Studies of Tertiary Amine Oxides. Part 13.[1] Solvent Effects on the Rate of Thermal Rearrangement of *N*-(2,4-Dinitrophenyl)piperidine *N*-Oxide

Abdul-Hussain Khuthier,* Salim Y. Hanna, and Khawla Y. Al-Mallah
Department of Chemistry, College of Science, University of Mosul, Mosul, Iraq

The rearrangement of *N*-(2,4-dinitrophenyl)piperidine *N*-oxide was studied in ten aprotic solvents. Different correlations of the first-order rate coefficients ($k_{obs.}$) with several solvent parameters were examined for the ten solvents with a range of 45 units in dielectric constant; the multiparameter equations of Krygowski and Fawcett, Koppel and Palm, and Kamlet and Taft were all examined. The $k_{obs.}$ values were correlated reasonably well with the Lewis basicity of the solvent, Gutmann's donor number, and Dimroth's $E_T(30)$ parameter when hydrogen-bond-donor solvents were excluded.

Aromatic nucleophilic substitutions have received considerable attention.[2–5] The influence of the solvent of the relative rates and mechanisms has been the subject of extensive study.[6–9]

The rearrangement of *N*-arylpiperidine *N*-oxides to 1-aryloxypiperidines[10,11] can be considered as an internal aromatic nucleophilic substitution which proceeds by intramolecular nucleophilic attack of oxygen on the aryl carbon atom. (The mechanism may be referred to as S_NAr_i: substitution nucleophilic aromatic internal.) The influence of solvent on the rate of this rearrangement has been reported for only a few examples.[11] Thus the rate of isomerisation of 1-(4-nitrophenyl)-piperidines and -morpholine *N*-oxides has been correlated with the dielectric constants of aprotic solvents.[11a] However, the rate of rearrangement of 1-(2,4-dinitrophenyl)piperidine *N*-oxides showed a complex and not easily understood relationship with solvent.[11b]

We now report a study of solvent influence on internal aromatic nucleophilic substitution as represented by the rearrangement of 1-(2,4-dinitrophenyl)piperidine *N*-oxide to 1-(2,4-dinitrophenoxy)piperidine (Scheme 1).

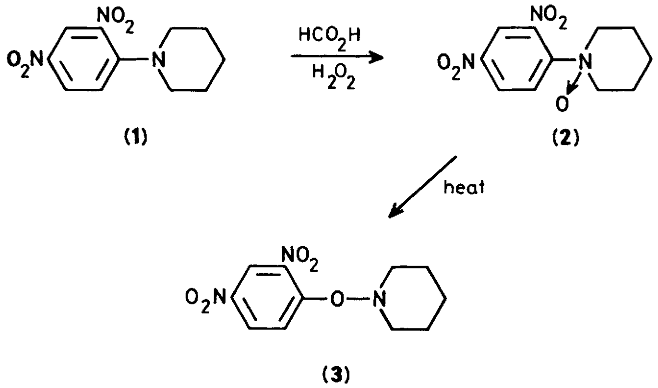
Results and Discussion

The reaction of piperidine with 1-fluoro-2,4-dinitrobenzene produced *N*-(2,4-dinitrophenyl)piperidine. Oxidation of this base with $HCO_2H–H_2O_2$ gave the corresponding *N*-oxide in good yield as a crystalline solid. The *N*-oxide readily rearranges upon heating in an appropriate inert solvent, to give 1-(2,4-dinitrophenoxy)piperidine in quantitative yield[11b] (Scheme 1).

The reaction is clearly first order in the *N*-oxide and the rate constant is solvent-dependent. The experimental results for the reaction in ten aprotic solvents are gathered in Table 1.

Correlation Analysis.—In order to test which of the currently available parameters best reflect the experimentally observed solvent effects on the present rearrangement we examined the results with single- and multi-parameter equations. The correlation of rate with any single parameter of Table 1 was poor ($r < 0.6$); thus no single parameter alone is satisfactory for this system. The parameters considered included the bulk dielectric constant (ε), the Dimroth–Reichardt $E_T(30)$ scale,[12] the solvatochromic parameter π* of Taft *et al.*,[13] Lewis basicity (or nucleophilicity) (*B*) and Lewis acidity (or electrophilicity) (*E*),[14] the Kirkwood function of dielectric constant f(ε), the function of the square of the refractive index $f(n)^2$, and Gutmann's Acceptor (A.N.) and Donor (D.N.) numbers.[15]

In addition to these single parameters some multiple-parameter models were used. Equations (1)—(5) show the



Scheme. 1.

Table 1. Solvent parameters for correlation analysis[a]

No.	Solvent	$\log k^b + 4$	E_T	*B*	E^c	π*	f(ε)	$f(n)^2$	β	D.N.
1	$CHCl_3$	0.539	39.1	39	3.36	0.76	0.356	0.21	*d*	−17
2	$MeNO_2$	0.970	46.3	59	5.26	0.80	0.481	0.195	*d*	6
3	PhCl	1.141	37.5	45	0.64	0.71	0.377	0.235	0.071	−2
4	PhBr	1.152	37.5	49		0.794	0.373	0.270	0.069	−1
5	PhMe	1.160	33.9	54	1.32	0.54	0.241	0.226	0.112	2
6	PhH	1.165	34.5	52	2.15	0.59	0.232	0.228	0.10	0
7	Dioxane	1.186	36.0	128	4.21	0.55	0.222	0.203	0.369	77
8	Me_2SO	1.420	45.0	192	3.3	1.0	0.484	0.221	0.749	141
9	THF[e]	1.460	37.4	145	−0.2	0.58	0.407	0.197	0.55	90
10	Me_2NCHO	1.468	43.8	166	2.5	0.88	0.480	0.204	0.69	107

[a] References cited in the text. [b] First-order rate constant at 20 °C. [c] Taken from ref. 7. [d] Non-hydrogen-bonding acceptor. [e] Tetrahydrofuran.

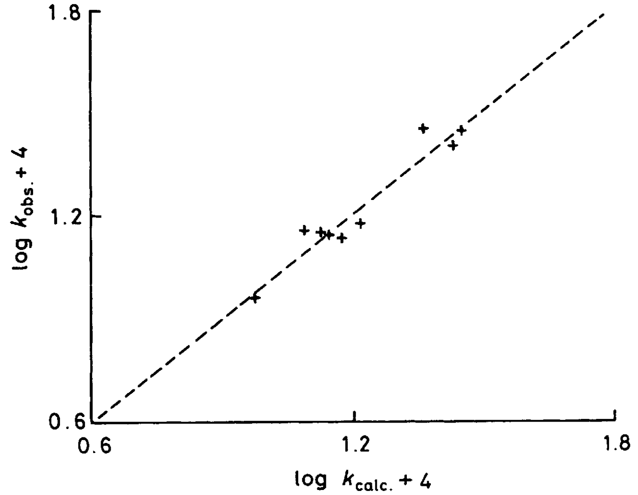


Figure 1. Plot of log $k_{obs.}$ *vs.* log k calculated according to equation (5)

$$\log k = -2.98 + 0.0036\text{D.N.} (\pm 0.001) \quad (1)$$
$$n = 10, r = 0.56$$

$$\log k = -2.32 + 0.0041\text{D.N.} (\pm 0.001) - 0.0174E_T (\pm 0.016) \quad (2)$$
$$n = 10, r = 0.62$$

$$\log k = -1.64 + 0.004\text{D.N.} (\pm 0.001) - 0.049E_T (\pm 0.03) + 1.528\text{f}(\varepsilon) (\pm 0.135) \quad (3)$$
$$n = 10, r = 0.69$$

$$\log k = -2.17 + 0.004\text{D.N.} (\pm 0.001) - 0.046E_T (\pm 0.035) + 1.53\text{f}(\varepsilon) (\pm 1.46) + 2.07\text{f}(n)^2 (\pm 0.521) \quad (4)$$
$$n = 10, r = 0.69$$

$$\log k = -1.866 + 0.002\text{D.N.} (\pm 0.0004) - 0.039E_T (\pm 0.01) + 1.38\text{f}(\varepsilon) \quad (5)$$
$$n = 9, r = 0.93$$

stepwise regression analysis of Krygowski and Fawcett.[16] The introduction of $\text{f}(n)^2$ did not produce any improvement. However, considerable improvement was obtained by excluding $CHCl_3$ from equation (3), which then becomes (5) (Figure 1).

Equations (6) and (7) show the Taft–Kamlet analysis.[13] Non-hydrogen-bonding-acceptor solvents in Table 1 were excluded.

$$\log k = -2.89 + 0.481\beta (\pm 0.076) \quad (6)$$
$$n = 8, r = 0.86$$

$$\log k = -2.85 + 0.59\beta (\pm 0.189) - 0.13(\pi^* + d\delta) (\pm 0.20) \quad (7)$$
$$n = 8, r = 0.88$$

Equations (8)—(11) involve Kopple–Palm analysis.[14] The E parameter was not available for PhBr, so the stepwise regression involved nine data points only. Here use of B alone was unsuccessful but the introduction of E produced some improvement. Further introductions of $\text{f}(n)^2$ and $\text{f}(\varepsilon)$ parameters were insignificant.

$$\log k = -3.19 + 0.0037B (\pm 0.001) \quad (8)$$
$$n = 9, r = 0.57$$

$$\log k = 3.02 + 0.0037B (\pm 0.001) - 0.066E (\pm 0.035) \quad (9)$$
$$n = 9, r = 0.73$$

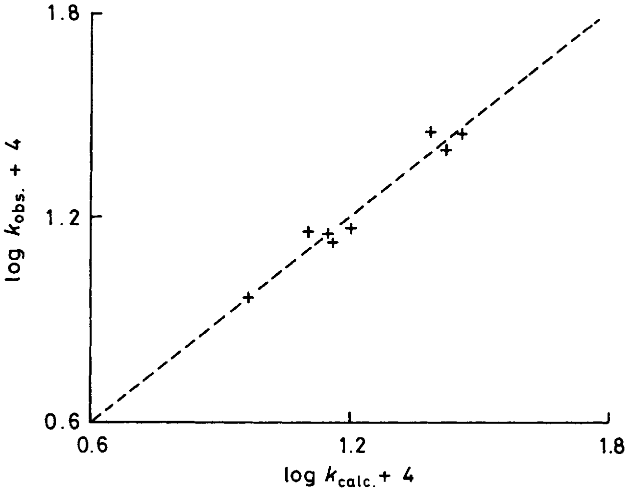


Figure 2. Plot of log $k_{obs.}$ *vs.* log k calculated according to equation (12)

$$\log k = -3.57 + 0.003B (\pm 0.001) - 0.058E (\pm 0.04) + 2.355\text{f}(n)^2 (\pm 5.28) \quad 10)$$
$$n = 9, r = 0.745$$

$$\log k = -3.477 + 0.004B (\pm 0.001) + 2.12\text{f}(n)^2 (\pm 6.0) - 0.14\text{f}(\varepsilon) (\pm 0.77) \quad (11)$$
$$n = 9, r = 0.747$$

If the data for chloroform were excluded from the two-parameter equation (9), a significant improvement was obtained [equation (12)] (Figure 2). The two-parameter equation (12) in B and E is comparable in performance with the three-parameter equation (5) with D.N., E_T, and $\text{f}(\varepsilon)$.

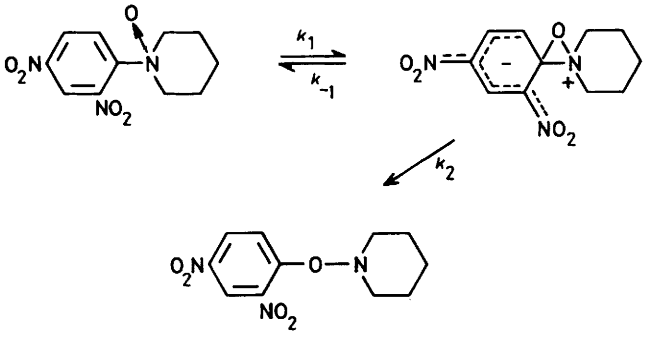
$$\log k = -2.98 \pm 0.0027B (\pm 0.0003) - 0.049E (\pm 0.008) \quad (12)$$
$$n = 8, r = 0.96$$

It is concluded that the best correlation of solvent with the rate of the present rearrangement is represented by the Krygowski–Fawcett three-parameter equation (5), with Gutmann's donor number (D.N.), the Dimroth–Reichardt $E_T(30)$, and the Kirkwood function $\text{f}(\varepsilon)$, which express the role of solvent in terms of solvent nucleophilicity, dielectric constant, and refractive index. The Kopple–Palm equation (12) is also successful in expressing the solvent effect ($CHCl_3$ excluded), in terms of Lewis basicity and Lewis acidity parameters. The large deviation of $CHCl_3$ from both of these treatments is due to the fact that this solvent may be considered a hydrogen-bond donor,[13] and slightly protic in character.[17] This property makes chloroform liable to form hydrogen-bonded complexes with the *N*-oxide so that the ground state can acquire additional solvent stabilization. This results in an increase in reaction activation energy and therefore decreases the rate. This reasoning is supported by the fact that 4-nitrophenylpiperidine *N*-oxide rearranges in alcohols at a significantly lower rate than in non-protic solvents.[11a]

Table 2. First-order rate constant and activation parameters for the rearrangement of the *N*-oxide (**2**)

Solvent	10^4k_{20}/ s^{-1}	$\Delta H^{\ddagger}$/kcal mol^{-1}	$\Delta S^{\ddagger}$/cal mol^{-1} K^{-1}	$\Delta G^{\ddagger}$/kcal mol^{-1}
$CHCl_3$	3.46	21.14 ± 0.6	−2.19 ± 2.2	21.78 ± 1.2
$MeNO_2$	9.35	20.4 ± 1.3	−2.7 ± 4.3	21.19 ± 2.5
PhCl	13.82	19.84 ± 1.4	−3.87 ± 4.7	20.97 ± 2.7
PhBr	14.2	19.63 ± 1.2	−4.54 ± 3.4	20.96 ± 2.1
PhMe	14.45	18.66 ± 0.6	−7.8 ± 2.2	20.94 ± 1.2
PhH	14.61	17.85 ± 0.9	−10.55 ± 3.2	20.94 ± 2.0
Dioxane[a]	15.35	16.34 ± 0.4	−15.5 ± 4.0	21.06 ± 1.6
Me_2SO	26.42	19.67 ± 1.0	−3.16 ± 3.0	20.59 ± 1.8
THF[a,b]	28.78	17.29 ± 0.4	−11.09 ± 4.0	20.65 ± 1.6
Me_2NCHO[a]	29.37	17.7 ± 0.38	−9.6 ± 3.8	20.63 ± 1.5

[a] Taken from ref. 11*b*. [b] Tetrahydrofuran.



Scheme 2.

Activation Parameters.—The activation parameters are listed in Table 2. The energy of activation changes only slightly with changes in solvent polarity and is generally small. It is slightly bigger in non-hydrogen-bonding-acceptor solvents ($CHCl_3$ or $MeNO_2$). The low values are consistent with the concerted mechanism, since the energy lost in breaking the C–N bond in (**2**) is partly compensated by the energy gained in forming the new C–O bond in (**3**). The negative values for the entropy of activation is also consistent with the proposed mechanism, since considerable loss of entropy is associated with the formation of the cyclic activated complex (Scheme 2). Certainly the rearrangement does not proceed by a radical-combination mechanism as proposed for the Meisenheimer rearrangement in other *N*-oxide molecules,[18] since such a process is usually associated with a positive $\Delta S^{\ddagger}$

It is worth noting that a linear relationship exists between $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ for rearrangement of the amine oxide (**2**) in different solvents (Figure 3; $r = 0.95$). The slope of such a plot is the isokinetic temperature.[19] The linearity indicates a single interaction mechanism whereby change in medium affects the isomerisation.

Mechanism.—The isomerisation of the *N*-oxide (**2**) shows first-order kinetics. The data presented here and elsewhere[11] strongly point to a concerted intramolecular mechanism in which the negative charge of the attacking oxygen atom is delocalised over the dinitropentadienide system and shielded by the two nitro groups. The positive charge is localised on the nitrogen atom and is exposed to solvent molecules (*i.e.* there is charge separation in the transition state). Therefore the extent of solvation will depend strongly on the nucleophilic solvating capability of the solvent, *i.e.* on the Lewis basicity, for which the parameters *B* and D.N. are the preferred measures. The dependence on *E* with a negative coefficient may indicate that the electrophilic solvent stabilises the reactant amine oxide relative to the transition state (Scheme 2).

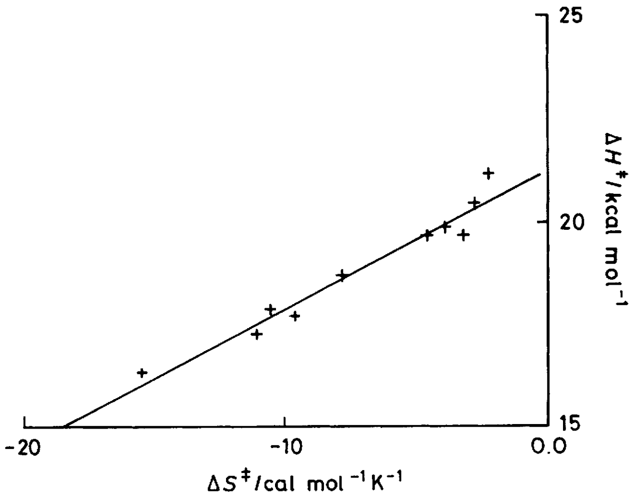


Figure 3. Plot of $\Delta H^{\ddagger}$ *vs.* $\Delta S^{\ddagger}$ in various solvents for the thermal rearrangement of the *N*-oxide (**2**)

Experimental

Reagents and Solvents.—(2,4-Dinitrophenyl)piperidine *N*-oxide (**2**) and 1-(2,4-dinitrophenoxy)piperidine (**3**) were prepared and characterised as previously described.[11] Nitromethane was kept over calcium chloride for several days and then distilled at reduced pressure. *N*,*N*-Dimethylformamide was kept over potassium hydroxide pellets for several days and then distilled at reduced pressure. Dimethyl sulphoxide (spectroscopic grade) was kept over molecular sieves for several days and distilled at reduced pressure. Chloroform was washed with water, dried ($CaCl_2$), and distilled. Dioxane was refluxed over sodium wire for 10 h and then distilled. Tetrahydrofuran was refluxed with lithium aluminium hydride and distilled. Reagent grade benzene, toluene, bromobenzene, and chlorobenzene were kept over sodium wire for several days and then fractionally distilled.

The middle fraction of each solvent was kept over molecular sieve (4 Å) and used for kinetic studies.

Kinetic Procedures.—The kinetics were studied spectrophotometrically. A Pye-Unicam SP800 instrument with thermostat attachment was used. The temperature of the cuvette was maintained constant within ±0.1 °C. A stock solution was prepared by dissolving freshly prepared amine oxide (**2**) in the appropriate solvent. Standard solutions of (**2**) were prepared by dilution with solvent kept at constant temperature. Measurement of the absorbance at $\lambda_{max.}$ of the rearrangement product began immediately. In all cases the 'infinity' value A_{∞} was determined experimentally for each run by leaving the solution of the amine oxide at the specified temperature until there was no further change in absorbance. All the kinetic runs were carried out in duplicate to 90% completion at four or five temperatures. Reaction rate constants were calculated from the slope of $\ln(A_{\infty} - A_t)$ *vs.* time; the error in $k_{obs.}$ was $\leqslant$2—3% for all the solvents. The energies of activation were calculated from the linear regression of ln *k* *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.

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