Studies of Tertiary Amine Oxides. Part 14.[1] Protic Solvent Effects on the Rate of Thermal Rearrangement of *N*-(2,4-Dinitrophenyl)piperidine *N*-oxide

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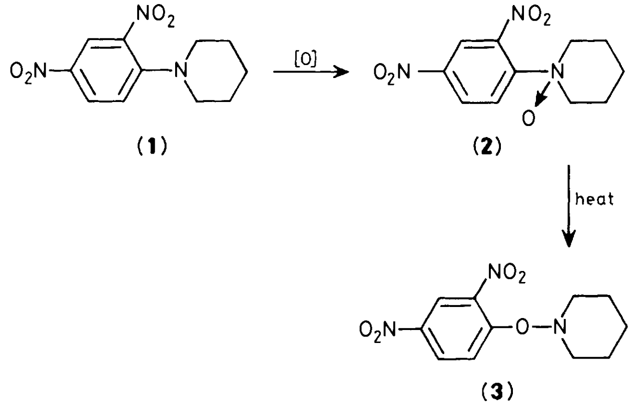
The rate of rearrangement of *N*-(2,4-dinitrophenyl)piperidine *N*-oxide has been studied in 15 hydroxylic solvents. The first-order rate coefficients (k_{obs}) have been successfully correlated with different solvent parameters. The results are explained in terms of the nucleophilic solvation capability of the solvent which in turn supports the previously proposed three-membered ring-activated complex. Moreover, the role of the HBD ability of the solvent in this reaction is also pronounced, particularly since reaction in alcohols exhibits lower reactivity and higher enthalpy and entropy of activation compared with aprotic solvents.

In a recent paper[1] we examined the solvent effects on the thermal isomerization of *N*-(2,4-dinitrophenyl)piperidine *N*-oxide (**2**), as a model of the so-called internal aromatic nucleophilic substitution (S_NAr_i), in ten aprotic solvents. It was shown that the rate coefficients (k_{obs}), are reasonably well correlated with Lewis basicity of the solvent, Gutmann's donor number, and the Dimroth–Reichardt E_T value, when hydrogen-bond donor solvents were excluded. However, the highly specific properties of hydroxylic solvents, such as inter- or intra-molecular hydrogen-bonding, acidity and basicity, and self-association merit the assessment of their relative influence on this model of internal aromatic nucleophilic substitution. Hence the kinetic studies of (**2**) were undertaken in fifteen protic solvents.

Results and Discussion

N-(2,4-Dinitrophenyl)piperidine (**1**) was prepared by the reaction of 1-fluoro-2,4-dinitrobenzene with piperidine. Oxidation of the tertiary amine was achieved by means of $HCO_2H-H_2O_2$. The resulting tertiary amine oxide underwent smooth and quantitative isomerization to the *O*-arylhydroxylamine (**3**) when heated in an appropriate solvent (Scheme 1). The rate of this isomerization has been studied in fifteen hydroxylic solvents (Table 1).



Scheme 1.

As in the case of aprotic solvents, the rate of isomerization of the amine oxide (**2**) in protic solvents was followed spectrophotometrically. In all cases the reaction follows first-order kinetics. The rate coefficients of the reaction in protic solvents together with those in aprotic solvents,[1] were gathered in Table 2. A glimpse at those values clearly indicates the dramatic decrease of the reaction rate in alcohols by comparison with aprotic solvents ($k_{THF}/k_{MeOH} = 130$; $k_{DMF}/k_{MeOH} = 152$; $k_{DMSO}/k_{MeOH} = 186$). Despite the high polarity of alcohols, a similar decrease in reactivity was observed for the isomerization of 4-(nitrophenyl)piperidine amine oxides in alcohols compared with the less polar aprotic solvents.[2] This must be associated with the strong solvation of the reactant by alcohols *via* hydrogen-bonding, basicity, acidity, polarization, *etc.* since amine oxide is a dipolar molecule. The hydrogen-bonded amine oxide is far less reactive than the free molecule. In other words, the hydrogen-bonded amine oxide must be desolvated prior to the formation of the three-membered ring transition state required by the mechanism of the present rearrangement[12] (Scheme 2).

$$R_3\overset{+}{N}-\overset{-}{O}\cdots H-O-R \rightleftharpoons R_3\overset{+}{N}-\overset{-}{O} + HOR$$

hydrogen-bonded *N*-oxide
(solvated)
less reactive

free *N*-oxide
more reactive

$\downarrow$ rearrangement

Scheme 2.

In addition to these observations, the roughly exponential decrease in the rate of rearrangement of 4-nitrophenylpiperidine *N*-oxide in THF, with the molar percentage of the added water,[2] also supports the rationale that hydrogen-bonding is responsible for the observed decrease in rate. Also the trend in reactivity follows the structural features of alcohols, *e.g.* the rate in secondary or tertiary alcohols is, on average, 2 or 5 times that in primary alcohol, respectively.

It was shown previously that solvent effects in aprotic solvents are successfully correlated by the Koppel–Palm bi-parametric equation and Krygowski–Fawcett three-parameter equation when $CHCl_3$ is excluded.[1] In the present work, the results were examined with single- and multi-parameter equations. Correlations involve 15 data points except for solvents for which values are not available in the literature (Table 1). The correlations of rate coefficient log k at 50 °C with single parameters, the dielectric function $f(\varepsilon)$, Dimroth–Reichardt E_T value,[3,4] the refractive index function $f(n)$,[2] Lewis basicity B,[3] Lewis acidity E,[3] steric substituent constant E_s,[5] or the number of γ-hydrogen atoms $n\gamma_H$,[7] were poor ($r \leqslant 0.6$). However, a more satisfactory correlation was observed either with Taft's polar substituent constant σ^*,[5] or the basicity parameter as indicated by the solubility of hydrogen chloride in alcohol (L)[6] ($r = 0.9$ and 0.94, respectively).

Table 1. Rate constant and solvent parameters used for multiple linear correlation.[a]

Solvent	$\log k_{50}$	B	E	$E_{T(30)}$	σ^*	E_s	L	$n_H\gamma$	$f(\varepsilon)$	π^*	α	β
Methanol	−3.446	114	14.9	55.5	0.0	0.0	0.857	0	0.477	0.586	0.99	1.014
Ethanol	−3.142	117	11.6	51.9	−0.1	−0.07	0.943	0	0.469	0.540	0.85	0.949
Propanol	−3.155	119	10.6	50.7	−0.115	−0.36	0.957	3	0.464	0.534	0.766	0.884
Butanol	−3.148	119	10.3	50.2	−0.13	−0.39	0.965	2	0.457	0.503	0.710	0.746
Pentanol	−3.132	120	9.7	49.2	−0.13	−0.4	0.968	2	0.448	—	—	—
Hexanol	−3.131	120	9.6	49.0	—	—	0.968	2	0.445	—	—	—
Heptanol	−3.196	120	9.6	48.5	−0.13	−0.4	0.970	2	0.438	—	—	—
Octanol	−3.150	121	10.1	48.7	—	—	0.971	2	0.430	—	—	—
Isopropyl alcohol	−2.803	122	8.7	48.6	−0.19	−0.47	1.029	0	0.460	0.505	0.687	0.773
Isobutyl alcohol	−3.094	119	7.4	48.6	−0.125	−0.93	0.971	6	0.458	—	—	—
s-Butyl alcohol	−2.729	122	7.4	47.1	−0.21	−1.13	1.043	3	0.454	—	—	—
Cyclopentanol	−2.798	123	7.7	47.0	−0.15	−0.51	—	—	0.454	—	—	—
Cyclohexanol	−2.749	124	7.4	47.4	—	—	1.031	4	0.451	—	—	—
2-Methoxyethanol	−2.596	119	12.5	52.3	—	—	—	—	0.454	—	—	—
t-Butyl alcohol	−2.441	125	5.2	43.9	−0.3	−1.54	1.115	0	0.441	0.534	0.436	0.615

[a] References cited in text.

Table 2. Rate constants and activation parameters for the rearrangement of (**2**) in protic and aprotic[a] solvents.

Solvent	$k_{50}{}^b/10^4\ \mathrm{s^{-1}}$	$\Delta H^\ddagger$/kcal mol^{-1}	$\Delta S^\ddagger$/cal mol^{-1} k^{-1}
Methanol	3.58	26.11 ± 0.7	+6.3 ± 3.2
Ethanol	7.21	23.02 ± 0.6	−1.79 ± 2.1
Propanol	6.99	25.17 ± 1.1	+4.79 ± 3.1
Butanol	7.11	25.35 ± 0.5	+5.4 ± 3.5
Pentanol	7.38	24.59 ± 1.7	+3.1 ± 1.0
Hexanol	7.39	25.36 ± 0.9	+7.00 ± 4.2
Heptanol	6.36	25.83 ± 0.8	+6.65 ± 3.6
Octanol	7.08	24.97 ± 0.9	+4.19 ± 2.4
Isopropyl alcohol	15.71	25.62 ± 1.0	+7.79 ± 4.0
Isobutyl alcohol	8.04	22.62 ± 1.1	−2.81 ± 4.5
s-Butyl alcohol	18.65	25.76 ± 1.3	+8.56 ± 4.0
Cyclopentanol	15.91	24.97 ± 0.9	+5.80 ± 3.2
Cyclohexanol	17.81	22.35 ± 0.8	−2.08 ± 2.1
2-Methoxyethanol	25.3	21.45 ± 0.7	−4.16 ± 3.8
t-Butyl alcohol	36.19	22.76 ± 0.8	+0.6 ± 2.5
$CHCl_3$	110.5	21.14 ± 0.6	−2.19 ± 2.2
$MeNO_2$	265.5	20.4 ± 1.3	−2.7 ± 4.3
PhCl	359.6	19.84 ± 1.4	−3.87 ± 4.7
PhBr	356.6	19.63 ± 1.2	−4.54 ± 3.4
PhMe	310.9	18.66 ± 0.6	−7.8 ± 2.2
PhH	276.2	17.85 ± 0.9	−10.55 ± 3.2
Dioxane	228.1	16.34 ± 0.4	−15.5 ± 4.0
DMSO	666.7	19.67 ± 1.0	−3.16 ± 3.0
THF	467.6	17.29 ± 0.4	−11.09 ± 4.0
DMF	544.0	17.7 ± 0.38	−9.6 ± 3.8

[a] Activation parameter taken from ref. 1. [b] Values calculated from activation parameters.

In addition to single parameters, some multiple parameter models were also examined. Equations (1)–(4) below involve a Koppel–Palm analysis by stepwise regression.[3]

$$\log k = -12.212 + 0.076B(\pm 0.017) \qquad (1)$$
$$r = 0.6 \qquad n = 15 \qquad \mathrm{cf}^* = 0.01$$

$$\log k = -13.421 + 0.100\,B(\pm 0.027) - 8.417 f(n)^2 (\pm 5.281) \qquad (2)$$
$$r = 0.66 \qquad n = 15 \qquad \mathrm{cf} = 0.01$$

$$\log k = -26.984 + 0.181\,B(\pm 0.046) - 9.961 f(n)^2 (\pm 4.848) + 0.084 f(\varepsilon)(\pm 0.044) \qquad (3)$$
$$r = 0.75 \qquad n = 15 \qquad \mathrm{cf} = 0.01$$

When 2-methoxyethanol was excluded, equation (3) becomes:

$$\log k = -18.505 + 0.120\,B(\pm 0.007) + 5.575 f(\varepsilon)(\pm 1.670) - 7.788 f(n)^2 (\pm 1.850) \qquad (4)$$
$$r = 0.967 \qquad n = 14 \qquad \mathrm{cf} = 0.01$$

The improvement of correlation upon exclusion of 2-methoxyethanol can be rationalized in terms of intramolecular hydrogen-bonding between the O–H and the OMe groups[3] which in turn relatively diminish the interactions with the $\overset{+}{N}$–$\overset{-}{O}$ dipole of the amine oxide molecule.

However, a less satisfactory correlation was obtained between log k and B, $f(\varepsilon)$ and E[equation (5)] when 2-methoxyethanol was also excluded:

$$\log k = -16.285 + 0.082\,B(\pm 0.020) - 0.031\,E(\pm 0.023) + 8.163 f(\varepsilon)(\pm 2.350) \qquad (5)$$
$$r = 0.923 \qquad n = 14 \qquad \mathrm{cf} = 0.01$$

The negative coefficient of E in equation (5) indicates that Lewis acidity retards this reaction, opposing the accelerating effect of solvent basicity and polarization.

The next two equations (6) and (7) involve Taft's polar substituent constant σ* and the Kirkwood dielectric function $f(\varepsilon)$:

$$\log k = -3.53 - 3.593\sigma^* \pm (0.401) \qquad (6)$$
$$r = 0.9 \qquad n = 11 \qquad \mathrm{cf} = 0.01$$

The correlation with Taft's polar substituent constant reflects the HBD ability of the hydroxylic solvents which strongly solvate the amine oxide molecule (Scheme 2) and thus a negative coefficient of σ* is obtained in equation (6). This correlation is slightly improved upon the inclusion of the Kirkwood dielectric function:

$$\log k = -6.326 - 4.218\sigma^*(\pm 0.484) + 5.943 f(\varepsilon)(\pm 3.140) \qquad (7)$$
$$r = 0.93 \qquad n = 11 \qquad \mathrm{cf} = 0.01$$

The correlation between log k and the solubility function of HCl in alcohols L was also considered [equation (8)]:

$$\log k = -7.180 + 4.225\,L(\pm 0.316) \qquad (8)$$
$$r = 0.94 \qquad n = 13 \qquad \mathrm{cf} = 0.01$$

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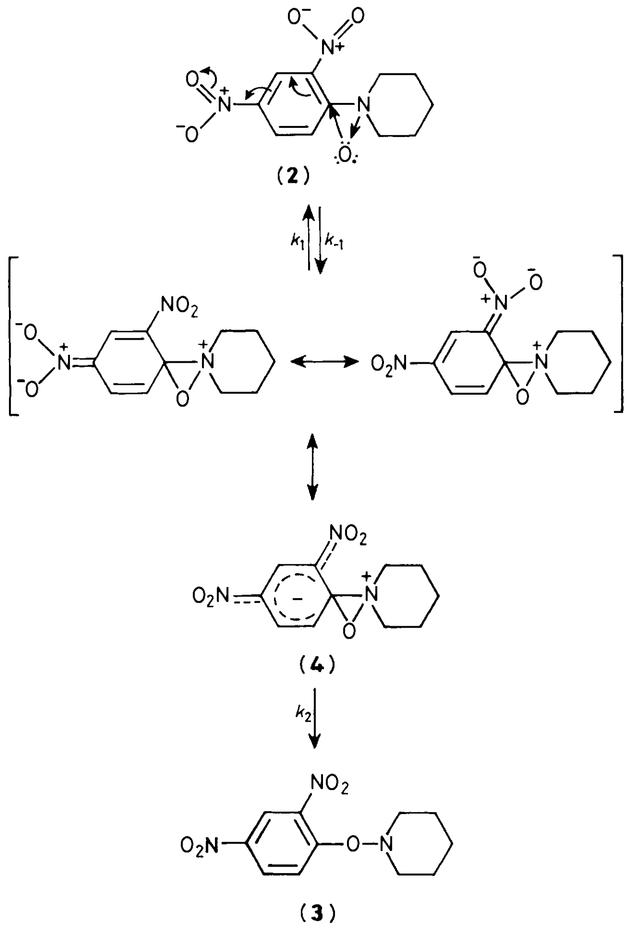
* cf = critical f value.



Scheme 3.

The introduction of Kirkwood function, showed a slight improvement in the correlation [equation (9)].

$$\log k = -9.639 + 4.689\,L(\pm 0.238) + 4.416\,f(\varepsilon)(\pm 1.120) \quad (9)$$
$$r = 0.977 \qquad n = 13 \qquad \mathrm{cf} = 0.01$$

The next set of equations (10)–(12) involve Kamlet–Taft parameters π^*,[8] α,[9] and β.[10] Values are available only for six alcohols (Table 1):

$$\log k = -1.697 - 1.791\alpha(\pm 0.303) \quad (10)$$
$$r = 0.9 \qquad n = 6 \qquad \mathrm{cf} = 0.01$$

$$\log k = -2.578 - 1.320\alpha(\pm 0.898) + 0.641\beta(\pm 1.135) \quad (11)$$
$$r = 0.91 \qquad n = 6 \qquad \mathrm{cf} = 0.01$$

$$\log k = -6.756 + 4.590\pi^*(\pm 2.970) - 0.655\alpha(\pm 0.850) + 2.131\beta(\pm 1.343) \quad (12)$$
$$r = 0.96 \qquad n = 6 \qquad \mathrm{cf} = 0.01$$

Here the hydrogen-bonding donor parameter α enters the stepwise regression firstly with a negative coefficient; this clearly indicates the importance of hydrogen-bonding to the reactant rather than to the transition state. On the other hand, the inclusion of β and π^* is irrelevant, although r is slightly improved, but the regression coefficients of β [equation (10)] and α [equation (11)] have appreciable standard error, in a manner that may change the course of interactions.

Although there is no critical definition available for the conditions under which each parameter must be used, it seems that the best approach by which to understand the solvent effects in this reaction is primarily in terms of nucleophilicity (or basicity), dielectric constant function $f(\varepsilon)$ [(equations (4) and (9)], and hydrogen-bonding donating ability of the solvent [equation (10)]. The mechanism of the rearrangement of the amine oxide (**2**) to the product (**3**) is best described in terms of three-membered cyclic transition state (**4**)[2] (Scheme 3).

Conclusions.—The activation parameters (Table 2) and the correlation with a variety of solvent parameters are in accord with the expected three-membered cyclic transition state. In the transition state (**4**) the negative charge is dispersed within the aromatic ring system and shielded by the two nitro groups, while the positive charge is localized on the nitrogen atom and thus exposed to the solvent molecules. Therefore, the solvation depends on the nucleophilic solvation capability of the solvent for which the parameters B and L are the preferred measures.

In the present work, the reactions in alcohols exhibit relatively higher enthalpy and entropy of activation than in aprotic solvents (Table 2). The overall reaction involves the conversion of a hydrogen-bonded amine oxide entity into a non-hydrogen bonded transition state and alcohol. This means that the process of desolvation has a positive entropy and this positive entropy is responsible for the observed increase in $\Delta S^{\ddagger}$.

On the other hand, the observed linear relationship between $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ ($r = 0.94$) for the reaction of (**2**), indicates that all alcohols have the same impact on the rate of isomerization of (**2**) *i.e.* they affect the reaction *via* the same interaction mechanism.[11]

Experimental

Reagents and Solvents.—*N*(2,4-Dinitrophenyl)piperidine *N*-oxide (**2**) and 1-(2,4-dinitrophenoxy)piperidine (**3**) were prepared and characterized as previously described.[12] Solvents were purified according to standard procedure described in reference 13. The middle fraction from the fractional distillation of each solvent was kept over molecular seives (4 Å) and used for kinetic studies.

Kinetics.—Reaction rates were determined spectrophotometrically by monitoring absorbance at $\lambda_{\max}$ of the rearrangement product (**3**). A Pye-Unicam SP800 spectrophotometer supplied with a Haake NK22 type thermostat was used. The temperature of the cuvette was kept constant within ±0.1 °C. Runs were carried out in duplicate to 90% completion at four or five temperatures. For every run, the 'infinity' value A_∞ was determined experimentally by leaving the solution of the amine oxide at the specified temperature until there was no further change in absorbance.

Stock solution was prepared by dissolving the freshly prepared amine oxide (**2**) in the appropriate solvent. A sample of this solution was diluted with solvent kept at constant temperature. Measurement of absorbance at $\lambda_{\max}$ of (**3**) began immediately.

Rate coefficients were calculated from the slope of ln ($A_\infty - A_t$) *vs.* time, and the rate coefficients are accurate to within $\leqslant$2–3%. The activation parameters were calculated with correlation coefficient (r): $0.99 \leqslant r \leqslant 0.999$.

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