Studies of Tertiary Amine Oxides. Part 7.† Solvent Effects on the Rearrangement of *N*-Arylamine Oxides to *O*-Arylhydroxylamines. The S_Ni Mechanism[1]

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The rate of rearrangement of *N*-arylamine oxides (**4**) to *O*-arylhydroxylamines (**5**) was measured in different solvents. The rate of isomerisation of *p*-nitrophenyl *N*-oxides correlates with the dielectric constants of aprotic solvents and with the hydrogen-bonding ability of protic solvents. The rearrangement of *o*-nitrophenyl *N*-oxides shows much less variation in rate with solvent polarity. All kinetic results are explained in terms of an intramolecular cyclic mechanism (S_Ni).

Tertiary amine oxides are a class of organic compounds whose chemistry has received much attention, partly because a number of these compounds are pharmacologically active,[2] and partly because of the interesting thermal rearrangements they undergo to the corresponding *O*-alkylhydroxylamines. A number of tertiary amine oxides, *e.g.* trimethylamine oxide, are naturally occurring.[3] Metabolic *N*-oxidation of tertiary amine drugs is well documented.[4–6] Tertiary amine oxides having no β hydrogen undergo a thermal isomerisation known as the Meisenheimer rearrangement.[7]

$$\underset{(1)}{R^1R^2R^3N\text{–}O} \longrightarrow \underset{(2)}{R^1R^2NOR^3}$$

Only certain groups (R^3) show a tendency for migration from N to O. These include allyl,[8] benzyl,[9] neopentyl,[10] tetrahalogenopyridyl,[11] and homoadamantyl[12] groups. We have recently reported on the migration of a benzene nucleus from N to O in substituted dimethylaniline oxides[13] and in *N*-arylpiperidines.[14] This paper describes the effect of solvents on this rearrangement.

Results and Discussion

The tertiary amines (**3**) were prepared by reaction of the appropriate secondary amines with *o*- and *p*-nitrofluorobenzene. Oxidation of (**3**) with performic acid produced the crystalline *N*-oxides (**4**) in good yields. The detailed physical and spectral characteristics of the amines and the *N*-oxides have been reported elsewhere.[14] The amine oxides (**4**) undergo thermal rearrangement to yield *O*-arylhydroxylamines (**5**) (Scheme 1). The properties of (**5**) have also been described earlier.[14]

The rate of rearrangement of *N*-(nitrophenyl) amine oxides (**4a**—**i**) was followed by u.v. spectroscopy in both aprotic and protic solvents and in THF–H_2O. In all cases, the rates were clearly first order and rate constants were found to be sensitive to solvent and structural changes in *N*-oxide.

Rearrangement of N-(4-*Nitrophenyl*)*amine Oxides.*—In aprotic solvents, the rate of rearrangement of the *p*-nitro *N*-oxides (**4a**—**e**) was found to be directly proportional to the dielectric constant of the solvent (Table 1, Figure 1). The dependence of rate on polarity of solvent can be understood in terms of increased solvation in the more ionic transition complex required by the intramolecular cyclic mechanism (S_Ni) of Scheme 2.

The effect of substitution in the saturated heterocyclic ring on the rate of rearrangement is clear from Table 1. The rate is lowest for the morpholino compound (**4e**). This can be traced to the electronegative oxygen in the ring which makes the oxygen of the N–O function less nucleophilic. The highest rate of the series in any single solvent was found with the 2-methylpiperidino compound (**4b**). Two factors may be responsible for this high rate; the inductive effect of the methyl group at position 2 and the relief of steric compression on going from reactant to product. The rate of isomerisation in dioxane for the 4-methylpiperidino compound (**4d**) is eight times faster than for the piperidino compound (**4a**) and half as fast as for the 2-methyl compound. This is due only to the inductive effect of the methyl group in the heterocyclic ring of (**4d**).

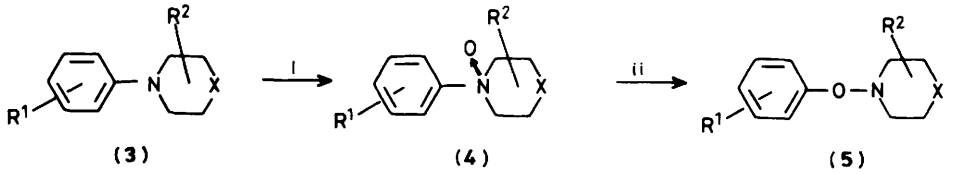
Much more striking is the dramatic rate-decreasing role played by hydrogen-bonding media. In hydroxylic solvents the rate of rearrangement is much smaller than in aprotic solvents, *e.g.* although ethanol has a higher dielectric constant than tetrahydrofuran (ε^{EtOH} 25, *vs.* ε^{THF} 7.5) the rate-constant ratio $k_{(4a)}^{THF}/k_{(4a)}^{EtOH}$ is 1.34×10^3.

Tables 2 and 3 list the rate constants in various alcohols and in THF–H_2O, respectively. The difference in rates of isomerisation in protic and aprotic solvents is largely due to hydrogen bonding. Hydrogen-bonded amine oxide molecules are far less reactive than non-hydrogen-bonded molecules. This is suggested by two observations. First, the rate of rearrangement decreases when water is added to THF; second, the rate decreases with increasing hydrogen-bonding ability of the alcohol. Among alcohols the rate of rearrangement is found to be in the order MeOH < EtOH < Pr^iOH < Bu^tOH. For example, for compound (**4b**) the rate is six times greater in Bu^tOH than in MeOH. This could be explained on the basis of the hydrogen-bonding ability of the alcohol. The bulk of Bu^tOH compared with methanol interferes sterically with formation of hydrogen-bonded amine oxide.

In THF–H_2O the effect of hydrogen bonding is once again indicated (Table 3). The rate of isomerisation drops largely when water is added to THF. For example $k_{(4b)}^{THF}/k_{(4b)}^{THF-15\%H_2O} = 1.8 \times 10^2$ and $k_{(4a)}^{THF}/k_{(4a)}^{THF-5\%H_2O} = 38$. Figure 2 shows the effect of added water on rate of rearrangement of compound (**4b**). The rate constant is inversely proportional to the number of moles of added water (Figure 3). Thus a linear decrease in the rate of rearrangement is observed with increasing hydrogen-bonding ability of the solvent.

Rearrangement of N-(2-*Nitrophenyl*)*amine Oxides.*—The rate of rearrangement of the *ortho* nitro compounds (**4f**—**i**) is much less sensitive to the solvent changes than that for the *p*-nitro congeners (Table 4). Contrary to the *p*-nitro compounds, a small decrease in rate of rearrangement of *o*-nitro *N*-oxides is indicated as the dielectric constant of the solvent is increased.

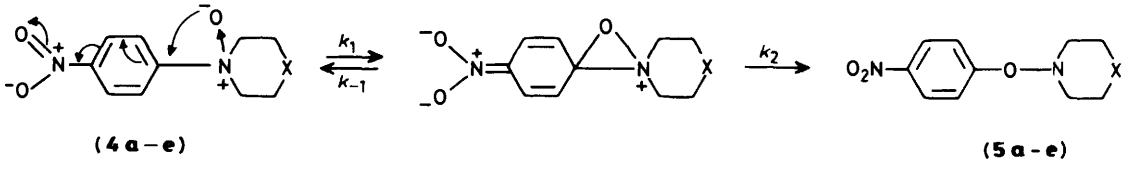
† Part 6 is ref. 16.



(3) (4) (5)

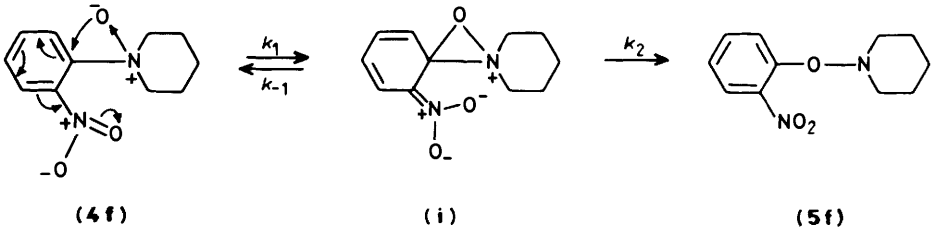
a; R^1 = 4-NO_2, R^2 = H, X = CH_2
b; R^1 = 4-NO_2, R^2 = 2-Me, X = CH_2
c; R^1 = 4-NO_2, R^2 = 3-Me, X = CH_2
d; R^1 = 4-NO_2, R^2 = 4-Me, X = CH_2
e; R^1 = 4-NO_2, R^2 = H, X = O
f; R^1 = 2-NO_2, R^2 = H, X = CH_2
g; R^1 = 2-NO_2, R^2 = 2-Me, X = CH_2
h; R^1 = 2-NO_2, R^2 = 3-Me, X = CH_2
i; R^1 = 2-NO_2, R^2 = 4-Me, X = CH_2

Scheme 1. *Reagents:* i, HCO_3H; ii, heat



(4a–e) (5a–e)

Scheme 2.



(4f) (i) (5f)

Scheme 3.

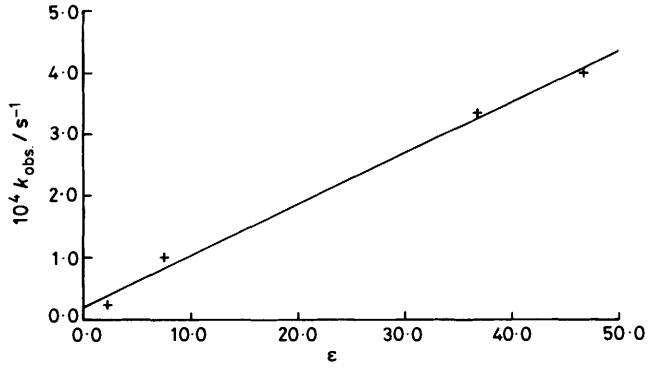


Figure 1. Variation of rate constant for rearrangement of (**4a**) with dielectric constant of aprotic solvents. Temp. 30 °C

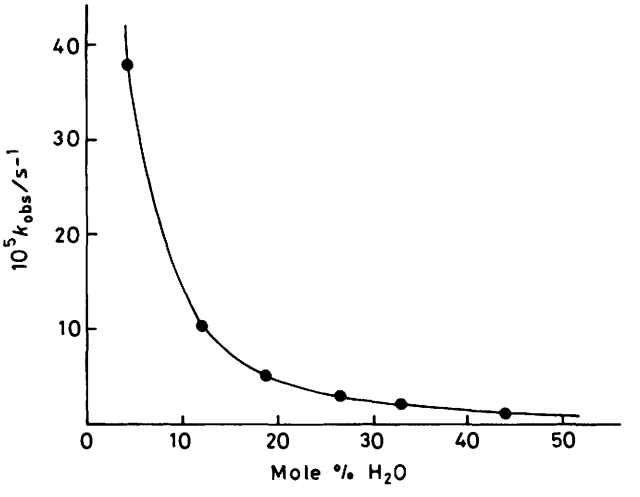


Figure 2. Variation of rate of rearrangement of (**4b**) with mole % added water in THF–H_2O. Temp. 30 °C

The fact that the rearrangement of *o*-nitrophenyl *N*-oxides shows much less variation in rate with solvent polarity could also be explained on the basis of the intramolecular cyclic mechanism (Scheme 3).

Inspection of Scheme 3 reveals that the geometry of the transition complex (or intermediate) (i) is such that the positive $\overset{+}{N}$–O pole can engage in direct electrostatic interaction with the negatively charged oxygen of the nitro group. This mutually satisfying electrostatic interaction decreases the need for solvation of these poles by external solvent molecules, and consequently the reaction rate is much less sensitive to changes in the solvent than is that for the *p*-nitrophenyl *N*-oxides.

It is of interest to note that the rate of rearrangement of the *N*-oxides of *p*-nitrophenylpiperidines is much faster in all solvents than the corresponding *o*-nitrophenyl congeners. For example, $k_{(4a)}^{30\,°C}/k_{(4f)}^{30\,°C}$ = 160 (dioxane), 920 (THF), and 4 500 (DMF) and $k_{(4d)}^{30\,°C}/k_{(4i)}^{30\,°C}$ = 1.4 × 10^3 (dioxane), 7.9 × 10^3 (THF), and 4.2 × 10^4 (DMF). The observed difference in rate between the two series is partly due to steric inhibition of conjugation of the *o*-nitro group with the ring. Inspection of Dreiding models clearly revealed a steric interference between the *o*-nitro group

Table 1. Kinetics[a] of rearrangement of *N*-(4-nitrophenyl)amine oxides in aprotic solvents

		$10^4\ k/s^{-1}$ [b]				
Solvent	ε	(4a)	(4b)	(4c)	(4d)	(4e)
Dioxane	2.21	0.23	3.72	0.096	1.88	0.024
THF	7.58	0.94	19.58	0.64	5.05	0.063
DMF	36.71	3.41	49.82[c]	1.81	28.41	0.297
DMSO	46.70	4.00				
		$\Delta H^{\ddagger}$/kcal mol^{-1}				
Solvent	ε	(4a)	(4b)	(4c)	(4d)	(4e)
Dioxane	2.21	19.67 ± 0.4	16.48 ± 0.3	21.3 ± 0.3	18.8 ± 0.4	22.75 ± 0.38
THF	7.58	19.24 ± 0.4	16.50 ± 0.4	19.8 ± 0.4	18.6 ± 0.3	22.9 ± 0.4
DMF	36.71	18.15 ± 0.4	18.2 ± 0.8	19.62 ± 0.4	17.5 ± 0.3	21.8 ± 0.4
DMSO	46.70	18.61 ± 0.5				
		$\Delta S^{\ddagger}$/cal mol^{-1} K^{-1}				
Solvent	ε	(4a)	(4b)	(4c)	(4d)	(4e)
Dioxane	2.21	−14.8 ± 4	−19.8 ± 3	−11.2 ± 4	−13.8 ± 3	−9.2 ± 4
THF	7.58	−13.4 ± 4	−16.5 ± 3.5	−12.1 ± 4.5	−12.2 ± 4	−6.8 ± 3
DMF	36.71	−14.5 ± 4	−9.0 ± 4	−10.9 ± 3.6	−10.9 ± 4	−7.3 ± 3.5
DMSO	46.70	−12.6 ± 4				

[a] Least-squares plots of ln*k* *vs.* $1/T$ were linear for all experiments. [b] Temperature 30 °C. [c] Calculated.

Table 2. Kinetics[a] of rearrangement of *N*-(4-nitrophenyl)amine oxides in alcohols

		$10^6\ k/s^{-1}$ [b]		$\Delta H^{\ddagger}$/kcal mol^{-1}		$\Delta S^{\ddagger}$/cal mol^{-1} K^{-1}	
Solvent	ε	(4a)	(4b)	(4a)	(4b)	(4a)	(4b)
Bu^{t}OH	11.6	0.47	3.94	23.4 ± 0.4	23.9 ± 0.3	−10.2 ± 4	−4.1 ± 1.7
Pr^{i}OH	19.4	0.12	2.52	26.3 ± 0.3	24.7 ± 0.4	−3.0 ± 2	−2.6 ± 2.6
EtOH	24.5	0.07	1.72	28.3 ± 0.4	25.1 ± 0.4	+2.0 ± 2	−2.1 ± 3.1
MeOH	32.7	0.023	0.67	29.6 ± 0.6	27.3 ± 0.3	+4.2 ± 3	+3.5 ± 4

[a,b] As Table 1.

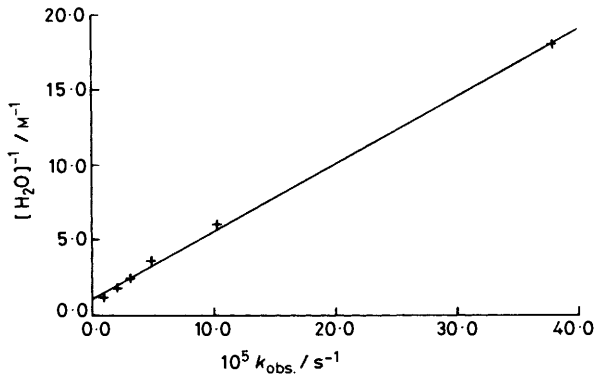


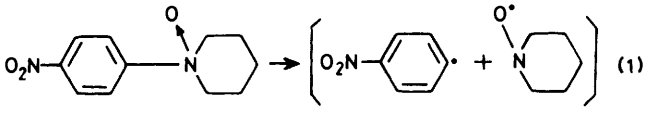
Figure 3. Plot of rate constant for rearrangement of (**4b**) against $1/[H_2O]$ in water–THF mixtures. Temp. 30 °C

and the axial and equatorial 2-H atoms of the piperidine ring. This crowding forces the *o*-nitro group to be inclined to the aromatic ring and not coplanar with it as in the *p*-nitro group. To the extent that the *o*-nitro group is inclined to the ring up to 90°, its conjugation with the aromatic ring will be reduced, thus reducing its ability to delocalise the incoming negative charge from the attacking oxygen of the ≥N–O function. Moreover, the differences in rate of isomerisation of the *p*-nitro and *o*-nitro *N*-oxides show large variations with solvents. The *para*:*ortho* ratio of rate increases as the dielectric constant of the solvent is increased. This is explicable in terms of the S_Ni mechanism. The transition complex for the *p*-nitro compounds is solvent stabilised while that of the *o*-nitro series is practically insensitive to solvent polarity.

Activation Parameters.—The energy of activation for the rearrangement of (**4a**—**i**) is little affected by the solvent and is generally small. The low $\Delta H^{\ddagger}$ value is consistent with a concerted mechanism in which the energy lost in breaking the carbon–nitrogen bond in (**4**) is compensated for in part by the energy gained in forming the new C–O bond in (**5**). The entropy of activation is negative in all cases, indicating a considerable decrease in randomness in the activated complex. This is in accord with the notion that a three-membered transition state is involved (Schemes 2 and 3).

The negative $\Delta S^{\ddagger}$ by itself excludes the intermediacy of free radical particles [equation (1)], and is more in support of a concerted process.

The rearrangement of tertiary *N*-oxides in some other



(1)

Table 3. Kinetics[a] of rearrangement of amine oxides (**4a,b**) in THF–water.

THF–H_2O (%v/v)	10^5 k/s^{-1} [b]		$\Delta H^{\ddagger}$/kcal mol^{-1}		$\Delta S^{\ddagger}$/cal mol^{-1} K^{-1}	
	(4a)	(4b)	(4a)	(4b)	(4a)	(4b)
0	9.39	195.8	19.24 ± 0.4	16.5 ± 0.4	−13.4 ± 4.0	−16.5 ± 3.5
1	2.42	37.9	20.37 ± 0.4	18.3 ± 0.3	−12.27 ± 2.0	−13.5 ± 1.7
2	1.04		22.2 ± 0.3		−7.9 ± 2.3	
3	0.31	10.66	23.7 ± 0.4	20.5 ± 0.3	−5.3 ± 2.0	−9.0 ± 2.0
5	0.25	5.66	24.13 ± 0.4	20.8 ± 0.3	−4.4 ± 2.7	−9.6 ± 2.0
7.5		3.4		21.7 ± 0.3		−7.3 ± 2.0
10		2.08		23.0 ± 0.4		−3.8 ± 1.7
15		1.06		23.9 ± 0.3		−2.6 ± 1.7

[a,b] As Table 1.

Table 4. Kinetics[a] of rearrangement of *N*-(2-nitrophenyl)amine oxides in aprotic solvents.

Solvent	ε	10^6 k/s^{-1} [b] (4f)	(4g)	(4h)	(4i)
Dioxane	2.2	0.14	10.38	5.81	0.13
THF	7.5	0.102	5.36	2.76	0.064
DMF	36.7	0.076	4.78	2.94	0.068

Solvent		$\Delta H^{\ddagger}$/kcal mol^{-1} (4f)	(4g)	(4h)	(4i)
Dioxane	2.2	24.8 ± 0.3	18.2 ± 0.4	19.2 ± 0.4	22.8 ± 0.3
THF	7.5	25.2 ± 0.3	22.15 ± 0.4	23.87 ± 0.3	23.6 ± 0.5
DMF	36.7	25.65 ± 0.4	20.4 ± 0.3	22.0 ± 0.4	24.5 ± 0.4

Solvent		$\Delta S^{\ddagger}$/cal mol^{-1} K^{-1} (4f)	(4g)	(4h)	(4i)
Dioxane	2.2	−8.0 ± 3.5	−21.2 ± 3	−19.7 ± 3.6	−14.7 ± 3
THF	7.5	−7.3 ± 2.4	−9.5 ± 4	−5.2 ± 3	−13.5 ± 3
DMF	36.7	−6.5 ± 3	−15.5 ± 3.7	−11.2 ± 5	−10.2 ± 4

[a,b] As Table 1.

systems[9] (*e.g.* *N*-benzyl-*N*-methylaniline *N*-oxide to *O*-benzyl-*N*-methyl-*N*-phenylhydroxylamine) is suggested to proceed by a radical cleavage–recombination mechanism. The rearrangement of the latter *N*-oxide in methanol is associated with a higher activation energy and a positive $\Delta S^{\ddagger}$ (+33 cal mol^{-1} K^{-1}) and this was taken to indicate a radical-pair mechanism. The results obtained in this and previous studies[14] are not consistent with a radical mechanism for the isomerisation of the *N*-oxides (**4a**—**i**) but with a concerted process. Thus the mechanistic difference depends on molecular environment and reactions.

Some changes of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ with changes in solvent have been observed in this study. These changes have some mechanistic implications and are found in Tables 2 and 3. With alcohols as solvents, it is clear that $\Delta H^{\ddagger}$ increases by 3—7 kcal mol^{-1} in passing from Bu^{t}OH to MeOH. A somewhat compensating entropy effect is seen in the increase in $\Delta S^{\ddagger}$ of *ca.* 7—14 cal mol^{-1} K^{-1} with the same solvent change. In alcohol, the hydrogen-bonded unreactive form of the amine oxide is predominant. The enthalpy associated with breaking an amine oxide–alcohol hydrogen bond must be added to the $\Delta H^{\ddagger}$ values for the rearrangement. In THF–water, a gradual increase in $\Delta H^{\ddagger}$ is observed as the proportion of water in the solvent is increased (Table 3). As water is added, the hydrogen-bonded unreactive molecules increase in proportion and this again adds to the enthalpy of activation an increment corresponding to breaking the hydrogen bond thus resulting in higher values of $\Delta H^{\ddagger}$ in this solvent composition.

In alcohols, or THF–water, the entropy of activation increases in value and becomes positive in methanol. In the overall reaction a hydrogen-bonded substrate is converted into a non-hydrogen-bonded transition state and a mole of alcohol or water is liberated into the medium. This equilibrium state is associated with a large positive entropy which must be added to the negative entropy associated with passage of non-hydrogen-bonded amine oxide to the three-membered transition state. Thus the overall entropy is positive or small negative.

Experimental

Instruments.—U.v. spectra were measured with a double-beam Pye–Unicam SP-800 spectrophotometer with SP-825 program controller; the temperature apparatus was of the Haake NK 22 type in which the stream of water is connected directly to the cell house.

A Hewlett–Packard 9830A PAC 9862 calculator plotter was used for plotting all kinetic data, using a polynominal regression program for plotting and calculating by the least-squares method.

Solvents.—Solvents used for kinetic measurements were purified as follows. THF was refluxed with lithium aluminium

hydride and fractionally distilled. Dioxane was purified by refluxing over sodium metal for 10 h and then fractionally distilled. Dimethylformamide was shaken with solid KOH for 3 h followed by fractional distillation, collecting the fractions at 152 °C. Absolute ethanol was redistilled. Methanol was dried by distillation from lithium aluminium hydride. Bu^{t}OH and isopropyl alcohol was purified according to reference 15. Dimethyl sulphoxide was of spectroscopic grade.

Starting Materials and Products.—The amines (**3a**—**i**) were prepared and purified as described earlier.[14] These amines were converted into their *N*-oxides by direct *N*-oxidation with performic acid as previously described.[14] Rearrangement of the *N*-oxide was performed in dioxane and the products were isolated and characterised as previously.[14]

Kinetics.—Reaction rates were determined spectrophotometrically by monitoring the absorbance at $\lambda_{max.}$ of the *N*-oxide (**4**) or the rearrangement product (**5**) as a function of time. Runs were carried out in triplicate at five temperatures (±0.2 °C) for each experiment up to at least three half-lives.

A stock solution was obtained by dissolving the amine oxide (0.01 g) in the appropriate solvent (10 ml). A sample of this solution was diluted with a thermostatted solvent in a volumetric flask (10 ml) to give (1—5) × 10^{-4}M solutions of the amine oxide. Measurement of absorbance at $\lambda_{max.}$ for the *N*-oxide or the rearrangement product was started immediately.

Reaction rate constants were calculated from the slope of $\ln(A_t - A_\infty)$ *vs.* time for experiments in which the rate of disappearance of the *N*-oxide was followed or from $\ln(A_\infty - A_t)$ *vs.* time in cases where the rate of product formation was followed. In all cases the least squares plots of $\log(A_t - A_\infty)$ or $\log(A_\infty - A_t)$ *vs.* time were linear.

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