[A CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF IOWA STATE COLLEGE]

The Question of Hydrogen Bonded Transition States in Nucleophilic Aromatic Substitution Reactions

BY M. F. HAWTHORNE[1]

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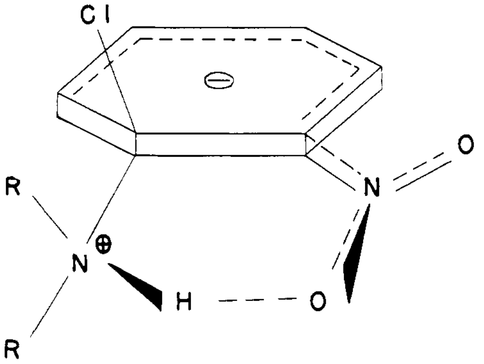
The rates of reaction of *o*- and *p*-nitrochlorobenzene with piperidine have been measured and it was observed that substitution of deuterium for hydrogen on the amino group of the nucleophile did not alter these rates of reaction. The displacement of chloride ion from the *ortho* compound by piperidine at 116° proceeds 80 times more rapidly than the similar reaction of the *para* compound. These results indicate that hydrogen bonding of amino hydrogen with the nitro group of *o*-nitrochlorobenzene probably does not exist in the transition state and thus cannot account for the greater reactivity of the *ortho* compound. An alternative explanation is presented.

Many previous kinetic studies of the nucleophilic displacement of halogen from compounds such as *o*- and *p*-nitrochlorobenzenes (I and II, respectively) indicate a striking inversion of relative reactivity of the *ortho* and *para* isomers when the attacking nucleophile is changed from alkoxide ions to primary or secondary amines.[2] Specifically, it is always observed that the *ortho*-substituted substrate gives the greater rate of displacement with primary or secondary amines while the *para*-substituted compound gives the greater rate with alkoxide ions.

Bishop, Cavell and Chapman[3] have recently explained the greater reactivity of substrates such as 2-chloro-5-nitropyridine, 2-chloro-3-nitropyridine and 2,4-dinitrochlorobenzene toward aniline than toward pyridine on the basis of the greater steric requirements of pyridine and the possible existence of hydrogen bonds in the transition states of the aniline reactions. This novel hydrogen bond hypothesis could possibly explain the occurrence of the rate inversion described above if hydrogen bonded transition states such as III do indeed exist in spite of the non-coplanarity of the *o*-nitro group with the benzene ring and the resulting loss of resonance stabilization in such structures. This paper records an experimental attempt to verify this hypothesis.

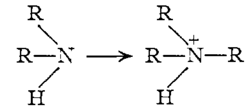


III

Results and Discussion

The substitution of deuterium for hydrogen has previously been of great value in kinetic studies of organic reactions which involve either the loosening[4,5] or complete breaking[6] of carbon–hydrogen bonds in the rate-controlling transition states. Therefore, it seemed logical that the question under examination which involves the formation of a weak hydrogen bond in the transition state III could be similarly solved by the substitution of deuterium for hydrogen on the amino nitrogen. Unfortunately, little information is available with respect to the direction or magnitude of this isotope effect[7] but it may be assumed to be generally small and with the deuterated hydrogen bond the most stable of the two in systems such as the one under consideration.

In addition to this primary isotope effect another small secondary isotope effect may arise from the effect of N-deuterium substitution on the apparent nucleophilicity of the secondary amine utilized in the formation of III. Such an effect would be formally similar to the rate-decreasing hyperconjugative isotope effect of Lewis and Boozer[4,5] and would be a direct result of the decrease of the force constant of the N–H bond when the secondary amine undergoes the change (A).



$$R_2N\text{—}H \longrightarrow R_3\overset{+}{N}\text{—}H$$

(A)

Table I records the results of the kinetic experiments carried out with I and II using both normal and N-deuteropiperidines as the nucleophiles. The solvent chosen for these rate determinations was anhydrous xylene since this material possesses a relatively low vapor pressure, has no ability to hy-

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[1] Iowa State College Research Associate, 1953–1954. Present address, Rohm and Haas Company, Redstone Arsenal Research Division, Huntsville, Alabama.

[2] See J. F. Bunnett and R. E. Zahler, *Chem. Revs.*, **49**, 304 (1951), for numerous examples of this rate inversion.

[3] R. R. Bishop, E. A. S. Cavell and N. B. Chapman, *J. Chem. Soc.*, 437 (1953).

[4] E. S. Lewis and C. E. Boozer, THIS JOURNAL, **76**, 791 (1954).

[5] C. E. Boozer and E. S. Lewis, *ibid.*, **76**, 794 (1954).

[6] M. Cohen and F. H. Westheimer, *ibid.*, **74**, 4387 (1952).

[7] W. H. Claussen and J. H. Hildebrand, *ibid.*, **56**, 1820 (1934), found that DF has a slightly higher vapor pressure than HF. Later, R. W. Long, J. H. Hildebrand and W. E. Morrell, *ibid.*, **65**, 182 (1943), observed that the F–D—F bond is 50 cal./mole more stable than the F–H—F bond in $(DF)_6$ and $(HF)_6$, respectively. This work taken along with that of G. N. Lewis and P. W. Schutz, *ibid.*, **56**, 493, 1002, 1913 (1934), on the vapor pressure differences of associated and non-associated substances when deuterated (*i.e.*, D-carboxyacetic acid, DCL and DCN) indicate that the deuterium bond is slightly more stable than the corresponding hydrogen bond. For additional examples see L. N. Ferguson, "Electron Structures of Organic Molecules," Prentice–Hall Inc., New York, N. Y., p. 57. Crystal structure studies have also shown isotope effects when the crystal lattice contains hydrogen bonds and deuterium is substituted for hydrogen. [See C. E. Nordman and W. N. Lipscomb, *J. Chem. Phys.*, **19**, 1422 (1951), for an explanation of these crystal phenomena and additional references.]

drogen bond and has no hydrogen atoms which may exchange with the labeled reactant or product.

TABLE I

RATES OF REACTION OF *o*- AND *p*-NITROCHLOROBENZENES (I AND II) WITH PIPERIDINE AND N-DEUTEROPIPERIDINE IN XYLENE AT 116 ± 0.2°

Substrate, nitrochlorobenzene	Nucleophile	Initial concn., mole/l. Substrate	Initial concn., mole/l. Nucleophile	k_2[a] (l./mole min.) $\times 10^4$
o-	Piperidine	0.509	0.0766	242 ± 1
o-	N-Deuteropiperidine	.509	.0786	242 ± 1
p-	Piperidine	.720	.0921	3.02 ± 0.02
p-	N-Deuteropiperidine	.720	.0943	3.02 ± .02

[a] Obtained from plot of log concentration nucleophile *vs.* time with an average deviation of not more than 0.5%. See Experimental part.

It was established that no extraneous isotope exchange occurred during the kinetic experiments by the recovery of both piperidinium chloride (m.p. 245°) and N,N-dideuteropiperidinium chloride (m.p. 248°) from the rate runs which utilized piperidine and N-deuteropiperidine, respectively. The higher melting point of the deuterated piperidinium salt might be attributed to the greater strength of deuterated hydrogen bonds in the crystal lattice.[8]

The results presented in Table I show that I reacts 80 times as fast as II with piperidine. Furthermore, the high precision obtained in the kinetic experiments and the fact that the piperidine and N-deuteropiperidine gave superimposable pseudo first-order rate plots with each substrate, point to the conclusion that the two isotope effects mentioned above are not detectable and that the hydrogen-bond hypothesis of Bishop, Cavell and Chapman[3] cannot be used as an explanation of the enhanced reactivity of *o*-nitrohalobenzenes toward primary and secondary amines.

It has recently been proposed by Hammond[9] in a publication dealing with the correlation of reaction rates with equilibria that the potential energy content of states which lie at similar points along the reaction coördinate are also similar. Using this general hypothesis and the assumption that the *ortho* nitro group of III may become coplanar with the benzene ring in states which have a near tetrahedral configuration about the carbon atom attacked,[10,11] it is possible to rationalize the rate inversion mentioned at the outset.

If one assumes, for purposes of discussion, that the displacement of chloride ion from both *o*- and *p*-nitrochlorobenzenes (I and II, respectively) by amines and alkoxide ions proceeds through the tetrahedral intermediates A and B, respectively,[12] and if one further assumes that the free energy content of the amine intermediate, A, will be higher than that of the alkoxide intermediate, B, due to the fact that the former contains internal charge separation, Fig. 1 may be constructed.

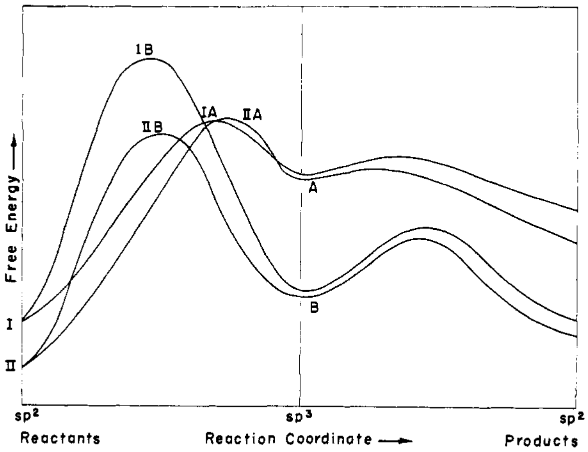

Fig. 1.—Plot of free energy *vs.* reaction coördinate for the reactions of *o*-nitrochlorobenzene (I) and *p*-nitrochlorobenzene (II) with alkoxides (curve B) and primary or secondary amines (curve A).

Figure 1 represents the free energy *vs.* reaction coördinate diagram for this situation derived directly from known relative rate data.[13] It should be noted that the reactants of both reactions involving *p*-nitrochlorobenzene have been assigned the same (arbitrarily) and a lower free energy content than those involving *o*-nitrochlorobenzene due to internal steric repulsion of the *ortho* nitro and chloro substituents and due to the damping of resonance in the ground state by this same steric interaction. The approximate positions of the four transition states, amine-*ortho* (IA), alkoxide-*ortho* (IB), amine-*para* (IIA) and alkoxide-*para* (IIB), have been assigned on the basis of Hammond's postulate.[9,13] It is seen by the inspection of Fig. 1 that the transition state configurations of the amine reactions (Ia and IIA) lie closer to the hypothetical tetrahedral intermediate than those of the alkoxide reactions (IB and IIB) and thus the nitro group of the *ortho*-substituted substrate may be allowed to become more nearly coplanar with the aromatic ring than in the corresponding alkoxide reaction. Such a situation should allow the *ortho*- and *para*-amine transition states (IA and IIA) to have nearly the same free energy content, and the difference in free energies of activation for the two reactions would be approximately equal to the

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[8] Similar melting point isotope effects have been observed many times previously, mainly with regard to acid hydrates. For example, J. M. Robertson and A. R. Ubbelohde, *Nature*, **139**, 564 (1937), report that the melting point of oxalic acid dihydrate changes from 99.8–100.7° to 95.9–97.5° on deuteration.

[9] G. S. Hammond, THIS JOURNAL, in press.

[10] This assumption must be essentially correct since such compounds as 2,4-dichloronitrobenzene suffer displacement of the 2-chloro substituent when attacked by nucleophiles. [See A. F. Holleman and F. E. Van Haeften, *Rec. trav. chim.*, **40**, 67 (1921) for examples.]

[11] For a fuller discussion of this phenomenon see the chapter which deals with aromatic substitution reactions in "Steric Effects in Organic Chemistry," edited by M. S. Newman, John Wiley and Sons, Inc., New York, N. Y., in preparation.

[12] A and B actually represent two intermediates each, one for the *ortho*-substituted substrate and one for the *para*-substituted substrate but for simplicity of discussion they are considered of equal energy content in each case. Similarly, the amine and alkoxide ion have been assigned identical energy contents although the alkoxide should be the most energetic of the two. This assumption does not affect the argument which follows.

[13] The relative free energies of reactants, transition states and products are known from kinetic, equilibrium and thermochemical data. The Hammond postulate, which applies only to potential energy terms, was utilized only to locate the probable position of *potential energy* maxima and the assumption is made that these maxima correspond to *free energy* maxima or transition states.

difference in ground state free energies of the two reactants, I and II. Thus, the amine reaction is more rapid with the *ortho*-substituted substrate.

Similar consideration of the alkoxide reactions would yield the conclusion that the *ortho*-alkoxide transition state (IB) would possess an energy content similar to that of the *para*-alkoxide transition state (IIB) if the *ortho* nitro group were not sterically constrained in such a manner as to prohibit coplanarity with the aromatic ring. However, this latter condition cannot prevail since the transition state configuration is relatively close to that of reactants and the *ortho*-alkoxide transition state cannot, therefore, obtain the maximum stabilization available from the *ortho* nitro group. In addition, the coulombic repulsion of the attacking anion and the negatively charged oxygen atom of the *o*-nitro group further increase the free energy content of this transition state relative to that of the *p*-substrate. The conclusion is, then, that the *ortho*-alkoxide transition state is of considerably higher free energy content than the *para*-alkoxide transition state and therefore the difference in reactant ground state free energies is more than cancelled with the result that *p*-nitrochlorobenzene is more reactive toward alkoxides than *o*-nitrochlorobenzenes.

Experimental

The *o*- and *p*-nitrochlorobenzenes (I and II, respectively) were Eastman Kodak Co. white label grade and were twice recrystallized from ethanol. The crystalline materials were stored in a desiccator over calcium chloride.

Xylene was J. T. Baker C.P. grade obtained as a mixture of isomers and dried by distillation from calcium hydride.

The piperidine was Eastman Kodak Co. white label and was dried previous to use by distillation from barium oxide, b.p. 104–104.5°, $n^{25}\text{D}$ 1.4509.

N-Deuteropiperidine.—To 17.0 g. of the dry piperidine described above was added 5 ml. of 99.8% deuterium oxide and 0.5 ml. of deuterated phosphoric acid prepared by the addition of phosphorus pentoxide to heavy water. The solution was refluxed for three hours and then repeatedly distilled from 5-g. batches of barium oxide until the boiling point became 104°.

The exchange and drying procedures were then repeated once more, yield 12.2 g., b.p. 104–105°, $n^{25}\text{D}$ 1.4502. The infrared absorption spectrum of this compound was obtained in the form of the pure liquid in a 0.1-mm. KBr cell using a Model 13 Perkin–Elmer instrument equipped with a rock salt prism and indicated a very large peak at 4.1 μ and a small peak at 3.0 μ. These peaks were attributed to N–D and N–H stretching, respectively, and it was assumed that the material was at least 80% isotopically pure.

Kinetic Procedure.—An 0.610 *M* stock solution of *o*-nitrochlorobenzene (I) and an 0.900 *M* stock solution of *p*-nitrochlorobenzene (II) were prepared in anhydrous xylene at 25.5°. Similarly, 0.472 *M* piperidine and N-deuteropiperidine solutions were prepared at 25.5°. These four solutions were utilized in all rate runs in order to insure uniformity.

The proper volumes of the above solutions were mixed at 25.5° and 5.00-ml. aliquots pipetted into test-tubes which were sealed off in the absence of atmospheric water at −78°. At zero time the tubes were placed in a thermostat which was regulated at 116 ± 0.2° and tubes were withdrawn at intervals.

The progress of the reaction was determined by potentiometric titration of the contents of each rate tube in chlorobenzene using a Beckman Model G *p*H meter and glass *vs.* silver–silver chloride electrodes with an 0.1003 *M* solution of perchloric acid in acetic acid. Since in each case the initial concentrations of the reactants were such that the kinetics should be expressed by a pseudo first-order relationship, plots of log piperidine (or N-deuteropiperidine) *vs.* time were prepared and the slopes of the straight lines determined. In each case the deviation of experimental points from this linear relationship was not greater than 0.5% and the lines were superimposable after translation of the log concentration coördinate.

Isolation of Deuterated Reaction Product.—Samples of the reaction mixtures from all runs which had approached complete reaction were rapidly filtered, washed with anhydrous xylene and placed in a desiccator over phosphorus pentoxide and the desiccator was evacuated rapidly. The melting point of the white crystalline piperidinium salts were determined. It was found that every rate run with the deuterated amine produced a piperidinium salt which melted at 248–249° while those runs which contained no deuterium gave piperidinium salts which melted at 245–246°. These melting points were consistently reproducible.

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