Slow Nitrogen Inversion–N–O Rotation in 2-Alkoxy-1,1,3,3-tetramethylisoindolines

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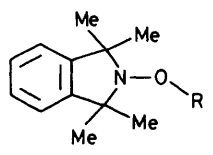
2-Alkoxy-1,1,3,3-tetramethylisoindolines appear to undergo a coupled N-inversion–N–O-bond-rotation with free energies of activation of approximately 55—75 kJ mol^{-1}.

We have recently prepared[1] a large number of 2-alkoxy-1,1,3,3-tetramethylisoindolines (**1**). The signals due to the ring methyl groups in both ^{1}H and ^{13}C n.m.r. spectra of these compounds are markedly dependent on the nature of the pendant R group and the temperature. At room temperature, they occur as a broad hump, a sharp singlet, or a doublet,† or (for chiral R) as three or four sharp singlets. In general, the signals occur as a multiplet at lower temperatures, coalesce to a broad hump at intermediate temperatures, and sharpen to a singlet at higher temperatures. This phenomenon is clearly due to the correspondence of the time-scales of the stereomutation process in these isoindolines and the n.m.r. experiment. The coalescence temperatures (T_c) and free energies of activation ($\Delta G_c^{\ddagger}$) have been determined for a series of these compounds, and for one compound in a series of solvents, from the effect of temperature on the ^{1}H n.m.r. spectra‡ using standard equations.[2,3] Values are given in Table 1.



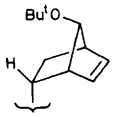
(**1**)

The subject of stereomutation in a wide range of alkoxyamines has recently been reviewed.[4,5] Stereomutation in alkoxyamines requires both inversion at the N atom and rotation about the N–O bond. Experimental and theoretical evidence based on simple alkoxyamines has been presented to show that the two processes occur sequentially and not simultaneously.[5] For example, semi-empirical calculations showed that the energy barrier to rotation about the N–O bond in *N,N*-dimethylhydroxylamine with N in the pyramidal ground state is less than half that with N in the planar transition state. Thus, much of the n.m.r. data has been used in an attempt to identify which of the two processes is rate-determining. Evidence is generally based on the observed changes in $\Delta G_c^{\ddagger}$ with the nature of the groups attached to the alkoxyamines and with the solvent. There is no doubt that in some cases inversion is rate-determining whilst in others rotation is rate-determining. However, in many cases the evidence is conflicting leading to uncertain conclusions.[5] With the structurally analogous sulphenamides, on the other hand,

† In the general case when R was not chiral, two ^{1}H resonances were observed separated by about 50 Hz at a field of 7 T, while the two methyl ^{13}C resonances always occurred at approximately δ 29.5 and 25.4, corresponding to methyl groups *syn* and *anti* to the nitrogen lone-pair respectively; see also, R. G. Bryant, *J. Chem. Educ.*, 1983, **60**, 933.

‡ Similar results were obtained by ^{13}C n.m.r. spectroscopy. For example (**1**, R = Me) had a coalescence temperature of 305 K and a free energy of activation of 57.5 kJ mol^{-1} while (**1**, R = CH_2Ph) had a coalescence temperature of 320 K and a free energy of activation of 60.7 kJ mol^{-1} ($CDCl_3$).

Table 1.

R	Solvent	$T_c(\pm 2)$/K	$\Delta\nu$/Hz	$\Delta G_c^{\ddagger}(\pm 0.5)$/kJ mol^{-1}
Me	$CDCl_3$	272	53.2	55.6
$-CH_2C(CO_2Me)=CH_2$	$CDCl_3$	285	50.8	58.5
	$CDCl_3$	315	50.3	64.9
$-CMe_2CO_2Me$	$(CD_3)_2SO$	>363	48.4	>75
CH_2Ph	CS_2	308	38.7	64.1
CH_2Ph	$CDCl_3$	285	32.7	59.5
CH_2Ph	CD_3OD[a]	275	41.4	56.8
CH_2Ph	$CDCl_3$, H^+ [b]	322	94.9	64.7

[a] Contains 20% $CDCl_3$. [b] 2 drops of CF_3CO_2H added.

the observed trends are clear-cut and indicate that in the majority of cases bond rotation is rate-determining.[5]

With the series of isoindolines studied in this work (Table 1) there is a definite increase in $\Delta G_c^{\ddagger}$ with increasing bulk of the substituent on oxygen, *i.e.* from methyl to primary to secondary to tertiary, there is a significant decrease in $\Delta G_c^{\ddagger}$ with solvent polarity, and there is also a considerable increase on protonation. These observations are inconsistent with either rotation or inversion being individually rate-determining; the bulk effect strongly suggests that rotation is involved whilst the solvent and protonation effects suggest that inversion is involved.[6] Bulk effects are unlikely to influence the inversion process, since these compounds are known to have close to normal pyramidal conformations at the N atom in the ground state§ (in some alkoxyamines, bulky substituents have caused a lowering of the inversion barrier due to destabilisation of the ground state[5]). Although there is little experimental information on the influence of solvents on pure rotational processes in alkoxyamines, it is most improbable that the observed substantial effects could be attributable to a pure rotational process. This and the more compelling evidence from the protonation experiment strongly suggest that inversion is part of the rate-determining process.

We have studied molecular models to consider the possibility that the rate-determining step for stereomutation in these sterically crowded alkoxyamines involves simultaneous inversion and rotation, *i.e.* a coupled motion. Unlike simple alkoxyamines, it is immediately apparent that rotation about the N–O bond has a very much easier path when the N atom is in the planar transition state than when it is in the pyramidal ground state.¶ Thus we consider that the stereomutation process in these isoindolines involves simultaneous inversion and rotation such that $\Delta G_c^{\ddagger}$ can be influenced by effects on either process as observed experimentally.

This conclusion is consistent with the observations of Bushweller *et al.*[7] who noted that in the case of simple alkylamines, the barrier to nitrogen inversion is generally significantly higher than that for rotation about C–N bonds but in the case of *hindered* amines such as *N*-t-butyl-*N*,*N*-dialkylamines, rotation and inversion may proceed *via* a common potential surface.

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References

1 See for example, R. D. Grant, P. G. Griffiths, G. Moad, E. Rizzardo, and D. H. Solomon, *Aust. J. Chem.*, 1983, **36**, 2447, and references contained therein.
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6 D. L. Griffith and J. D. Roberts, *J. Am. Chem. Soc.*, 1965, **87**, 4089.
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§ In the case of tertiary groups it was not possible to obtain the coalescence temperature as, above 363 K, decomposition to produce the stable nitroxide radical 1,1,3,3-tetramethylisoindol-2-yloxyl (and consequent line broadening) was apparent.

¶ An *X*-ray structure analysis on an alkoxyamine (**1**, R = 1-vinyl-5-oxopyrrolidin-2-yl) has established that the isoindoline nitrogen is indeed pyramidal (bond angle at N of 109.3°): W. K. Busfield, L. M. Engelhardt, P. C. Healy, I. D. Jenkins, S. Thang, and A. H. White, in preparation.