The Question of Activation by the *o*-Nitro Group in Nucleophilic Aromatic Substitution[1]

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The reactivities in dimethyl sulfoxide of a series of amines (piperidine, 2-methylpiperidine, and *trans*-2,6-dimethylpiperidine) toward fluoro-2,4-dinitrobenzene or fluoro-2-nitrobenzene are reported and compared with those already reported for fluoro-4-nitrobenzene in the same solvent or chloro-2,4-dinitrobenzene in benzene. It is found that the piperidine:2-methylpiperidine:*trans*-2,6-dimethylpiperidine rate ratios are closely similar to one another in the four series of reactions (about $1:2 \times 10^{-3}:3 \times 10^{-5}$, respectively). Moroever, the *ortho*:*para* activation ratio varies little and randomly (from 0.86 to 2.0) upon changing the nucleophile. These facts are interpretable in terms of a nearly tetrahedral transition state in which steric inhibition of resonance of the *o*-nitro group is not pronounced. Therefore, the large drop in rate observed on introducing 2- or 6-methyl groups in the piperidine reagent must be attributed primarily to steric compression of the amine moiety against the benzene carbons and hydrogens in the transition state. The ultraviolet spectra show that steric inhibition of resonance is very marked for all reaction products of the 2-nitro series, varies widely from one member to another in the 2,4-dinitro series, and is absent from all members of the 4-nitro series. The lack of correlation of reaction rates and resonance stabilization of the reaction products is also explained.

A large amount of information is available concerning the activation by the nitro group in nucleophilic aromatic substitution.[3,4] Concerning the *ortho*:*para* activation ratio, the values found in the various reactions are thought[3] to reflect a fine balance among several factors which are recognized as (a) the inductive effect of the nitro group (whereby *ortho* activation is expected to prevail) and (b) proximity effects. Thus, an *ortho*:*para* ratio smaller than unity in reactions with anionic nucleophiles is attributed to inhibition of resonance of the *o*-nitro group in the transition state owing to steric repulsions[3] and to repulsions between like charges.[3,5] In the reactions with protic amines, where the *ortho*:*para* ratio is greater than unity, this effect is thought to be overwhelmed by that of hydrogen bonding[4a] between an ammonium proton and the *o*-nitro group in the transition state. The "hydrogen-bonding" idea has been tested experimentally,[6] while no systematic study concerned with the "steric" or with the "repulsions between like charges" idea has ever appeared.

In the course of related work on the reactivity of fluoro-4-nitrobenzene with piperidine, 2-methylpiperidine or *trans*-2,6-dimethylpiperidine in dimethyl sulfoxide (DMSO) we have recently discovered that, although the reactivity range spanned by the amines is greater than 10^4, the insertion of a second nitro group in the *ortho* position to the substrate (fluoro-2,4-dinitrobenzene) does not drastically alter the pattern of relative rates.[7] These results seemed to suggest[7] that there is no pronounced steric inhibition of resonance of the *o*-nitro group in the transition state.

However, the two series of reactions had been carried out in two different solvents, DMSO for fluoro-4-nitrobenzene[7] and benzene for fluoro-2,4-dinitrobenzene.[8] As the kinetics of reactions of this kind are dramatically altered on changing the solvent from DMSO to benzene (*vide infra*), it seemed of interest to investigate the reactivities of both fluoro-4-nitrobenzene and fluoro-2,4-dinitrobenzene in the same solvent. Moreover, in order to appraise directly the influences of the steric requirements of the nucleophile on the *ortho*:*para* activation ratio by the nitro group, we decided to investigate the reactivity of fluoro-2-nitrobenzene toward piperidine, 2-methylpiperidine, or *trans*-2,6-dimethylpiperidine.

It seemed also of interest to investigate whether a correlation between reaction rate and resonance stabilization of the reaction products, like that reported[9] for certain aromatic nucleophilic substitution reactions, holds for the present reactions as well. To this end the ultraviolet spectra of the reaction products were obtained and are utilized here as a criterion to qualitatively estimating resonance stabilization.

Results

The choice of DMSO as a solvent in which to compare the reactivities of our substrates was demanded by the fact that the reactions of fluoro-4-nitrobenzene with sterically hindered piperidines are too slow in benzene to be followed conveniently.[10] Moreover, while the displacement of fluorine from some fluoronitrobenzenes by protic amines displays complex kinetics,[11] this is not so in DMSO where clean second-order kinetics are observed.[12]

Rate data for the reactions of piperidine, 2-methylpiperidine, or *trans*-2,6-dimethylpiperidine with fluoro-

(1) Supported by Consiglio Nazionale delle Ricerche, Roma.

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(3) J. F. Bunnett and R. J. Morath, *J. Amer. Chem. Soc.*, **77**, 5051 (1955).

(4) For recent contributions, see (a) S. D. Ross and M. Finkelstein, *J. Amer. Chem. Soc.*, **85**, 2603 (1963); (b) N. E. Sbarbati, *J. Org. Chem.*, **30**, 3365 (1965); (c) A. M. Porto, L. Altieri, A. J. Castro, and J. A. Brieux, *J. Chem. Soc., Ser. B*, 963 (1966); (d) J. Bourdon, D. Fisher, D. R. King, and J. C. Tatlow, *Chem. Comm.*, 65 (1965); (e) J. Bourdon, D. R. King, and J. C. Tatlow, *Tetrahedron*, **23**, 1347 (1967); (f) H. Suhr, *Ann.* **701**, 101 (1967). (g) C. W. L. Bevan, J. Hirst, and S. J. Una [*Nigerian J. Sci.*, **1**, 27 (1966)] are concerned with *meta* activation.

(5) M. F. Hawthorne, *J. Amer. Chem. Soc.*, **76**, 6358 (1954).

(6) Chlorine is displaced faster from chloro-4- than from chloro-2-nitrobenzene by a tertiary amine like triethylenediamine in benzyl alcohol[4a] whereas the reverse reactivity order is found when the nucleophile is a secondary amine like piperidine.[4a] Such an inversion of the reactivity order has been attributed to hydrogen bonding in the transition state for the reaction of the secondary amine with the *ortho*-substituted substrate. It is interesting, however, that chlorine is displaced much faster from chloro-2-nitrobenzene than from the *para* isomer by a nonprotic amine like pyridine in dimethyl sulfoxide.[4f]

(7) F. Pietra and F. Del Cima, *Tetrahedron Lett.*, 4453 (1966).

(8) F. Pietra and F. Del Cima, *ibid.*, 1925 (1966).

(9) F. Hawthorne and D. J. Cram, *J. Amer. Chem. Soc.*, **74**, 5859 (1952).

(10) The reaction between fluoro-4-nitrobenzene 0.05 *M* and 2-methylpiperidine 0.9 *M* in benzene at 100° proceeded to only about 15% in 40 days.

(11) (a) F. Pietra and A. Fava, *Tetrahedron Lett.*, 1535 (1963); (b) F. Pietra and D. Vitali, *ibid.*, 5701 (1966).

(12) H. Suhr, *Ber. Bunsenges. Physik. Chem.*, **67**, 893 (1963).

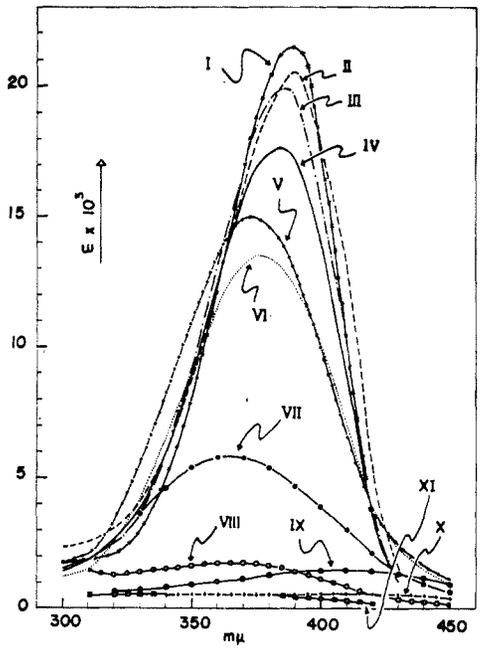

Figure 1.—The curves represent ultraviolet absorption spectra for the following compounds: I, N-4-nitrophenyl-*cis*-2,6-dimethylpiperidine; II, N-4-nitrophenyl-*trans*-2,6-dimethylpiperidine; III, N-4-nitrophenyl-2-methylpiperidine; IV, N-4-nitrophenylpiperidine; V, N-2,4-dinitrophenylpiperidine; VI, N-2,4-dinitrophenyl-2-methylpiperidine; VII, N-2,4-dinitrophenyl-*trans*-2,6-dimethylpiperidine; VIII, N-2,4-dinitrophenyl-*cis*-2,6-dimethylpiperidine; IX, N-2-nitrophenylpiperidine; X, N-2-nitrophenyl-2-methylpiperidine; XI, N-2-nitrophenyl-*trans*-2,6-dimethylpiperidine.

2,4-dinitrobenzene or fluoro-2-nitrobenzene in DMSO are reported in Table I. Formation of N-2,4-dinitro- or N-2-nitrophenylamines was quantitative (see the Experimental Section). Excellent kinetic plots were obtained up to 90% reaction completion in each case.

TABLE I

SECOND-ORDER RATE COEFFICIENTS FOR THE REACTIONS OF FLUORO-2,4-DINITROBENZENE OR FLUORO-2-NITROBENZENE WITH VARIOUS PIPERIDINES IN DMSO

Amine, *M*	Fluoro-2,4-dinitrobenzene, *M*	Fluoro-2-nitrobenzene, *M*	Temp, °C	k, mol^{-1} l. sec^{-1}
		Piperidine		
2.08×10^{-5}	9.8×10^{-6}		25	628
4.16×10^{-5}	1.96×10^{-5}		25	636
5.18×10^{-3}		3.11×10^{-4}	25	1.59×10^{-2}
3.26×10^{-2}		3.26×10^{-4}	25	1.61×10^{-2}
		2-Methylpiperidine		
4.90×10^{-4}	1.96×10^{-5}		25	0.64
1.17×10^{-3}	1.87×10^{-5}		25	0.69
0.791		5.40×10^{-2}	25	3.62×10^{-5}
0.500		5.30×10^{-2}	25	3.58×10^{-5}
		trans-2,6-Dimethylpiperidine		
1.42×10^{-2}	6.75×10^{-3}		25	0.010
3.34×10^{-2}	6.75×10^{-3}		25	0.012
0.397		7.00×10^{-2}	70	1.02×10^{-5}
0.589		7.25×10^{-2}	70	9.18×10^{-6}
0.589		7.25×10^{-2}	80	1.54×10^{-5}
0.589		7.25×10^{-2}	100	4.02×10^{-5}

Relative rates at a common temperature, and some activation parameters are reported in Table II for the substrates investigated here as well as for fluoro-4-nitrobenzene.[7] As the data for the latter compound were reported as a short communication,[7] some more experimental details are included in the Experimental Section for this compound as well.

The ultraviolet spectra of the N-substituted piperidines resulting from the reactions reported in Table II, together with those of N-4-nitrophenyl-*cis*-2,6-dimethylpiperidine,[7] and N-2,4-dinitrophenyl-*cis*-2,6-dimethylpiperidine,[8] are shown in Figure 1.

Discussion

Rate Data.—The reactions reported here are first order with respect to the amine, which means that there is no evidence for the existence of intermediates along the reaction path.[11,13] However, according to widely accepted ideas,[13] nucleophilic aromatic substitutions of this kind can be visualized as two-step processes in which formation of the intermediate is rate determining.

There are some interesting points to be noted from the data of Table II. (a) The reactivity range spanned by the three amines in the reactions with any single substrate encompasses a factor of more than 10^4 (columns 3, 7, and 11). (b) The patterns of relative rates for the reactions of each substrate with the three amines are fairly similar to one another (columns 3, 7, and 11). (c) The *ortho* : *para* activation ratio varies very little with changing amine (around unity) and without a definite trend. It is in fact 1.6, 2.0, and 0.86 for reactions with piperidine, 2-methylpiperidine, and *trans*-2,6-dimethylpiperidine, respectively (calculated from data in columns 2 and 6).

Finally, another interesting point emerges from the comparison of data of Table II with those already published.[8] (d) The pattern of relative rates found for the reactions of chloro-2,4-dinitrobenzene in benzene (1, 7.5×10^{-4}, and 4.7×10^{-6} for piperidine, 2-methylpiperidine, and *trans*-2,6-dimethylpiperidine, respectively)[8] is not drastically different from that pertaining to the corresponding reactions of fluoro-2,4-dinitrobenzene in DMSO (Table II).

Point a is a reflection of a large increase in steric compression in the transition state on increasing the bulk of the nucleophile. In fact, from an electronic point of view the substitution of methyl for hydrogen in the nucleophile should, if anything, increase the rate of reaction.

It is also clear that the above-discussed steric compression in the transition state cannot involve to any great extent the 2-nitro group. It is in fact easily recognizable that the trends observed in the rates (points b and c) cannot arise from a balance between steric compression involving the 2-nitro group in the transition state and such factors as (1) inductive effect being greater from the *ortho* than from the *para* position,[3] (2) inhibition of resonance of the 2-nitro group in the reagents,[3] and (3) "built-in-solvation."[3] Let us suppose in fact that steric compression involving the 2-nitro group in the transition state does increase steeply on going from piperidine to *trans*-2,6-dimethylpiperidine in the reactions of Table II. Then factors 1 and 2 cannot run in parallel opposition simply because they are independent of the nucleophile. There is no obvious reason, also, why the importance of "built-

(13) J. F. Bunnett and R. H. Garst, *J. Amer. Chem. Soc.*, **87**, 3875 (1965).

TABLE II

SECOND-ORDER RATE COEFFICIENTS, RELATIVE RATES (WITH RESPECT TO THE FASTEST AMINE FOR EACH SUBSTRATE), AND SOME ACTIVATION PARAMETERS FOR REACTIONS OF VARIOUS PIPERIDINES WITH NITRO-SUBSTITUTED FLUOROBENZENES IN DMSO AT 25°

	Fluoro-2-nitrobenzene				Fluoro-4-nitrobenzene[a]				Fluoro-2,4-dinitrobenzene	
Amine	k, mol^{-1} l. sec^{-1}	k_{rel}	$\Delta H^{\pm}$, kcal/mol	$\Delta S^{\pm}$, eu	k, mol^{-1} l. sec^{-1}	k_{rel}	$\Delta H^{\pm}$, kcal/mol	$\Delta S^{\pm}$, eu	k, mol^{-1} l. sec^{-1}	k_{rel}
Piperidine	1.60×10^{-2}	1			1.01×10^{-2}	1	8.0[b]	−43[b]	630	1
2-Methylpiperidine	3.60×10^{-5}	2.2×10^{-3}			1.76×10^{-5}	1.7×10^{-3}			0.65	1.0×10^{-3}
trans-2,6-Dimethylpiperidine	6.0×10^{-7}[c]	3.7×10^{-5}	12	−48	7×10^{-7}[c]	6.9×10^{-5}	11	−51	0.011	1.7×10^{-5}

[a] Data from ref 7. [b] Recalculated from rate data of ref 30. $\Delta S^{\pm} = -15.4$ eu, as reported in ref 30, is the result of a misprint or of an error in the calculation. [c] Extrapolated from data at higher temperatures.

in-solvation" should be augmented upon increasing the bulk of the nucleophile.[14]

Finally, consideration of point d suggests that the steric compression in the transition state of the reactions of Table II does not involve the leaving group to any considerable extent.

The above conclusions have been based on rate data at a single temperature. Systematic investigation of the temperature dependence of the rates has not been considered necessary because of the very wide ranges of reactivity spanned either by the nucleophiles with each substrate (point a) or by the substrates with respect to the same nucleophile [fluoro-2,4-dinitrobenzene is more than 10^4-fold faster than the other two substrates (Table II)]. Under such conditions a drastic change, due to temperature variation, of the trends observed among the data in Table II is conceivable only if the range of temperature covered is so wide that it may even be inaccessible experimentally in the solvent used (DMSO). On the other hand it may be noted that the reactions of *trans*-2,6-dimethylpiperidine with fluoro-2- or fluoro-4-nitrobenzene have similar activation parameters (Table II, lower row).

We are now in a position to draw some conclusions about the structure of the transition state for the reactions of Table II. The tetrahedral intermediate proposed by Bunnett[13] for aromatic nucleophilic substitution appears to be a good model for the transition state. In such a transition state repulsive interactions involving the 2-nitro group and the leaving group can be minimized as the 2-nitro group can adapt itself between the entering and the leaving group thus attaining coplanarity (or nearly so) with the benzene ring. The large drop in rate observed in the reactions of Table II on going from piperidine to 2-methylpiperidine and from this one to *trans*-2,6-dimethylpiperidine must then be attributed mainly to increased repulsive interactions between the nucleophile and the benzene ring carbons and hydrogens in the transition state.

The above observations are relevant to the problem, thus far little considered, of defining the conformation of the transition state. Thus, the present findings show that the preferred conformation of the transition state in the reactions of *o*-nitro-substituted substrates with all three amine reagents is one in which the piperidine carbons are turned away from the *o*-nitro group (if there is one as in the present case) and the ammonium hydrogen is turned toward *o*-nitro, available for hydrogen bonding. Thus, the various effects (inductive, hydrogen bonding, steric inhibition of resonance, etc.) of an *o*-nitro group can operate equally well with piperidine as with *trans*-2,6-dimethylpiperidine.

Whereas the present results obviously aid in clarifying why in the reactions of protic amines the *ortho*:*para* activation ratio is usually greater than unity, they have no very direct bearing on the question of what determines the *ortho* : *para* ratio in the reactions with alkoxide reagents.[3,4] This is due exactly to the fact that hydrogen bonding in the transition state holds the piperidine carbons away from the *o*-nitro group.

However, owing to the fact that *cis*-2,6-dimethylpiperidine is only six times less reactive than its *trans* isomer toward chloro-2,4-dinitrobenzene in benzene[8] (clearly, if the preferred conformation of the transition state is that pictured above, a methyl group must be closer to the *o*-nitro group in the case of the *cis*- than in that of the *trans*-amine) our results cast a little doubt[17] on the argument[3] that the difference in the *ortho*:*para* ratio, with methoxide or ethoxide reagents, between fluoro- and chloronitrobenzenes is attributable primarily to steric inhibition of resonance of the *o*-nitro group in the transition states of the reactions of *o*-chloronitrobenzenes.

Perhaps the importance of the "repulsions between like charges" idea[5] (see above) is even greater than was thought in the past.[3] However, even the latter idea alone is insufficient to rationalize consistently all the material published.

It is our opinion that a systematic investigation of reactions of anionic nucleophiles, in which steric effects are clearly defined, would be warranted.

Recently Crampton and Gold[18] and, independently, Servis[19] have discovered that, on mixing picryl methyl ether with methoxide in DMSO–methanol mixtures, addition of methoxide is faster to nuclear position 3 than to position 1, while the latter process gives the

(14) Factors 1 to 3 must also be of limited concern here. As for factor 1, it seems reasonable to assume that the inductive effect of the 2-nitro *vs.* that of the 4-nitro group is similar to that found in the case of 4- and 2-chlorine,[15] *i.e.*, only 7:1. Factor 2 is likely to be of little concern owing to the small size of fluorine.[16] In any event, the coplanar geometry is essential to the transition state, when the nitro group must accept electrons from the nucleophile, but not for the *o*-nitrophenyl halide molecule. Factor 3 must be of reduced importance owing to the high polarity of the solvent used (DMSO).[3]

(15) Data for chlorine are reported and discussed by J. F. Bunnett and R. E. Zahler, *Chem. Rev.*, **49**, 315 (1951).

(16) B. Capon and N. B. Chapmann, *J. Chem. Soc.*, 600 (1957).

(17) A prerequisite to our argument is, however, that the relative position of transition state and intermediate along the reaction coordinate is the same for reactions of both anionic and neutral nucleophiles. If Hawthorne's argument[5] is valid according to which the transition states for reactions of anionic nucleophiles is more reagentlike than those for reactions of neutral nucleophiles, our results have an even less direct bearing to the problem[3,4] of what determines the *ortho*:*para* ratio in the reactions of anionic nucleophiles.

(18) M. R. Crampton and V. Gold, *ibid.*, *Ser. B*, 893 (1966).

(19) K. L. Servis, *J. Amer. Chem. Soc.*, **89**, 1508 (1967).

thermodynamically more stable product. Crampton and Gold[18] suggested that the slowness of the reaction at position 1 is due to steric compression in the transition state and wrote, "The implied importance of these steric effects suggests that Meisenheimer complexes themselves are unlikely to be good models for the transition state of nucleophilic aromatic substitution reactions for systems containing *o*-substituents." We must urge against acceptance of the above generalization.[18] In fact, our results, obtained for reactions of *ortho*-substituted compounds (with only one *ortho* group) in which steric effects are well defined, can be rationalized only if a nearly tetrahedral structure, like that attributed to Meisenheimer complexes, is assumed for the transition state.

Resonance Stabilization of the Reaction Products.—A qualitative estimate of the relative resonance stabilization among the reaction products of the reactions of Table II can be obtained by examination of the ultraviolet spectra in Figure 1.

These spectra clearly show that the three series of compounds (4-nitro, 2-nitro, and 2,4-dinitro) fall into three different classes. The 4-nitro series shares the common characteristic of having a high intensity band (ϵ) at λ_{max} 380–390 mμ. The intensity of absorption (ϵ) increases slightly, but consistently, on going from the less to the more bulky amine (Figure 1). In sharp contrast the 2-nitro series exhibits very low absorption in the region 300–450 mμ. Methyl and dimethyl compounds present the lowest intensity without a pronounced maximum of absorption (Figure 1). The features of the spectra belonging to the 2,4-dinitro series diverge from those of the other two series; here the intensity of absorption (ϵ) decreases steadily from a very high value for the piperidine derivative to a very low one for the *cis*-2,6-dimethylpiperidine compound (Figure 1).

The spectra of the 4-nitro series in benzene (Figure 1) resemble closely those of 4-nitroaniline[20] and of its N-methyl and N-ethyl derivatives[20] in ethanol. Therefore, steric inhibition of ($>^+N{=}C_1 \rightarrow C_4{=}NO_2^-$) resonance, which has been excluded for the last compounds,[20] should also be absent from all the N-4-nitrophenylpiperidines of Figure 1.[21,22]

The very low absorptions of the compounds belonging to the 2-nitro series, compared with those of the 4-nitro series (Figure 1), cannot be attributed only to the shorter transition moments in the former series. In fact 2-nitroaniline exhibits a definite absorption band in ethanol which is much stronger (ϵ 5.2 $\times$ 10^3, λ_{max} 404 mμ)[20] than that of any of the 2-nitro amines of Figure 1. The logical conclusion[21] is that in the series of N-2-nitrophenylpiperidines of Figure 1 there is pronounced steric inhibition of ($>^+N{=}C_1 \rightarrow C_2{=}NO_2^-$) resonance. It seems also reasonable to assume that steric strain is relieved by rotation from planarity of both the $C_5H_{10}N-$ and the $-NO_2$ group. The latter point is appreciated more clearly by examination of the spectra of the compounds of the 2,4-dinitro series (Figure 1). According to the results obtained for 2,4-dinitroaniline and its N-methyl and N-ethyl derivatives,[20] the absorption band of Figure 1 for N-2,4-dinitrophenylpiperidine should be assigned to the ($>^+N{=}C_1 \rightarrow C_4{=}NO_2^-$) transition, while ($>^+N{=}C_1 \rightarrow C_2{=}NO_2^-$) resonance should be sterically inhibited. In fact, not even an inflection marks the position of the ($>^+N{=}C_1 \rightarrow C_2{=}NO_2^-$) transition in the spectrum of N-2,4-dinitrophenylpiperidine (Figure 1). Moreover, as band half-widths at half-height are about equal on both sides of the maximum of absorption (Figure 1), overlapping of absorption on the longer wave length side due to the ($>^+N{=}C_1 \rightarrow C_2{=}NO_2^-$) transition can be excluded. These findings suggest then that the 2-nitro group is completely out of the plane of the benzene ring in N-2,4-dinitrophenylpiperidine.

It is also of interest that a change from 2,4-dinitroaniline to its N,N-dimethyl or N,N-diethyl derivatives results in steric enhancement of ($>^+N{=}C_1 \rightarrow C_4{=}NO_2^-$) resonance,[20] as evidenced by the increase in the absorption attributed to the ($>^+N{=}C_1 \rightarrow C_4{=}NO_2^-$) electronic transition.[20] Here, on the contrary, going from N-2,4-dinitrophenylpiperidine to its dimethyl (*trans* or *cis*) derivatives produces pronounced steric inhibition of ($>^+N{=}C_1 \rightarrow C_4{=}NO_2^-$) resonance. In fact, a sharp decrease of intensity of absorption (ϵ) is observed on going from N-2,4-dinitrophenylpiperidine to its dimethyl (*trans* or *cis*) derivatives (Figure 1). A likely explanation is that in the cases of N-2,4-dinitrophenyl-*cis*-2,6-dimethylpiperidine or of its isomer the amino moiety has such large steric requirements that, besides rotating the *o*-nitro group out of the plane of the benzene ring, it is itself rotated from planarity. That the *o*-nitro group is sterically involved in inhibiting conjugation of the amino nitrogen in the latter compounds is also shown by the fact that in the 4-nitro series (Figure 1) there is no steric inhibition of ($>^+N{=}C_1 \rightarrow C_4{=}NO_2^-$) resonance.

Lack of Correlation of Reaction Rate and Resonance Stabilization of the Reaction Products.—Hawthorne and Cram have studied[9] the competitive reaction of L-(+)-α-phenylethylamine with DL-2-(*sec*-butyl)-4,6-dinitrochlorobenzene to give (−)-DL-2-(*sec*-butyl)-4,6-dinitro-N-(L-α-phenylethyl)aniline and the (+)-LL diastereomer. The latter diastereomer is slightly more stabilized by resonance (as judged from ultraviolet spectra) and is formed 1.22 times as fast as the former one.[9]

Such a correlation apparently does not hold for the reactions investigated in the present work. As shown above, while steric inhibition of resonance is absent in all reaction products of the 4-nitro series and increases markedly in the other two (2-nitro and 2,4-dinitro) on increasing the bulk around the amino nitrogen in the nucleophile, we have found that the patterns of relative rates (encompassing a factor greater than 10^4) in the three series of reactions are similar to one another. Moreover, the *ortho* : *para* ratio varies little and without any definite trend.

It can be argued that this apparent disagreement is due to the fact that in Cram's work[9] two *ortho* substituents are present, one of which has a tetrahedral geometry. Thus, while the steric interactions in the

(20) M. J. Kamlet, H. G. Adolph, and J. C. Hoffsommer, *J. Amer. Chem. Soc.*, **86**, 4018 (1964).

(21) We are aware of the ultraviolet spectral changes that *p*-nitroanilines undergo on changing from a nonpolar aprotic solvent like carbon tetrachloride to ethanol.[22] However, such changes are small enough that, for the present purposes, we can safely compare our ultraviolet spectra in benzene with others in ethanol.

(22) (a) J. H. P. Utley, *J. Chem. Soc.*, 3252 (1963); (b) M. J. Kamlet, *Israel J. Chem.*, **1**, 428 (1963).

reaction products can be released in the transition state owing to the favorable geometry of the nitro group (our case), this is not possible in the reactions studied by Cram.[9] In the tetrahedral transition state of these reactions the ammonium proton is turned toward the *o*-nitro group, which probably does not undergo steric inhibition of resonance, while the 2-*sec*-butyl group, also due to its tetrahedral geometry, must interfere sterically with the entering group even in the transition state.

Perhaps the results of our work suggest that the subtle difference between the rates of the reactions studied by Cram[9] originates from steric repulsions in the transition state involving the entering group and the 2-*sec*-butyl group at a greater extent than the 2-nitro group. This is an interesting question that remained thus far unsolved (see the discussion by Hammond and Hawthorne).[23]

Experimental Section

Melting points were taken on a Kofler apparatus and are uncorrected.

Materials. **DMSO** (Erba) was fractionally distilled (N_2 atmosphere, column as described below for 2-methylpiperidine, 20 mm, reflux ratio 8°1). Central cuts were collected and redistilled at 20 mm over calcium hydride (N_2 atmosphere) before use. **Fluoro-2-nitrobenzene** (Fluka) was fractionally distilled (18 mm, N_2 atmosphere). Fractions containing less than 0.1% total impurities (vpc,[24] Apiezon on Chromosorb W 80–100 mesh, 135°, retention time 7 min) were used. **Fluoro-4-nitrobenzene** (Schuchardt) and **fluoro-2,4-dinitrobenzene** (Fluka) were recrystallized several times from absolute ethanol. Piperidine (Erba) was refluxed over sodium metal for several hours and then distilled under an N_2 atmosphere. Fractions containing less than 0.1% total impurities (vpc,[24] 20% 1-hydroxyethyl 2-heptadecenyl glyoxalidine on 60–80 mesh KOH-washed Chromosorb W, 80°) were used. Commercial **2-methylpiperidine** (Eastman, White Label) was fractionally distilled under N_2 atmosphere (column 3 ft × $^3/_8$ in. packed with Fenske glass helices $^1/_{10}$ in. and equipped with a thermostated jacket, 100 mm, 60°, reflux ratio 35:1) and redistilled under reduced pressure over Na–K alloy before use. After this treatment, vpc[24] (column as before for piperidine, 88°) did not show any contamination. *trans*-2,6-Dimethylpiperidine after three fractional distillations under the conditions already reported[8] (reflux ratio 40:1) did not show any contamination (retention times in vpc,[24] under the conditions already reported,[8] were 15 and 10 min for the *trans* and the *cis* isomer, respectively). **N-2-Nitrophenylpiperidine**, mp 78° (lit.[25] 81°), **N-4-nitrophenylpiperidine**, mp 103–104° (lit.[25] 105.5°), **N-2,4-dinitrophenylpiperidine**, mp 95–95.5° (lit.[25] 92°), and **N-2,4-dinitrophenyl-2-methylpiperidine**, mp 72–73° (lit.[26] 67°), were prepared by standard procedures. **N-2,4-Dinitrophenyl-*trans*-2,6-dimethylpiperidine** and its *cis* isomer were those used in a previous work.[8]

N-2-Nitrophenyl-2-methylpiperidine, obtained as orange needles, mp 27–27.5° (lit.[27] 75°), picrate mp 142–143 from ethanol (lit.[27] 141–142°), was prepared by the reaction of fluoro-2-nitrobenzene with 2-methylpiperidine. The pure materials (in a molar ratio of 1:2 of fluoro compound over amine) were sealed in a pyrex tube and heated at 100° for seven days. Then the reaction mixture was poured into ice water and a red-brown viscous oil was separated. Plc[28] (benzene) of this material showed a yellow band at R_f 0.8 which gave yellow crystals the melting point of which did not rise over 27–27.5° after several recrystallizations from petroleum ether (30–50°). The yield was 75%. The same material was obtained in 80% yield from the reaction of the same reagents in DMSO (fluoro compound 0.1 *M*, amine 1.4 *M*, temperature 25°, reaction time 5 days). The pmr spectrum[29] supported the proposed structure showing absorption attributed to the three-proton (doublet, δ 0.87, J = 6 cps) of the methyl group, the six-proton (broad absorption, centered at δ 1.6) of both the β- and the δ-methylene groups, the three-proton (complex pattern, δ 2.4–3.4) of both the α-methylene and the methine groups, and the four-proton (complex pattern centered at δ 7.25) of the aromatic ring. *Anal.* Calcd for $C_{12}H_{16}N_2O_2$: C, 65.4; H, 7.3; N, 12.7. Found: C, 65.5; H, 7.6; N, 12.7.

N-2-Nitrophenyl-*trans*-2,6-dimethylpiperidine was prepared by the reaction of fluoro-2-nitrobenzene with *trans*-2,6-dimethylpiperidine. The two reagents (in a molar ratio 1:2 of fluoro compound over amine) were sealed in a pyrex tube and heated at 100° for 5 days. The reaction mixture was then poured into ice water and the solid that separated out was purified by plc[28] (benzene). The yellow band at R_f 0.8 gave orange crystals which, after recrystallization from petroleum ether (30–50°), melted at 52.5–53.5°. The yield was 70%. The pmr spectrum[29] supported the proposed structure showing absorption attributed to the six-proton (doublet δ 0.90, J = 6.5 cps) of the methyl groups, the six-proton (broad absorption centered at δ 1.6) of the methylene groups, the two-proton (broad absorption centered at δ 3.4) of the methine groups, and the four-proton (complex pattern δ 6.9–7.6) of the aromatic ring. *Anal.* Calcd for $C_{13}H_{18}N_2O_2$: C, 66.6; H, 7.7; N, 11.9. Found: C, 66.7; H, 7.8; N, 11.9.

N-4-Nitrophenyl-2-methylpiperidine, mp 61.5–62.5° (lit.[30] 59.5–60.0), was prepared by the reaction of fluoro-4-nitrobenzene with 2-methylpiperidine by the last method above. Recrystallization from methanol gave yellow crystals (yield 85%) which did not show a sharp melting point. However, the pmr spectrum[29] of this material remained unchanged after sublimation at 50° (5×10^{-4} mm) and afforded yellow crystals with a sharp melting point (61.5–62.5°). The pmr spectrum[29] supported the proposed structure showing absorption attributed to the three-proton (doublet, δ 1.2, J = 6.3 cps) of the methyl group, the six-proton (broad absorption centered at δ 1.7) of both the β- and the δ-methylene groups, the three-proton (complex pattern, δ 2.8–4.4) of both the α-methylene and the methine groups, and the four-proton (A_2X_2 system,[31] δ_A 8.07, δ_X 6.74, J_{AX} = 9.3 cps) of the aromatic ring. *Anal.* Calcd for $C_{12}H_{16}N_2O_2$: C, 65.4; H, 7.3; N, 12.7. Found: C, 65.5; H, 7.5; N, 12.6. Only a few details were reported about the preparation of **N-4-nitrophenyl-*cis*-2,6-dimethylpiperidine**.[7] We add now that the solvent, dry DMSO, and unreacted amine were removed *in vacuo* at 100° after reaction. The remaining yellow solid showed three yellow bands on plc[28] (glacial acetic acid) at R_f 0.1, 0.4, and 0.9. Band R_f 0.1 corresponded to the compound mentioned above, mp 147–149°. In the pmr spectrum[29] the A_2X_2 system,[31] attributed to the aromatic protons is characterized by δ_A 8.05, δ_X 6.69, and J_{AX} = 9.6 cps. The proposed structure is now fully supported by double resonance experiments which show that the absorption at δ 1.81[7] is attributable to the methylene groups. Thus, the broad absorption at δ 4.21[7] becomes a well-defined quartet attributable to a methine coupled with a methyl group (J = 6.3 cps) on irradiation at δ 1.81.

Kinetics.—The reaction kinetics were followed by measuring the increase in absorbance at the absorption maximum (Figure 1) of N-4-nitro-, N-2-nitro-, or N-2,4-dinitrophenylamines (406 and 350 mμ for N-2-nitrophenyl-2-methylpiperidine and N-2-nitrophenyl-*trans*-2,6-dimethylpiperidine, respectively). A Beckman DU spectrophotometer equipped with a thermostated cell compartment was used. At the chosen wavelengths, the absorption due to both the reagents and other reaction products was negligible. Beer's law plots were determined at the absorption maximum of each compound (in benzene–DMSO mixtures for the N-4-nitro- and N-2-nitro series; in DMSO for the other one). Straight lines passing through the origin were obtained in all cases (up to 6×10^{-4} *M* compounds, which was the highest

(23) G. S. Hammond and M. F. Hawthorne in "Steric Effects in Organic Chemistry," M. S. Newmann, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, p 195.

(24) A Perkin-Elmer Model 810 gas chromatograph with 6 ft × $^1/_8$ in. columns, a flame-ionization detector, and a flow rate of 25 cc of N_2/min was used.

(25) E. Lellmann and W. Geller, *Ber.*, **21**, 2281 (1888).

(26) O. L. Brady and F. R. Cropper, *J. Chem. Soc.*, 507 (1950).

(27) O. Meth-Cohn, R. K. Smalley, and H. Suschitzky, *ibid.*, 1666 (1963).

(28) Preparative layer chromatography was carried out over a 2-mm-thick silica gel layer activated at 110° for 1 hr.

(29) A Varian nmr spectrometer Model DA-60IL was used. Determinations were run on 10% solutions in $CDCl_3$ with TMS as an internal standard at 28°.

(30) H. Suhr, *Ann.*, **689**, 109 (1965).

(31) As the internal chemical shift exceeds 30 cps, the A_2X_2 system ("A" refers to the protons in *ortho* position to the nitro group) can be adequately described by first-order analysis. See J. Martin and B. P. Dailey *J. Chem. Phys.*, **37**, 2594 (1962).

concentration used). In all cases the absorption spectrum (over the 300–450-mμ range) of the reaction mixture after several half-lives corresponded within 2% to the "mock" infinity prepared by the appropriate N-nitrophenylamine. To achieve this result it was necessary to exercise extreme care in the purification of the reacting amines. This was essential in the reactions of fluoro-2-nitrobenzene or fluoro-2,4-dinitrobenzene with excess of the more bulky amines. Thus, if less hindered amines were present as impurities, the experimental infinity was substantially higher than the "mock" one. This is because the less hindered amines are more reactive (Table II) and give final products with higher molar absorbance (Figure 1).

In the case of slow reactions, samples of the reaction mixture were sealed under nitrogen into Pyrex tubes which were then placed at the desired temperature and cooled at room temperature; the content was diluted (50- to 2500-fold) with benzene and immediately transferred into a stoppered cuvette for the spectral analysis (the absorbance was determined against that of benzene–DMSO solutions of the same composition; 10-mm matched quartz cuvettes were used). The combined processes of cooling and diluting the sample with benzene practically stopped the reaction. In the case of more rapid reactions, carried out at 25°, the solutions of the two reagents were mixed and then samples of the reaction mixture were withdrawn at time intervals by means of a pipet in an atmosphere of dry N_2 and diluted with benzene as above. In the case of very rapid reactions, 100–300 μl of the appropriate amine solution was added to 3 ml of the solution of the appropriate fluoronitro compound contained in a 10-mm stoppered quartz cuvette in the spectrophotometer cell compartment. In this instance mixing was ensured by stirring the solution while adding the amine and, when possible, by vigorously shaking the cuvette after the process of mixing the reagents. The reverse process of adding 100–300 μl of the solution of fluoronitro compound to 3 ml of the amine solution gave the same rate values.

Rate coefficients were calculated by first-order plots when a large excess of amine was used, and by second-order plots in other cases. The stoichiometry used in the calculations was, in all cases, that shown by the equation below for the reaction of fluoro-2,4-dinitrobenzene with piperidine.

$$(O_2N)_2C_6H_3F + 2C_5H_{10}NH = (O_2N)_2C_6H_3NC_5H_{10} + C_5H_{10}NH_2{}^+F^-$$

Ultraviolet Spectra.—Ultraviolet spectra over the range 300–450 mμ were determined in benzene solutions (Figure 1) using a Beckman DU spectrophotometer with matched 10-mm, stoppered quartz cuvettes. Concentration never exceeded 4×10^{-4} *M* (Beer's law was obeyed in benzene as well).

Registry No.—I, 15822-69-2; II, 15822-70-5; III, 15822-71-6; IV, 6574-15-8; V, 839-93-0; VI, 15822-74-9; VII, 15889-61-9; VIII, 15822-76-1; IX, 15822-77-2; X, 15822-78-3; XI, 15822-79-4.

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Homolytic Decompositions of Hydroperoxides. I.[1] Summary and Implications for Autoxidation

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This paper summarizes and integrates the conclusions of the four succeeding papers which present experimental details on decompositions of hydroperoxides. Purely thermal decompositions by homolysis to alkoxy and hydroxy radicals have been experimentally approached but never fully attained. All decompositions of hydroperoxides are induced to a greater or lesser degree by metals or other sources of free radicals. The induced reactions are simple in principle; they depend mostly on competitions between nonterminating and terminating interactions of peroxy radicals (eq 3 and 4 below), competitions among two hydrogen abstractions by alkoxy radicals (from hydroperoxides or from reactive solvents in eq 2 and 9), and cleavage of alkoxy radicals by eq 7. These competitions depend on the hydroperoxide, solvent, and temperature. Decompositions induced by catalytic quantities of several metal salts are similar except for the participation of both metal and hydroperoxide in radical production. The complex kinetics of metal-catalyzed decompositions are ascribed to extensive association of metal salts and soaps in organic solvents and the constantly changing coordination of oxygen-containing compounds with the metals as the decompositions progress.

Traditionally, thermal decompositions of hydroperoxides, metal ion catalyzed decompositions, and decompositions by free-radical initiators have been treated as separate phenomena; yet all of these involve hydroperoxides in the presence of free radicals and are subject, to some extent,[3–5] to a concomitant radical-induced chain decomposition. The nature of this induced chain has been elucidated previously for simple cases.[6–8] This series of papers explains more complex aspects of this chain decomposition and shows how it operates as a unifying factor for all homolytic decompositions of hydroperoxides.

This report summarizes conclusions based on our own investigations and those of previous workers, and suggests some of their applications for autoxidations of hydrocarbons.

Free-Radical-Induced Decompositions

Background.—Hydroperoxides of all types are particularly labile toward attack by free radicals. An understanding of this destructive process, which is basic to our investigation, is facilitated if the initiating radicals are not generated by the hydroperoxides themselves. Decompositions of *t*-BuO_2H in benzene or chlorobenzene at 20–60°, initiated by di-*t*-butylperoxy oxalate (DBPO),[4,6] 2,2′-azobis(2-methylpropionitrile) (ABN),[9] and photolysis of hypochlorites[5] have elucidated a general mechanism. In the simplest instance,

(1) Parts II–V: R. Hiatt, *et al.*, *J. Org. Chem.*, **33**, 1421, 1428, 1430, 1436 (1968). Equations are numbered consecutively in papers I–V.

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(3) C. Walling, "Free Radicals in Solution," John Wiley and Sons, Inc., New York, N. Y., 1957, p 504.

(4) S. W. Benson, *J. Chem. Phys.*, **40**, 1007 (1964).

(5) W. H. Richardson, *J. Amer. Chem. Soc.*, **87**, 1096 (1965).

(6) R. Hiatt, J. Clipsham, and T. Visser, *Can. J. Chem.*, **42**, 2754 (1964).

(7) D. B. Denny and J. D. Rosen, *Tetrahedron*, **20**, 1137 (1962).

(8) A. Factor, C. A. Russell, and T. G. Traylor, *J. Amer. Chem. Soc.*, **87**, 3692 (1965).

(9) J. R. Thomas, *ibid.*, **87**, 3935 (1965).