Configurational Stability of Pyramidal Nitrogen in Spiro-oxaziridines

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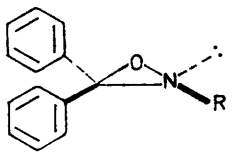
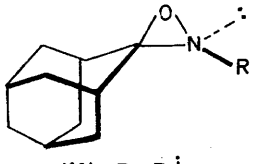
Several optically active spiro-oxaziridines, whose stabilities were sufficient to obtain nitrogen inversion barriers without decomposition, have been synthesized. The magnitude of these barriers is markedly dependent on the nature of both nitrogen and carbon ring substituents. The relatively small solvent effect on the rate of racemization is attributed to the low basicity of the nitrogen atom and also to steric inhibition of solvation. Nitrogen inversion at ambient temperature in one oxaziridine was observed.

ATTEMPTS over many years to isolate a stable nitrogen invertomer from amines have been frustrated by the low barriers to inversion. The incorporation of the nitrogen atom into a ring system and the presence of an additional neighbouring heteroatom increases the barrier, a phenomenon demonstrated experimentally in oxaziridines by the preferential formation of one enantiomeric [1-3] or one diastereomeric [1,4,5] form. Subsequent calculations [6] gave a barrier of *ca.* 32 kcal mol^{-1} for nitrogen atom inversion in oxaziridines. This heterocyclic system may be well suited for obtaining accurate experimental data on pyramidal inversion by kinetic methods. In practice however, the paucity of information available about inversion barriers in oxaziridines (compared with aziridines) is probably a result of the relative thermal instability and chemical reactivity of many oxaziridines. Thus in previous reports,[5,7] on the magnitude of nitrogen inversion barriers in oxaziridines, thermal decomposition was frequently noted.



(I) R = Pr^i
(II) R = Bu^t

(III) R = Pr^i
(IV) R = Bu^t



(V) R = Pr^i
(VI) R = Bu^t

The present results were obtained using optically active oxaziridines (I)—(VI) resulting from asymmetric oxygen atom transfer between (+)-peroxycamphoric acid and the imine,[1,2] the nitrogen and carbon ring substituents generally being selected to minimize decomposition under the experimental conditions employed. The racemization process was followed polarimetrically using a thermostatically controlled cell and an automatic photoelectric instrument. The possibility of decomposition was examined by using n.m.r. spectroscopy analytically in conjunction with an inert reference compound; no decomposition during the racemization studies was detected. The results of racemization of these oxaziridines are given in Table 1.

TABLE 1

First-order rate constants for thermal racemization of oxaziridines [a]

Compound	T/K	10^6k/s^{-1}	$\Delta G^{\ddagger}$/ kcal mol^{-1} [b]	Period of observation (h)
(I)	382·9	15·4 ± 0·3	31·55	5
	386·4	20·9 ± 0·9	31·60	2
(III)	384·8	34·9 ± 0·5	31·10	6
	386·8	39·9 ± 0·6	31·15	5
(V)	378·3	40·4 ± 1·8	30·45	3
	381·0	45·9 ± 0·4	30·55	5
(II)	333·2	87·7 ± 0·3	26·20	6
	351·7	751·0 ± 8·0	26·20	1
(IV)	332·6	277 ± 1·0	25·40	2
	342·4	841 ± 2·0	25·40	1
(VI)	335·1	780·0 ± 15·0	24·90	1
	293·0	3·46 ± 0·05	24·85	71

[a] All measurements were carried out using spectral grade tetrachloroethylene. [b] The quoted $\Delta G^{\ddagger}$ values refer to nitrogen inversion; the rate of nitrogen inversion is equal to half the rate (k) for racemization. The error in $\Delta G^{\ddagger}$ is $\leqslant$0·01 kcal mol^{-1}.

The rates of nitrogen inversion obtained for *N*-isopropyloxaziridines were always greater than those found by racemization of the corresponding *N*-t-butyl analogues. This result is in accord with previous observations [7] and may be interpreted in terms of the larger non-bonded interactions associated with the t-butyl group which causes further pyramidal destabilization relative to the planar transition state. The range of values shown for molecules bearing either an *N*-t-butyl (*ca.* 1·35 kcal mol^{-1}) or an *N*-isopropyl group (*ca.* 1·15 kcal mol^{-1}) clearly demonstrates the influence of geminal ring carbon atom substitution which is similar to the effect found in aziridines.[8] A possible interpretation [based on a comparison of values for (I) and (III) or (II) and (IV)] is that the steric requirements of aryl groups in a particular conformation may be slightly lower than those of a cyclic methylene group. This explanation should however be considered with caution in view of the small differences in $\Delta G^{\ddagger}$, the possible

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differences in solvation, electronic repulsions (or attractions) particularly between the aryl rings and the nitrogen lone pair, and conjugation between the aryl and oxaziridine rings.

N-t-Butyladamantanespiro-3′-oxaziridine (VI) is of particular interest for several reasons: (i) the oxaziridine ring does not have unsaturated or polar substituents and thus inter- and intra-molecular interactions should be relatively small; (ii) this crystalline oxaziridine displayed high chemical stability under a range of conditions; and (iii) the inversion barrier (Table 1) is lower than those previously reported for oxaziridines. Oxaziridine (VI) was thus considered to be the most satisfactory compound in Table 1 for a detailed kinetic study of solvent and temperature effects.

The value of solvent variation as an indicator of a pyramidal inversion mechanism is well established in aziridines.[9] The results in Table 2 show that the rate

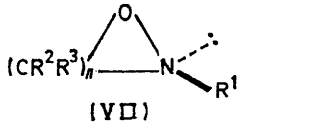
TABLE 2

A solvent study of first-order rate constants for racemization of oxaziridine (VI) at 323 K

Solvent	10^6k/s^{-1}	$\Delta G^{\ddagger}$/kcal mol^{-1} [a]
n-Heptane	219 ± 2	24·81
Carbon tetrachloride	210 ± 1	24·83
Tetrachloroethylene	182 ± 2	24·92
o-Dichlorobenzene	161 ± 1	25·00
Ethanol	157 ± 1	25·02
Ethanol–water (4 : 1)	139 ± 2	25·10

[a] The error in $\Delta G^{\ddagger}$ is $\leqslant \pm 0{\cdot}05$ kcal mol^{-1}. (See also footnote *b* in Table 1.)

of nitrogen inversion in (VI) is relatively insensitive to the solvent. These observations contrast with nitrogen inversion studies in several other systems where polar or hydroxylic solvents have been reported to increase the barriers by *ca.* 2 kcal mol^{-1}.[8,9] It is probable that the present diminution can be explained by the presence of a neighbouring heteroatom; however an increase of *ca.* 1·2 kcal mol^{-1} has been reported for perhydro-1,2-oxazolidines (VII; R^1 = Me, R^2 = R^3 = H, n = 3) and perhydro-1,2-oxazines (VII; R^1 = Me, R^2 = R^3 = H, n = 4).[10-12] Solvation of the oxaziridine ring in (VI) may be



(VI)

R^1 = alkyl, R^2,R^3 = H or alkyl

hindered by the considerable bulk of both the adamantyl and t-butyl substituents which would thus diminish the solvent effects. A recent report[13] of pyramidal inversion in acyclic chloramines showed no significant solvent effects. As in the latter example, the present results may be attributed mainly to the low basicity of the nitrogen atom (a common feature of stable nitrogen pyramids), but with an additional contribution from steric inhibition of solvation. Evidence has been reported[14] for preferential protonation of the oxygen rather than the nitrogen atom in oxaziridines.

Although the data in Table 2 indicate that for oxaziridine (VI) (VII; R^1 = Bu^t, R^2, R^3 = adamantylidene, n = 1)] $\Delta G^{\ddagger}$ is increased only by *ca.* 0·3 kcal mol^{-1} during the change from hydrocarbon to hydroxylic solvents (at identical temperatures), the trend is significant in view of the relatively small experimental error. The decrease in the rate of nitrogen inversion with polarity of solvent is in agreement with other systems[8] and is due to stabilization of the ground state which will have a larger net dipole than the transition state. Similarly the growth of $\Delta G^{\ddagger}$ values with increasing proton donor properties of the solvent is analogous to that observed in perhydro-1,2-oxazolidines and -1,2-oxazines,[10-12] but in view of the very small differences between the rates in o-dichlorobenzene and aqueous ethanol the effect of hydrogen bonding to the nitrogen lone pair in oxaziridine (VI) would appear to be small.

The nitrogen inversion barrier in the spiroadamantane (VI) was sufficiently low for the compound to show an appreciable decrease in optical activity over several hours at room temperature. It was thus necessary to utilize it immediately after synthesis and to store it at low temperature. While it was possible to isolate (VI) in an optically stable crystalline form, attempts to increase the optical purity by recrystallization (by analogy with previous successful efforts[4,7]) were hindered by the concomitant racemization process. This would appear to be the first report of an oxaziridine which undergoes a ready stereomutation at ambient temperature.

In order to determine $\Delta S^{\ddagger}$ and $\Delta H^{\ddagger}$ for pyramidal inversion the racemization of (VI) was studied over a range of temperatures in tetrachloroethylene and in n-heptane. While the former solvent has been used previously in oxaziridine inversion studies,[5,7] the latter was expected to provide a better analogy with the gas phase.[9]

A wide range of $\Delta S^{\ddagger}$ values has previously been found for nitrogen inversion although in general values of *ca.* +5 cal mol^{-1} K^{-1} have been assumed.[8] The present result of *ca.* −1 cal mol^{-1} K^{-1} is close to the expected value for an intramolecular pyramidal inversion process in the absence of any appreciable differential solvent effects.[8,15] Similarly both the activation energy (E_a) and the frequency factor (A) were in accord with expectations for such a unimolecular first-order reaction. The relative accuracy of these results stems from the mild experimental conditions, and the lack of decomposition or interaction with solvents.

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EXPERIMENTAL

Kinetics.—For temperatures below 333 K, the solutions were racemized in a thermostatically controlled polarimeter cell (±0·1 K). The instrument used was a Perkin-Elmer 141 automatic polarimeter and readings were taken at appropriate time intervals. Rotations were recorded as an average value from several readings; the average deviation was ±0·002°. At the outset of each kinetic experiment, *p*-dimethoxybenzene was added as an internal standard. On completion of the observations, the solutions were rechecked for decomposition by n.m.r. spectroscopy using a Varian A60 spectrometer. For temperatures above 333 K, the solutions were heated in an oil-bath (±0·1—0·2 K); aliquot portions were sequentially pipetted into sample tubes and quenched in an ice-bath, and the optical rotations were measured at 293 K.

The first-order rate constants of racemization were calculated from the slope ($-k/2{\cdot}303$) obtained from the best straight line (linear least squares) plot of $\log_{10}\alpha$ *versus* time. The Arrhenius activation energy [8] was calculated from the slope ($-E_a/2{\cdot}303R$) and the frequency factor A from the intercept of the best straight line (linear least squares) plot of $\log_{10}k$ *versus* $1/T$. $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ were determined from a plot of $\log_{10}(k/T)$ *versus* $1/T$. It should however be noted that the rate constant used in the Arrhenius and Eyring equations was the rate constant for nitrogen inversion and not the rate constant for racemization; the latter is twice the former.[16] All calculations were carried out using an Olivetti P602 desk computer and a linear regression (least squares) programme.

Imine and Oxaziridine Syntheses.—The imine precursors of oxaziridines (I)—(IV) were synthesized according to the literature procedures.[17-19] The previously unreported *adamantylidene-isopropyl-* and *-t-butyl-amines* were synthesized by the titanium chloride catalysed route;[17,20] isopropyl, 80% yield, b.p. 60° at 0·15 mmHg (Found: C, 81·5; H, 11·2; N, 7·55. $C_{13}H_{21}N$ requires C, 81·6; H, 11·05; N, 7·3%); and t-butyl, 79% yield, b.p. 115° at 1·5 mmHg (Found: C, 81·8; H, 11·3; N, 7·0. $C_{14}H_{23}N$ requires C, 81·9; H, 11·3; N, 6·8%).

TABLE 3

First-order rate constants for thermal racemization of oxaziridine (VI) in tetrachloroethylene and n-heptane at different temperatures [a]

Solvent	T/K	10^6k/s^{-1}	$\Delta H^{\ddagger}$/kcal mol^{-1}	E_a/kcal mol^{-1}	$\log_{10}(A$/s$^{-1})$	$\Delta S^{\ddagger}$/cal mol^{-1} K^{-1}
Tetrachloroethylene	335·1°	780·00 ± 15·0				
	323·0	182·0 ± 2·0				
	313·0	57·10 ± 0·9	24·3 ± 0·3	25·1 ± 0·3	13·0 ± 0·2	−1 ± 1
	303·0	13·80 ± 1·1				
	293·0	3·46 ± 0·02				
n-Heptane	333·0	713·00 ± 7·0				
	323·0	219·00 ± 2·0				
	313·0	17·20 ± 0·8	24·4 ± 0·4	25·0 ± 0·4	13·3 ± 0·3	−1 ± 1
	303·0	17·60 ± 0·4				
	293·0	3·96 ± 0·03				

[a] All activation parameters refer to nitrogen inversion.

TABLE 4

Optically active oxaziridines

Compound	Yield (%)	M.p. (°C) [a] [b.p.(mmHg)]	$[\alpha]_D^{20}$ (°) [b]	Formula	Found (%) C	Found (%) H	Found (%) N	Required (%) C	Required (%) H	Required (%) N
(I)	80	44	−35·2	$C_{16}H_{17}NO$	80·6	7·3	5·7	80·4	7·2	5·9
(II)	90	102	−82·1 [c]	$C_{17}H_{19}NO$	80·9	7·7	5·3	80·7	7·6	5·5
(III)	55	[68—72(10)] [d]	−3·1 [e]							
(IV)	80	[35(0·1)]	−16·3	$C_{10}H_{19}NO$	71·1	11·5	8·3	71·0	11·3	8·3
(V)	65	[66(0·2)]	−8·2	$C_{13}H_{21}NO$	75·2	10·2	6·9	75·3	10·2	6·8
(VI)	90	57—58	−5·3	$C_{11}H_{23}NO$	75·9	10·2	6·3	76·0	10·5	6·3

[a] Solids were crystallised from aqueous methanol. [b] All optical rotations were measured in spectral grade chloroform immediately after oxidation of imine without recrystallization or distillation (which could alter both m.p. and $[\alpha]_D$). [c] Previously reported $[\alpha]_D^{25}$ −54° (chloroform) increasing to $[\alpha]_D^{25}$ −258° (chloroform), m.p. 117·5—118·5°, on recrystallization.[7] [d] Lit.,[18] b.p. 72—74 °C at 8 mmHg. [e] Previously reported $[\alpha]_D^{25}$ −4·6° (neat.)[2]

Oxaziridines were prepared in two steps from the corresponding ketones *via* the imines by low temperature oxidation with (+)-peroxycamphoric acid.[1,2] The physical properties of all oxaziridines are given in Table 4.

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