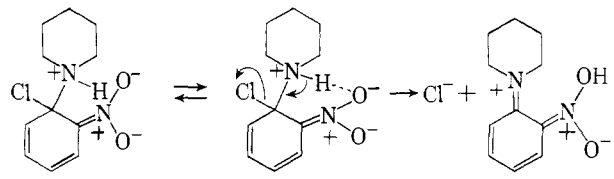
The reactions with a tertiary amine thus afford no exception to the generalization that a k_o/k_p ratio greater than one is observed only in those substitutions which involve a proton removal during some stage of the transformation. These are, of course, the very reactions for which there exists the possibility for a hydrogen-bonded transition state with the *o*-substituted substrate. In the reaction of *o*-nitrochlorobenzene with 1,4-diazabicyclo(2.2.2)octane the transition state structure almost certainly contains neighboring positive and negative poles on nitrogen and oxygen, respectively. There is electrostatic interaction between these oppositely charged centers, but there is no possibility for hydrogen-bond formation, and the *ortho*:*para* ratio observed is that characteristic of the reactions with alkoxides and phenoxides and unlike that found with primary and secondary amines.

These results lend support to Chapman's[3] proposal in its original form as opposed to Bunnett's[1] modification of it. It remains only to reconcile the Chapman hypothesis with the failure to observe a deuterium isotope effect in the reactions of *o*- and *p*-nitrochlorobenzene with piperidine in xylene.[4] If the rate-determining step involves simply a breaking of the N–H bond, a large isotope effect, with a maximum factor as large as 8 or 9 in rate, is to be expected.[15] Since no isotope effect was found, the rate-determining step cannot be merely the breaking of the N–H bond. It may, however, involve breaking or partial breaking of the N–H bond accompanied by a simultaneous forming or partial forming of another bond to the same hydrogen. Such a single step of bond breaking–bond making might well fail to exhibit a measurable isotope effect. This is highly probable when the hydrogen transfer is from the donor to the acceptor in a hydrogen-bonded complex, since substitution of deuterium for hydrogen does not, in general, have a large effect on the energetics

(11) C. L. Jackson and W. F. Boos, *Am. Chem. J.*, **20**, 444 (1898).
(12) J. Meisenheimer, *Ann.*, **323**, 205 (1902).
(13) H. K. Hall, Jr., *J. Org. Chem.*, **28**, 223 (1963).
(14) A. Zaki and H. Fahim, *J. Chem. Soc.*, 270 (1942).
(15) K. Wiberg, *Chem. Rev.*, **55**, 713 (1955).

of hydrogen bonding.[16] The replacement of deuterium for hydrogen in even the strongest hydrogen bond, the F· · · H—F bond, changes the heat of formation by only 50 cal. mole^{-1}.[17]

Still another explanation lies in the possibility that the rate-determining step is a concerted process including breaking or partial breaking of the N–H bond together with breaking of the C–Cl bond. In this case, of course, the isotope effect would be masked. One such possible concerted process is illustrated below. The



hydrogen bonding increases the mobility of an electron pair in the N—H · · · O bond and facilitates the changes indicated by the arrows. A process of the type shown is fully consistent with the observed *ortho:para* ratio and the absence of a deuterium isotope effect.

(16) P. B. D. De La Mare, in "Progress in Stereochemistry," Vol. II, W. Klyne and P. B. D. de la Mare, Ed., Academic Press, Inc., New York, N. Y., 1958, p. 85.

(17) R. W. Long, J. H. Hildebrand, and W. E. Morell, *J. Am. Chem. Soc.*, **65**, 182 (1943).

[CONTRIBUTION FROM THE CENTRAL BASIC RESEARCH LABORATORY, ESSO RESEARCH AND ENGINEERING CO., LINDEN, N. J.]

Photobromination of Alkyl Halides, an Unusual Orienting Effect in the Bromination of Alkyl Bromides

BY WARREN THALER

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An investigation of the halogenation of several alkyl and cycloalkyl halides revealed that the photobromination of alkyl bromides is quite different from the bromination of other alkyl halides, and from alkyl halide halogenations in general. The chlorination of alkyl bromide gave the expected isomer distribution; preferential attack occurred at positions remote from the bromine substituent. Bromination of alkyl chloride also showed the usual polar orienting effect; however, this higher activation energy reaction also gave a large amount of bromination on the substituent bearing carbon while primary hydrogens were essentially unreactive. Unlike other free radical halogenations of alkyl halides, which frequently give a multitude of products, the bromination of alkyl bromides was highly selective, giving 84–94% of the vicinal dibromide isomer. The influence of the bromine substituent directing the attack of a halogen atom to the adjacent carbon is contrary to other radical halogenations of substituted alkanes, in which this position has been demonstrated, generally, to be one of the least reactive positions in the molecule. A neighboring group effect has been postulated to explain the observed results.

The directive influence of polar substituents in free radical halogenation reactions has received considerable attention.[1–5] These studies have demonstrated that halogenations occur preferentially at positions removed from the electron-withdrawing substituent. The results are consistent with the theory that the electronegative attacking radicals prefer positions of high electron density and (with the possible exception of the α-position, which can give resonance-stabilized radicals) preferentially abstract hydrogens from carbon atoms, which are furthest from the electron-withdrawing substituents.

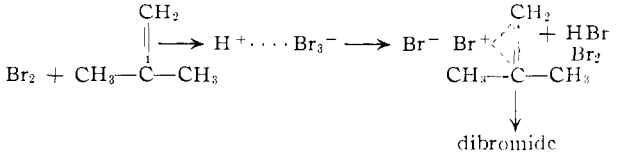
Some experiments which were carried out in this Laboratory involving the free radical bromination of alkyl halides revealed some unusual isomer distributions, which appeared to be inconsistent with predictions that can be made from the existing theories regarding polar orientations. This paper concerns itself with these apparent anomalies.

Results

Bromination of Bromocyclohexane.—Examination by vapor phase chromatography (v.p.c.) of reaction mixtures from some preliminary experiments involving the photobromination of bromocyclohexane revealed essentially one peak in addition to that of unreacted excess bromocyclohexane. The material corresponding to this peak was fractionated by v.p.c. Its elemental analysis was consistent with that of a dibromocyclohexane. The infrared spectrum was identical with that reported for *trans*-1,2-dibromocyclohexane.[6] Comparison of the v.p.c. and refractive index of this material with that of an authentic sample prepared by the addition of bromine to cyclohexene[7] confirmed the identity of this material as *trans*-1,2-dibromocyclohexane. Similar brominations involving random temperatures ranging from 20–80° showed no difference in the v.p.c. of the reaction mixtures.

Standard conditions were then chosen, and a five-fold molar excess of alkyl halide was used for all subsequent brominations which were conducted in the liquid phase at 60° in sealed Pyrex tubes.

The appearance of only one out of seven isomeric dibromocyclohexanes suggested that perhaps this was not a free radical process but instead involved the elimination of HBr from bromocyclohexane, followed by the ionic addition of bromine to cyclohexene to give *trans*-1,2-dibromocyclohexane. Similar reactions are known to occur with *tertiary bromides*, particularly when the adjacent hydrogen is tertiary.[8] This "dark reaction" was postulated to occur by a mechanism in which a bromine molecule brings about the ionization of the tertiary bromide, followed by a reaction of a second bromine molecule with the high energy π-complexed form of the carbonium ion.



(1) For a summary of some of the pertinent literature through 1955 see C. Walling, "Free Radical in Solution," John Wiley & Sons, Inc., New York, N. Y., 1957, pp. 356–376.

(2) M. S. Kharasch, W. S. Zimmt, and W. Nudenberg, *J. Org. Chem.*, **20**, 1432 (1955).

(3) (a) C. Walling and M. F. Mayahi, *J. Am. Chem. Soc.*, **81**, 1485 (1959); (b) C. Walling and B. B. Jacknow, *ibid.*, **82**, 6113 (1960).

(4) L. Horner and L. Schaläfer, *Ann.*, **635**, 31 (1960).

(5) (a) P. S. Fredricks and J. M. Tedder, *J. Chem. Soc.*, 144 (1960); (b) *ibid.*, 3520 (1961).

(6) M. S. Kharasch, J. S. Sallo, and W. Nudenberg, *J. Org. Chem.*, **21**, 129 (1956).

(7) H. Greengard, *Org. Syntheses*, **12**, 126 (1932).

(8) G. A. Russell and H. C. Brown, *J. Am. Chem. Soc.*, **77**, 4025 (1955).