Solvent Effects on Aromatic Nucleophilic Substitutions. Part 3.[1] The Kinetics of the Reaction of 2,4-Dinitrochlorobenzene with Piperidine in Aprotic Solvents

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The kinetics of the reaction between 2,4-dinitrochlorobenzene and piperidine were studied in nitromethane, *NN*-dimethylformamide, ethyl acetate, dioxane, and 1,1,1-trichloroethane at 15, 25, and 40 °C. This reaction was chosen as the simplest example of aromatic nucleophilic substitution. Different correlations of the second-order rate coefficients k_A with several solvent parameters were examined for this and earlier work combining 13 aprotic solvents in all with a range of 43 units in the dielectric constants (ε) in the series. It was found that the $E_T(30)$ parameter is the most useful available measure of the solvent influence in the present reaction if hydrogen-bond donor (HBD) solvents are excluded; the deviation from linearity of these solvents is explained as arising from the highly exposed strong negative charge on Dimroth's betaine which gives a high E_T value to HBD solvents. Conversely, the correlation is remarkably successful for the hydrogen-bond acceptor (HBA) solvents since the positive charge in the present reaction is buried similarly to that in the model solute, and the amine hydrogen of the zwitterionic intermediate, ZH, is strongly involved in an intramolecular hydrogen bond. Aliphatic, aromatic, and polychlorinated aliphatic solvents are all well correlated.

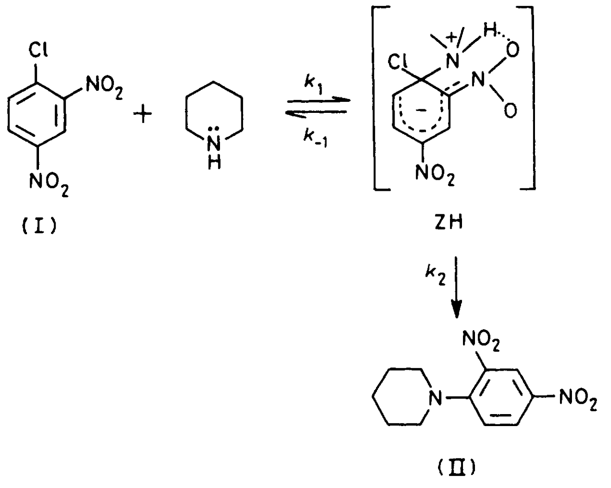
That solvent considerably influences physical properties[2] and chemical reactivity[3] is a well established phenomenon. In aromatic nucleophilic substitutions, interactions of the substrate and/or the intermediate(s) with the solvent molecules may be extensive and complex, and although the influence of the solvent has been long recognized[4-6] there has been little systematic study on the several ways that solvents may affect reaction rates.

For these reactions the two-step mechanism depicted in the Scheme is fully established: breakdown of the zwitterionic σ intermediate, ZH, can occur spontaneously or by a base-catalysed mechanism. Regarding this last step the solvent may modify the relative rates[5] and mechanisms. While in protic solvents it occurs by a rate-limiting proton transfer[7] (recently questioned),[8] in aprotic solvents the situation is still unclear[7] and subject to controversy.[9-11]

In addition to the nonspecific coulombic, inductive, and dispersion interactions others such as specific hydrogen-bond (where the solvent may act as donor or acceptor), electron-pair donor, electron-pair acceptor, and solvophobic interactions may all play a part; the problem is to identify and to assess the relative importance of these various factors. The purpose of our work is to contribute progress to our understanding of the solvent influence in aromatic nucleophilic substitution. We started with one of the simplest systems, the reaction of 2,4-dinitrochlorobenzene with piperidine in several aprotic solvents.

Results and Discussion

As mentioned in the Introduction, base catalysis may assist the breakdown of the intermediate ZH and a rate dependence of higher order than one has been observed for aromatic nucleophilic substitution (ANS) of poor nucleofugues (*e.g.* for X = F or OCH_3 kinetics of second[4] and even third[11,12] order in amine have been reported). Although *a priori* no base catalysis is expected for the better nucleofugue chloride, to confirm this for aprotic solvents the influence of amine concentration in the reactions in nitromethane, *NN*-dimethylformamide, ethyl acetate, 1,1,1-trichloroethane, dioxane, and toluene was studied. In all cases the reactions were carried out under pseudo-first-order conditions; they yielded the expected *N*-(2,4-dinitrophenyl)piperidine (II) in quantitative yield, and proved to be first order in substrate. The second-order rate coefficients k_A calculated from the experimental pseudo-first-order rate coefficients, k_ψ, are gathered in Table 1, for the reactions at 25 °C. As can be observed no significant acceleration in rate is observed for increasing amounts of amine in all the solvents studied. The same has previously been observed for reactions carried out in benzene,[13] and in chlorobenzene, tetrahydrofuran, acetone, and dimethyl sulphoxide.[14] When the reaction was performed in cyclohexane a slight increase in rate was observed (k_3/k_2 = 4.1);[1] this mild acceleration cannot be regarded as a base-catalysis effect but rather as a consequence of the increased polarity of the medium provoked by the addition of piperidine to a solvent of very low dielectric constant (ε 2.0)[15] and to special solubility problems in this solvent.[1] Table 2 gathers the results of the reactions carried out in the solvents first mentioned except toluene, at 15 and 40 °C. From the data in Tables 1 and 2, and others in the literature,[2] the activation parameters for the reaction of 2,4-



Scheme.

Table 1. Reaction of 2,4-dinitrochlorobenzene (**I**) with piperidine in aprotic solvents at 25 °C. Search for amine catalysis [a]

	Solvent					
[Piperidine]/M	DMF	Nitromethane	Ethyl acetate	Trichloroethane	Dioxane	Toluene
0.0012	111	78.4				
0.0020	112	78.4				
0.0024					11.1	
0.0032	112	79.4				
0.0040	112	79.9				
0.0048					11.0	
0.0052	113	79.3				
0.0060			26.6	18.9		
0.0100					10.8	
0.0120			26.9	18.6		
0.0180			26.4	19.0		
0.0240			26.9	19.2	10.9	6.62
0.0320			26.7	18.7	11.0	6.68
0.0400			26.8	19.0		6.59
0.0720					10.9	6.64

[a] [(I)] = 10^{-4}M, values of $10^2\,k_A$ l mol^{-1} s^{-1}.

Table 2. Reaction of 2,4-dinitrochlorobenzene (**I**) with piperidine in aprotic solvents [a]

	$10^2\,k_A$/l mol^{-1} s^{-1}	
Solvent	15 °C	40 °C
Dioxane	7.24	19.7
1,1,1-Trichloroethane	12.8	30.4
Ethyl acetate	18.3	45.6
Nitromethane	53.2	136.0
NN-Dimethylformamide	74.3	190.0

[a] [(I)] = 10^{-4}M.

Table 3. Second-order reaction rate coefficient, k_A, at 25 °C and activation parameters for the reaction of 2,4-dinitrochlorobenzene (**I**) with piperidine in aprotic solvents [a]

Solvent	10^2k_A/ l mol^{-1} s^{-1}	$\Delta H^‡$/ kJ mol^{-1}	$\Delta S^‡$/ JK^{-1} mol^{-1}
Cyclohexane	3.84	24.3	199.2
Benzene	7.83	23.0	183.3
Chloroform	8.65	24.4	191.6
Dioxane	11.0	27.5	179.1
1,1,1-Trichloroethane	18.9	23.4	188.7
Chlorobenzene	20.2	25.2	182.0
Ethyl acetate	26.7	24.9	180.7
Tetrahydrofuran	29.5	24.7	180.3
Acetone	49.1	22.8	182.4
Nitromethane	79.1	25.6	169.0
NN-Dimethylformamide	112.0	25.6	166.5
Dimethyl sulphoxide	193.0	23.8	167.8

[a] [(I)] = 10^{-4}M.

dinitrochlorobenzene with piperidine in 13 solvents were calculated and they are shown in Table 3.

The absence of base-catalysis in this system permits the inference that hydrogen bonding of the intermediate ZH (which *a priori* one might expect to be important) to a hydrogen-bond acceptor solvent is not relevant. This, together with the fact that in similar systems no ion-pair formation was observed [16] suggests specific solvent effects are unimportant in this system. The next problem is which of the currently available parameters best reflects the experimentally observed solvent effects on the present reaction, *i.e.*, which is the best measure of the 'solvent polarity' [17] or, in the present context, more properly called 'solvent dipolarity', [18] as a description of the dipole–dipole effects. In Table 3 solvents have been placed in order of increasing reaction rate but it can be observed that the increase in rate is not caused solely by a decrease in energy of activation or increase in the entropy of activation, but rather to a random combination of both. Solvent interactions on this reaction are then expected to be of a complex nature.

The limitations of considering the bulk dielectric constant in interpreting the solvent influence on rate have often been pointed out [19] and shown for the present system. [14] Several other parameters have been proposed, *e.g.* the Dimroth–Reichardt $E_T(30)$ scale, [3b,17] the solvatochromic parameters π^* of Taft *et al.*, [18] Hildebrand's parameter δ_H, [20] Lewis basicity (or nucleophilicity) (B) and acidity (or electrophilicity) (E) parameters, [21] Gutmann's 'Acceptor' (AN) and 'Donor' (DN) numbers, [22] Kosower's values, [23] *etc.*

In addition to these single parameters some multiple-parameter models have been proposed to unravel some of the different properties of the medium. Thus Koppel and Palm [24] propose the four-term equation (1) to rationalize the solvent

$$XYZ = XYZ_0 + yY + pP + eE + bB \tag{1}$$

influence on the property *XYZ* where *Y* represents the polarity (a function of the dielectric constant); *P* corresponds to the 'polarizability' (a function of the refraction index), and *B* and *E* are the Lewis nucleophilicity and electrophilicity parameters, respectively. In similar vein Taft *et al.* propose a two-parameter expression (2) where we used '*g*' to design a changing 'greek

$$XYZ = XYZ_0 + s^* + b'g' \tag{2}$$

letter' representing Hildebrand's solubility parameter δ_H (associated with the energy needed to make a suitably sized cavity in the bulk solvent), [25] the hydrogen-bond acceptor (HBA) acidity, α, [26] or hydrogen-bond donor (HBD) basicity β [27] of the solvent, depending on which of the three solvent properties is most important in defining the solvent dependence of the XYZ 'solute' property. Koppel and Palm's analysis has been successfully used by Chapman *et al.* in several studies on the influence of the solvent in the reactions of diazodiphenylmethane with carboxylic acids. [28] The equation derived by Taft *et al.* has recently been shown to correlate a considerable number of physical properties and chemical reactivity. [3a,29] Other multi-parameter equations [30–33] have been less extensively examined.

Table 4. Some frequently used parameters for the aprotic solvent of the present study[a]

No.	Solvent	$E_T(30)$	π^*	δ_H	B	E	AN	DN	Z	$f(n^2)$
1	Cyclohexane	31.2	0.00	8.20	25	0			52.8	0.2031
2	Toluene	33.9	0.54		54	+1.32				0.2264
3	Benzene	34.5	0.59	9.15	52	+2.15	8.2	0.1	54.0	0.2267
4	Chloroform	39.1	0.76	9.24	39	+3.36	23.1	4.0	63.2	0.2095
5	Dioxane	36.0	0.54	9.73	128	+4.21	10.8	14.8	65.4	0.2020
6	1,1,1-Trichloroethane	36.2	0.49		35	−1.57				0.2072
7	Chlorobenzene	37.5	0.71	9.50	45	+0.64				0.2345
8	Ethyl acetate	38.1	0.55	8.90	89	+1.54		17.1	62.8	0.1844
9	Tetrahydrofuran	37.4	0.58	9.30	145	−0.20	8.0	20.0		0.1968
10	Acetone	42.2	0.68	9.60	123	+2.10	12.5	17.0	65.7	0.1793
11	Nitromethane	46.3	0.80	12.61	59	+5.28	20.5	2.7		0.1879
12	*NN*-Dimethylformamide	43.8	0.88	11.76	166	+2.50	16.0	26.6	68.5	0.2047
13	Dimethyl sulphoxide	45.0	1.00	13.00	192	+3.30	19.3	29.8	71.1	0.2204

[a] References cited in text.

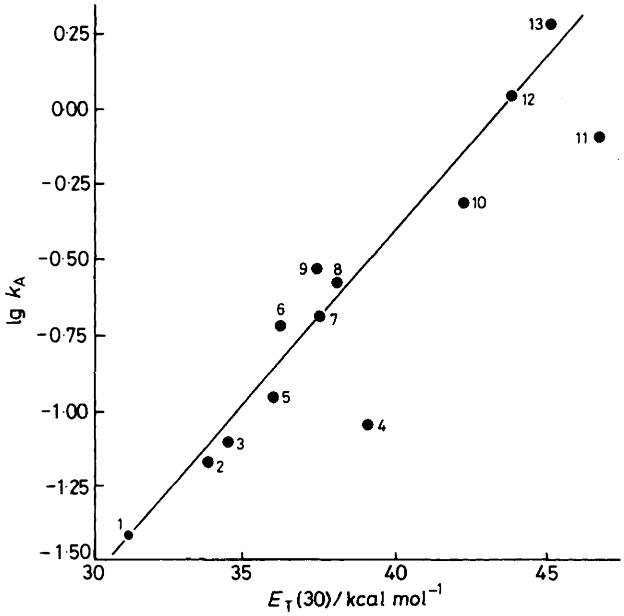


Figure 1. Correlation of log k_A with the $E_T(30)$ values for the reaction of 2,4-dinitrochlorobenzene with piperidine at 25 °C

Notwithstanding the success of the multi-parameter equations, it is known that with a greater number of parameters the correlation of a given data set becomes statistically less significant. For this reason, and since the reaction chosen is of the simplest kind, we consider first the single-parameter linear free-energy relationships, which are gathered in Table 4.

The relationship between the data of Table 1 and Hildebrand's parameter, δ_H, gives a low correlation coefficient (r 0.860) which suggests that δ_H is not a satisfactory parameter for this system. This parameter has been regarded recently as an index of the solvent dipole–solvent dipole interactions which are interrupted in forming a cavity for the solute. In the present case major solvent reorganization will be needed when forming the dipolar intermediate ZH and it has been shown that with polar solutes the sensitivity of the reaction to δ_H is not always correlated with the solute size, and hence with the size of the cavity to be formed in the solvent.

Figure 1 shows the plot of log k_A *versus* the $E_T(30)$ values. It is worth remarking that for the wide range of solvent polarity examined (E_T 31.2—46.3) the correlation is satisfactory (r 0.918). The regression is significantly improved if chloroform and nitromethane are eliminated (r 0.981). The first solvent that was noticed to depart from linearity was chloroform [14] and two reasons could be formulated for the anomalous behaviour: (a) chloroform being a polychlorinated solvent, influence of polarizability on the reaction and on the system of measurement of E_T could be different or (b) the difference could lie with the differing ability of the solutes to form hydrogen-bonds. In Dimroth's betaine the strong negative charge on the phenoxide oxygen in the electronic ground state can acquire an additional solvent stabilization by hydrogen-bonding with the chloroform molecules; this will result in increased energy for the charge transfer form the stabilized ground state to the less polar excited state, and, consequently, in an increased E_T (the E_T values of protic solvents are greater than those of comparable dipolar aprotic solvents). The hydrogen-bond donor abilities of chloroform have been previously noted in other systems [34] and since in the intermediate ZH (Scheme) no additional stabilization is expected by hydrogen-bond donor solvents, we favour reason (b) for the anomalous effect of chloroform and suggest that for this kind of solvent the E_T values are 'too high' to give satisfactory correlation in ANS.[14] To test this assessment against reason (a), the reaction was studied in 1,1,1-trichloroethane and nitromethane. As Figure 1 shows the polychlorinated solvent correlates well, while the hydrogen-bond donor nitromethane departs from the line. E_T Values of 35 and 42 for chloroform and nitromethane respectively, would be required to give a satisfactory correlation of k_A.

An alternative possibility is that chloroform and nitromethane exert special solvent effects on this reaction which makes the values for k_A abnormally low. There are few studies of ANS in these solvents: of the 68 different ANS recently reviewed [4a] only one (picryl chloride plus imidazole) has been performed in chloroform and there is no report of reactions in nitromethane. The reaction of (**I**) with n-butylamine has been studied in chloroform [35] and the k_A value (2.2×10^{-4} l mol^{-1} s^{-1}) is slightly lower than that obtained in benzene (3.9×10^{-4} l mol^{-1} s^{-1}). The k_A for the reaction of (**I**) with piperidine in chloroform reported in Table 2 is similar to the reaction rate in benzene.[36] Therefore there is no reason to assume any special solvent effect of chloroform on the present reaction. Since the positive charge is buried in the ZH intermediate similarly to the model (Dimroth's betaine), and the amine hydrogen is strongly involved in the intramolecular hydrogen-bond with the *ortho*-nitro oxygen, hydrogen-bond acceptor solvents such as THF, dioxane, acetone, DMF, and DMSO are all satisfactorily correlated with the standard $E_T(30)$ values. The same can be said about the aromatic solvents.

In Gutmann's approach [22] the total medium effects are

Table 5. Summary of linear regressions

Solvent parameter	Solvents[d]	log k_o[a]	m[b]	r[c]
$E_T(30)$	1—13	−4.616	0.1031	0.918
$E_T(30)$	1—3, 5—10, 12, 13	−5.136	0.1189	0.981
π^*	1—13	−1.670	1.648	0.776
π^*	1, 8—13	−1.460	1.698	0.997
B	1—13	−1.237	0.006 73	0.733
E	1—13	−0.8151	0.092 44	0.343
DN	3—5, 9—13	−0.9340	0.031 57	0.342
AN	3—5, 8—13	−0.9547	0.032 43	0.679
Z	1, 3—5, 8, 10, 12, 13	−0.652	0.079 69	0.857
δ_H	1, 3—5, 7—13	−0.460	0.2851	0.859

[a] Intercept of the regression line with the ordinate. [b] Slope of the regression line. [c] Correlation coefficient. [d] See Table 4.

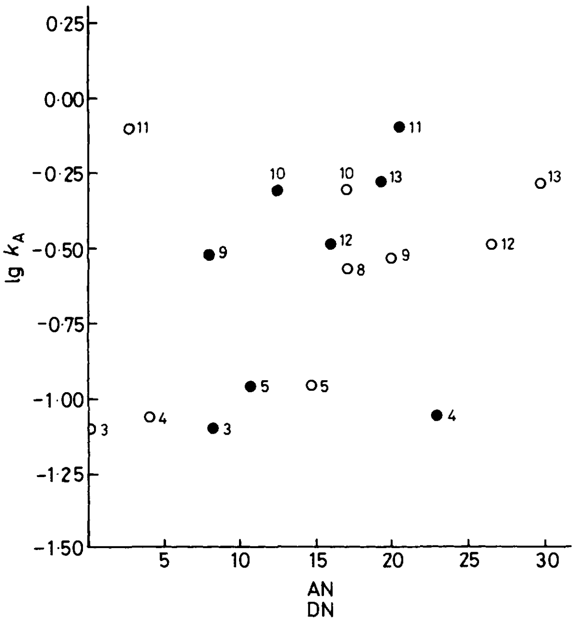


Figure 2. Correlation of log k_A with: ○ AN and ● DN parameters for the reaction of 2,4-dinitrochlorobenzene with piperidine at 25 °C

described in terms of the electron-pair donor and electron-pair acceptor properties of the solvent. The correlation of the present log k_A with the Gutmann acceptor numbers (AN) was analysed; the poor correlation coefficient obtained (Table 5) and the solid points in Figure 2 indicate that the AN are not satisfactory parameters. As is known for aprotic solvents AN is a measure of solvent polarity–polarizability and in the present reaction the polarizability was shown not to play an important role. Even worse, as expected, is the attempted correlation with the DN numbers. As pointed out previously,[37] DN is a reasonably good measure of the ability of the solvent to serve as an electron-pair donor only for oxygen bases.

The solvent parameter B is primarily a measure of the Lewis basicity of the solvent against CH_3OD as the standard substrate and is related to the donor numbers. On the other hand, it is widely accepted that the Lewis electrophilicity parameter E largely relates to the E_T parameter. E, together with the function of the dielectric constant rate dependence, as has been recently pointed out by Chapman and his co-workers,[38] after Fawcett and Krygowski's[39] remarks, is not as good a measure of the solvent 'polarity' as the E_T. As can be observed in Table 5, good correlations of log k_A with B or with E were not obtained.

Kosower's Z parameter is closely related to Gutmann's AN and the E_T values, and for aprotic solvent can be considered not only a measure of the electrophilic character of the solvent but also as a good measure of the 'solvent polarity'. The correlation obtained (r 0.857, for eight solvents) is slightly worse than with the E_T values for 13 solvents.

Consideration of the correlation with Taft's solvatochromic parameter π^* has been left to the end. π^* Is related to the ability of a bulk solvent to stabilize a charged or a dipolar solute by virtue of charge–dipole or dipole–dipole interactions. It is therefore expected to be an appropriate parameter to account for the solute–solvent interactions in the reaction shown in the Scheme where the transition state forms a dipolar intermediate. Nevertheless, the correlation coefficient for log k_A *versus* π^* (Table 5) is not as good as that obtained for the E_T values. π^* And E_T values are usually correlated by an equation in which a term α (the solvent acidity) is added to the π^* value. The solvents that deviate from the log k_A–π^* correlation line have $\alpha = 0$ and therefore the correlation cannot be improved by its inclusion. It has recently been shown[18] that a set of 'select' solvents can be chosen whose effects are well accounted for by π^* when solvent–solute hydrogen-bonding interactions are absent. If the correlation is done with this set of aliphatic non-polychlorinated select solvents, the correlation coefficient is highly satisfactory (Table 5). Of the solvents examined in the present study the aromatic benzene, toluene, and chlorobenzene, and also dioxane depart from the line. It is known that dioxane resembles THF in many aspects and π^* for dioxane is close to that for THF (Table 4). It has been suggested that when a dioxane molecule is near a given molecule, the latter 'sees' only part of the dioxane molecule and hence regards dioxane as having a dipole. Alternatively, when solvating the solute dioxane may adopt a boat conformation which has an appreciable dipole moment. However, in the present reaction neither of these alternative explanations ascribing a special solvent effect to dioxane seems to be valid. The positive charge is buried in the intermediate ZH and the amine hydrogen (which might participate in hydrogen-bonding with dioxane) is engaged in the internal hydrogen-bond with the *ortho*-nitro oxygen. Therefore, the reaction rate resembles more that in benzene solution than that in THF.

Regarding Koppel and Palm's[24] multi-parametric equations several combinations were tried by multiple regression analyses of the data of Table 3. Stepwise regression shows that the order of the decreasing significance of the different parameters is E_T, B, and E. The two-parameter equation (3) has r 0.954 and s

$$\log k_A = -4.099 + 0.0831\,E_T + 0.0028\,B \qquad (3)$$

0.168 [s 0.212 for the one- (E_T) parameter equation]. The partial confidence levels are 99.99% (E_T) and 95% (B). Equation (3) explains 91% of the variance compared with 84.3% for the single-(E_T) parameter equation.

In the three-parameter equation (4) (r 0.982, s 0.111) the introduction of E accounts for *ca.* 60% of what is left unexplained by the two-parameter equation (3). A considerable difference is again observed between the partial confidence levels: 99.999% for E_T and 99% (B); 99% (E). Collinearities between E_T and the other *explanatory* variables were examined and found to be sufficiently small ($r' < 0.5$) to warrant the preceding treatment.

$$\log k_A = -4.726 + 0.1036\,E_T + 0.002\,71\,B + 0.078\,11\,E \qquad (4)$$

In conclusion, at present the overall situation is that as a single-solvent parameter allows correlation of the rate with E_T, and it would be expected to be similar for all ANS where complications arising from the hydrogen-bond donor ability of the solvent, base-catalysed breakdown of the intermediate ZH (or any other kind of rate-determining rupture of the ZH pathway) or strong solute–solute interactions (such as association of the amine reagents) are not present. According to the classification of solvent scales suggested by Knauer and Napier[40] all the parameters examined are both cybotactic region and model process probes and in view of the above results it can be concluded that the model reaction that defines the E_T parameter is the one which bears the greater resemblance to the transition state for this type of ANS with regard to the influence of solvent interactions.

Nevertheless, in the view of the recent success of some multiparameter equations in predicting medium effects on many types of physicochemical properties and chemical reactivities it is expected that in more complex systems which will be reported such as protic solvents and reactions where base-catalysis is observed, multi-parameter equations may prove preferential to the single-parameter correlations reported here.

Experimental

Reagents and Solvents.—2,4-Dinitrochlorobenzene (**I**) was crystallized from ethanol to constant m.p. 51—52 °C. *N*-(2,4-Dinitrophenyl)piperidine was prepared as previously described,[14] m.p. 92—93 °C (lit.,[16a] 91—92 °C). Piperidine was kept over sodium wire, refluxed for 12 h, and then fractionated over sodium; the fraction of b.p. 64 °C, stored in the dark under nitrogen, was used. Nitromethane was kept over calcium chloride for several days, and then distilled at reduced pressure (fraction b.p. 49—50 °C at 130 mmHg was used). *NN*-Dimethylformamide was kept over potassium hydroxide pellets for several days and then twice distilled at reduced pressure (fraction b.p. 48—49 °C at 20 mmHg was used). Ethyl acetate was refluxed with acetic anhydride and a small amount of sulphuric acid for 6 h, then distilled, dried over anhydrous potassium carbonate, and redistilled (fraction b.p. 74—75 °C was used). 1,1,1-Trichloroethane treated with concentrated hydrochloric acid (10/1 v/v) was then washed with 10% aqueous sodium carbonate, dried with calcium chloride, and twice distilled (b.p. 71—72 °C). Dioxane was refluxed with 1N-hydrochloric acid under nitrogen for 10 h, then treated with potassium hydroxide, and the aqueous layer separated. The acetaldehyde-free dioxane was kept over fresh potassium hydroxide pellets for one day, then for several hours over sodium wire, and fractionated over sodium wire under nitrogen (b.p. 101 °C). All the solvents were kept over 4 Å molecular sieves and stored in special vessels which allow delivery without air contamination.

Kinetic Procedures.—The kinetics of the reactions were studied spectrophotometrically.[41] A Perkin-Elmer 124 spectrophotometer was used with 1.00 cm silica cells. In all cases pseudo-first-order kinetics were observed. Standard solutions of (**I**) and of piperidine were prepared in the desired solvent at room temperature. The reactions were run by mixing known amounts of each solution in the thermostatted cells of the spectrophotometer, recording the optical densities at 400 nm. The pseudo-first-order, k_ψ, and second-order, k_A, rate coefficients were obtained as previously described.[41] In all the cases the 'infinity' value, A_∞, was determined experimentally for each run at the working temperature. This value agreed, within experimental error, with the 'theoretical' value calculated from application of Beer's law to solutions of the *N*-(2,4-dinitrophenyl)piperidine (**II**) in the working solvent. The energies of activation were calculated from the linear regression of ln k_A *versus* $1/T$ by the least-squares method and the entropies of activation were calculated by the standard formula derived from the absolute theory of reaction rates. All the kinetic runs were carried out at least in duplicate; the error in k_A is $\leqslant 2$—3% for all the solvents examined. Values of $\Delta H^\ddagger$ are accurate to *ca.* ± 0.1 kcal mol^{-1} and values of $\Delta S^\ddagger$ to ± 2 cal mol^{-1} K^{-1}. The present units for the activation parameters have been used instead of the recommended SI units since they are still found more frequently in this type of study.

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