N-Acyloxaziridines: Characterization of both Nitrogen Inversion and N–C(O) Bond Rotation in an Amido System

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Variable temperature ^{13}C NMR investigations reveal that the *N*-acyl oxaziridine system can exhibit two independent stereodynamic processes: nitrogen inversion becomes slow on the NMR timescale at *ca.* −20 °C ($\Delta G^{\ddagger}$ 10.9–11.9 kcal mol^{-1}) and at *ca.* −60 °C rotation about the N–C(O) bond also becomes slow ($\Delta G^{\ddagger}$ 10.2 kcal mol^{-1}).

It is well known that amides normally have a considerable barrier to rotation about the N–C(O) bond, typically 15–20 kcal mol^{-1}.‡ Indeed, this stereodynamic process has probably been the subject of more NMR investigations than any other.[1] In contrast there appear to have been no NMR measurements of the barrier to inversion at amido nitrogen,§ and inversion and rotation in N–C(O) systems have not previously been characterized in the same molecule. Molecular orbital calculations indicate that the inversion barrier in amido systems is usually either extremely small or non-existent (coplanar trigonal nitrogen).[3]

We now report on some amido derivatives **1–4**, which exhibit highly unusual inverse behaviour in that the barrier to inversion at nitrogen is considerable and indeed higher than the barrier to N–C(O) rotation.

The ^{1}H and ^{13}C NMR spectra of the *N*-acyloxaziridines **1–4**, recorded at ambient temperature, were fully in accord with their structure though the ^{1}H NMR spectra were less informative owing to the complex overlapping signals from the cyclohexyl moiety.¶

On cooling below 0 °C (in CD_2Cl_2 solution) the ^{13}C NMR signal attributed to the cyclohexyl α-carbons (C-4/C-8) in compounds **1–4** broadened and between −15 and −40 °C split into two signals of equal intensity (Fig. 1). None of the other ^{13}C NMR signals exhibited similar behaviour in this temperature range.‖

Assuming conventional geometry, the only conceivable stereodynamic process which, when rendered slow on the NMR timescale could lead to the chemical shift nonequivalence of C-4 and C-8 is inversion at the nitrogen atom. Slow rotation about the N–C(O) bond or slow cyclohexyl ring inversion would be expected to lead to unequal splitting of all the ^{13}C NMR signals owing to the presence of unequally populated rotamers or invertomers (see below). The marked upfield shift of C-4 relative to C-8 (Table 1) by the γ-effect of a *syn* nitogen substituent is typical of a slowly inverting oxaziridine nitrogen as observed, for example, in the *N*-diphenylphosphinoyl analogue of **1–4** where C-4 and C-8 resonate at δ 30.5 and 36.1, respectively under conditions of slow nitrogen inversion.[5]

The nitrogen inversion barriers in **1–4** (Table 1), determined by iterative computer lineshape analysis,[6] are to our knowledge the lowest reported for an oxaziridine and the highest experimentally determined for an *N*-carbonyl system. The *N*-acyl group lowers the oxaziridine inversion barrier from 31.1 kcal mol^{-1} in the *N*-isopropyl analogue[7] to *ca.* 12 kcal mol^{-1} in **1–4**. This large effect is due to strong stabilizing

Table 1 Dynamic ^{13}C NMR data for the first stereodynamic process (nitrogen inversion) in *N*-acyloxaziridines[a]

Compound	δ_C[b] C-4	C-8	T_C/°C[c]	k_1/s^{-1}	$\Delta G_1^{\ddagger}$[d] /kcal mol^{-1}[e]
1	31.3	34.8	−17.9	400	11.8
2	31.3	34.8	−15.2	450	11.9
3	31.5	34.7	−37.2	360	10.9
4	30.4	34.2	−28.1	150	11.8

[a] Determined in CD_2Cl_2 solution at 67.8 MHz **1–3** or at 22.5 MHz **4**. [b] Measured between −30 and −45 °C where nitrogen inversion was slow on the NMR timescale. [c] Coalescence temperature of C-4/C-8 signals at which the exchange rate k_1 was determined. [d] Accuracy ±0.1 kcal mol^{-1}. [e] 1 cal = 4.184 J.

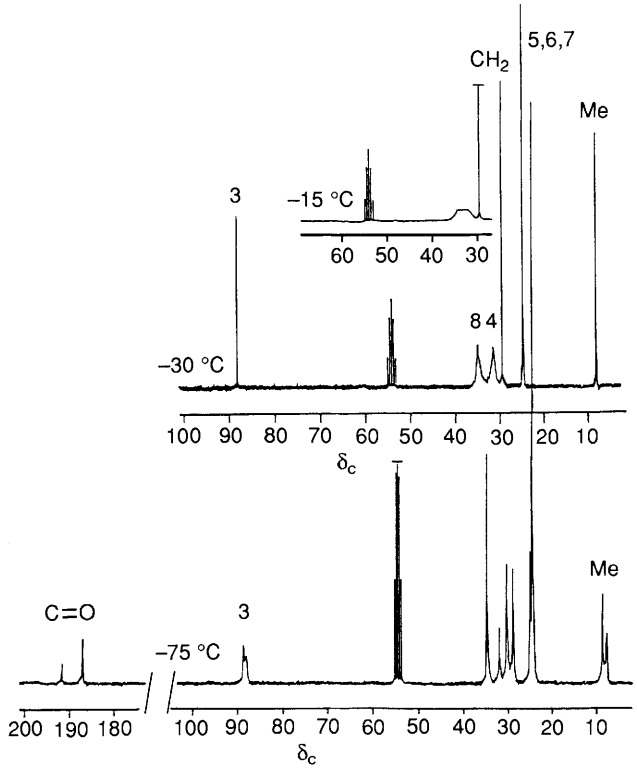

Fig. 1 ^{13}C NMR spectra (67.8 MHz, CD_2Cl_2) of **2** at −75 (lower), −30 (middle) and −15 °C (upper). The multiplet signal at δ 54 is due to the solvent.

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‡ 1 cal = 4.184 J.

§ Nitrogen inversion barriers have, however, been measured in a urea derivative containing an aziridine ring and in carbamate esters containing aziridine or trisaziridine moieties.[2] The N–C(O) π-conjugation in these compounds is weaker than that in amides.

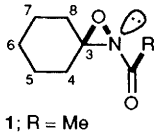
¶ The *N*-acyloxaziridines **1–4** and **6** were prepared by the method reported by Schmitz and Schramm[4] involving *in situ* acylation of 1-oxa-2-azaspiro[2.5]octane. It was found to be advantageous to use freshly prepared hydroxylamine-*O*-sulfonic acid rather than commercial material. Satisfactory elemental microanalyses were obtained for the previously unreported compounds **2**, **3** and **6**.

‖ In principle, slow nitrogen inversion should also cause inequivalence of C-5 and C-7. However these carbons are rather distant from the nitrogen substituent hence a small unresolved chemical shift difference is not unexpected (this signal is also overlapped by C-6).

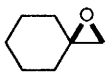
Table 2 Dynamic ^{13}C NMR data for the second stereodynamic process in *N*-acyloxaziridines[a]

Compound	Signal	δ_{major}[b]	δ_{minor}[b]	Rotamer ratio	T_C/°C[c]	k_2/s^{-1}[d]	$\Delta G_2^{\ddagger}$[d,e] /kcal mol^{-1}
1	C-4	30.2	32.2	1.0:0.61	−57.2	160 (260)	10.3 (10.1)
2	CH_3	8.4	7.5	1.0:0.65	−65.8	102 (160)	10.1 (9.9)
3	CH_2Ph	42.4	43.1	1.0:0.60	−72.1	48 (81)	10.1 (9.9)

[a] Determined in CD_2Cl_2 solution at 67.8 MHz **1** and **3** or at 100.0 MHz **2**. [b] Measured at *ca.* −80 °C where the second process was slow on the NMR timescale. [c] Coalescence temperature of the designated signals at which the exchange rate k_2 was determined. [d] Values quoted are major → minor rotamer; values in parentheses are minor → major rotamer. [e] Accuracy ±0.2 kcal mol^{-1}.



1; R = Me
2; R = Et
3; R = CH_2Ph
4; R = $C_6H_4NO_2$-4



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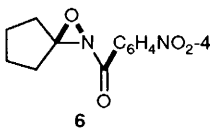

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π-conjugation in the transition state for nitrogen inversion where the oxaziridine nitrogen is coplanar. However this conjugative effect is probably weak in the pyramidal ground state owing to the high s-character of the oxaziridine nitrogen lone pair electrons. Support for this view comes from the IR carbonyl stretching frequencies of 1740 for **1–3** and 1710 cm^{-1} for **4**, which are abnormally high for *N*-carbonyl systems.

On further cooling below −40 °C, the acyl carbonyl, the alkyl signals and the cyclohexyl C-3 and C-4 signals in compounds **1–3** broadened to differing extents. At *ca.* −75 °C these signals were split into two components of unequal intensity, see Fig. 1. This second stereodynamic process is assigned to slow rotation about the N–C(O) bond as it causes the largest chemical shift splitting of the C-4, R group, and especially the C=O signals (Fig. 1).

Lineshape analysis at the coalescence temperature for appropriate signals afforded the torsional barriers reported in Table 2.[6] These barriers are much lower than those for N–C(O) rotation in conventional amides owing to the reduced π-conjugation in *N*-acyloxaziridines. Indeed, there could be a considerable steric component in the N–C(O) rotational process in **1–3**. Compound **4** did not show evidence of this second stereodynamic process in the ^{13}C NMR spectra, presumably owing to either a lower N–C(O) torsional barrier or to an undetected proportion of the minor rotamer.

On further cooling below −80 °C many of the ^{13}C signals in compounds **1–4** started to broaden again and at *ca.* −95 °C they were split into two new components of unequal intensity. Lineshape analysis of this third stereodynamic process gave free energies of activation in the range 8.7–9.5 kcal mol^{-1}. This third stereodynamic process is assigned to slow cyclohexyl ring inversion as the measured barriers are similar to that reported for cyclohexyl ring inversion in 1-oxaspiro[2.5]octane **5**, $\Delta G^{\ddagger}$ 9.1 kcal mol^{-1}, though the possibility that the second process is due to cyclohexyl ring inversion and the third process is N–C(O) bond rotation cannot be completely excluded. Further support for the assignment of the third process to ring inversion derives from the observation that compound **6**, the cyclopentyl analogue of **4**, does not exhibit any dynamic ^{13}C NMR behaviour in the temperature range −70 to −130 °C. At −50 °C compound **6** showed a large splitting (3.3 ppm) of the C-4/C-7 resonance and a small splitting (0.6 ppm) of the C-5/C-6 resonance owing to slow nitrogen inversion.

Received, 11th May 1992; Com. 2/02429B

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