Conformational assignments and a nitrogen inversion process in some 3-acyloxy-1,3-oxazinanes by NMR and X-ray analysis

Syed M. A. Hashmi,[a] Mohammed I. M. Wazeer,[a] M. Sakhawat Hussain,[a] Joseph H. Reibenspies,[b] Herman P. Perzanowski[a] and Sk. Asrof Ali*[a]

[a] *Chemistry Department, King Fahd University of Petroleum and Minerals, Dhahran 31261, Saudi Arabia*
[b] *Texas A & M University, College Station, TX 77840, USA*

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The stereochemistry of the preferred conformers of several 3-acyloxy-1,3-oxazinanes has been established by NMR spectroscopy. A strong anomeric effect stabilizes the conformation having an equatorial orientation of the lone pair on nitrogen. A nitrogen inversion process was found to be the rate-limiting process in the conformational equilibria. The range of $\Delta G^{\ddagger}$ values was found to be 60–71 kJ mol^{-1}. Solid state structures as determined by X-ray diffraction confirm the findings of the NMR study.

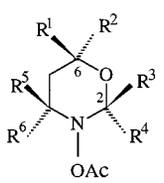
The nitrogen stereochemistry as well as preferred conformations of a variety of 1,3-oxazinanes have been studied in some detail.[1–6] The conformation and configuration of these compounds as well as ring and nitrogen inversion barriers have been established using NMR spectroscopy. Theoretical calculations[2] on 3,5-dimethyl-1,3-oxazinane predicted that the chair conformation is preferred over the twist form by an energy difference of approximately 21 kJ mol^{-1}, which is essentially of the same order of magnitude as for unsubstituted cyclohexane (23 kJ mol^{-1}). Analysis[2] based on ^{1}H NMR data for 2-methyl-1,3-oxazinanes indicated that the carbon moiety of the ring is somewhat flattened in comparison to cyclohexane. However it has been shown for the highly substituted saturated oxazines that the conformational equilibria includes sizable proportions of both the chair and twist forms. Both 3-methyl- and 3,6-dimethyl-1,3-oxazinane have been shown[2,3] to favour an *N*-axial methyl group in an approximate ratio of 60 : 40.

Fast nitrogen inversion and ring inversion (with comparable energy barriers) often complicate the conformational analysis of the saturated oxazinanes as well as other heterocycles. However, the nitrogen inversion barrier is expected to be much higher[7,8] where an electronegative oxygen is directly attached to the nitrogen, as in 3-acyloxy-1,3-oxazinanes **5** (Scheme 1). To the best of our knowledge the stereochemistry and inversion barriers of 3-acyloxy-1,3-oxazinanes have not been reported to date, and herein we report the synthesis and NMR study of the conformational behaviour, nitrogen inversion barriers and anomeric effect in these compounds (Table 1) having a variety of substituents.

Results and discussion

The 3-acyloxy-1,3-oxazinanes required for the present work were prepared as outlined in Scheme 1. As reported,[9] the isoxazolidines **1** having no hydrogen at C3, on MCPBA-induced ring opening, afforded either the nitrone **3** in equilibrium with its cyclic tautomer **4** or a mixture of **2**, **3** and **4** in case of isoxazolidines having a C3-H. The nitrone **3** ⟺ hydroxylamine **4** equilibrium constants[9] depend on the number of substituents and the positions they occupy. In a few cases the equilibrating mixtures of **3** and **4** were prepared[9] by the condensation reaction of 3-hydroxylaminopropan-1-ol with

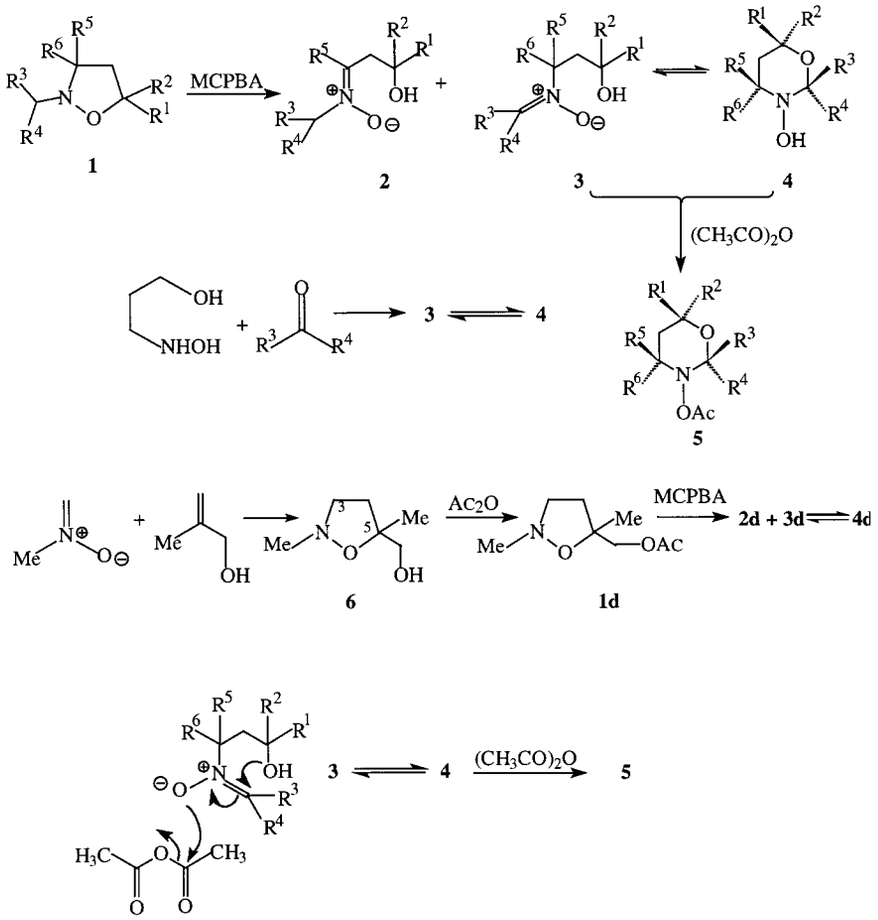
Table 1 Free energy of activation ($\Delta G^{\ddagger}$) for major ⟺ minor isomerization in $CDCl_3$ and percentage composition of the conformers



5

5	R^1	R^2	R^3	R^4	R^5	R^6	Composition[a] of conformers (%)	$\Delta G_f^{\ddagger}$/ kJ mol^{-1} [b]	$\Delta G_r^{\ddagger}$/ kJ mol^{-1} [c]
a	H	H	H	H	H	H	~100 (**A**)	63.4	63.4
b	$CH_2OSiMe_2Bu^t$	H	H	H	H	H	~100 (**A**)	—	—
c	H	H	Me	H	H	H	95 (**A**) 5 (**E**)	ND[d]	ND[d]
d	CH_2OAc	Me	H	H	H	H	75 (**A**) 25 (**D**)	64.4	61.7
e	H	H	Me	Me	H	H	~100 (**A**)	60.5	60.5
f	Ph	H	Me	H	H	H	92 (**A**) 8 (**E**)	67.3	61.2
g	Ph	H	H	H	H	Et	77 (**A**) 23 (**D**)	60.8	57.8
h	Ph	H	Me	H	Et	H	93 (**A**) 7 (**E**)	71.0	64.6
i	Ph	H	H	H	Me	Me	~100 (**A**)	—	—

[a] Type of conformer (from Scheme 2) shown in parenthesis. [b] For the Major→Minor isomerization at 298 K. [c] For the Minor→Major isomerization at 298 K. [d] Not determined.



Scheme 1

formaldehyde, acetaldehyde and acetone (Scheme 1). In most cases it is rather difficult to isolate the hydroxylamine **4** in pure form unless the equilibrium favours the cyclic form overwhelmingly. This is indeed a problem in the study[10] of the inversion barriers and conformational analysis of the 3-hydroxy-1,3-oxazinanes **4**. However the tautomerization process can be arrested by acetylating the hydroxy substituent. Either the nitrone **3** or the cyclic hydroxylamine **4** or a mixture of both on treatment with acetic anhydride leads to the formation of the acetylated derivative **5**. As shown in Scheme 1, the nitrone functionality is activated by acetic anhydride (Lewis acid) towards the internal attack by the γ-hydroxy group.

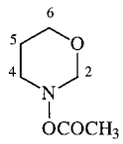
The diacetyl derivative **5d**, one of the important compounds required for our investigation, was prepared as shown (Scheme 1). The isoxazolidine **6**, prepared by cycloaddition reaction of *N*-methylmethyleneamine *N*-oxide with methallyl alcohol, on treatment with acetic anhydride afforded the acetyl derivative **1d** which was converted to **5d** *via* the sequence discussed above.

Most of the oxazinanes studied showed broad ^{1}H NMR signals at 0 °C to ambient temperatures. However lowering the temperature resulted in the sharpening of the signals, and at sufficiently low temperatures (0–30 °C) the spectra revealed the existence of two equilibrating isomers in most cases. The conformational equilibria of the 3,6-disubstituted derivatives are shown in Scheme 2. The conformation **A** with an axially disposed acyloxy group and an equatorial substituent at C6 is assumed to be the most stable isomer. The axial preference is attributed to the anomeric stabilization owing to the antiperiplanar n–σ* interaction involving the equatorial nitrogen lone pair with the antibonding orbital of the C–O bond.[11,12] The conformer **A** has the lone pair and bonds around N–O formally eclipsed[3] and N–O bond rotation has to traverse a pathway with a very high energy barrier of *ca.* 50 kJ mol^{-1} to the less stable staggered conformations. All the conformers (**A**–**H**) can manifest an anomeric effect involving the antiperiplanar equatorial lone pair on oxygen and the σ* orbital of the C–N bond. However this interaction is not so significant since the C–N bond is a relatively weak acceptor and oxygen a relatively weak donor. Ring inversion is expected to be a relatively much faster process with a barrier[1] of around 37 kJ mol^{-1}. However, the electronegative oxygen attached to nitrogen raises the nitrogen inversion to such an extent that both the inversion and N–O bond rotation have considerable and comparable energy barriers. As a consequence, there has been considerable controversy[13,14] as to whether nitrogen inversion or N–O rotation or a complex composite of both in an energy saving pathway is the rate limiting process.

A typical spectral feature[1–6,15] of 1,3-dioxane, six-membered lactones and oxazinanes in their chair conformation is that the C5 axial hydrogens resonate at lower field than the equatorial hydrogens. The conformer with a large $J_{2a,2e}$ value of 11.5 Hz has an equatorial lone pair and axial substituent at nitrogen, whereas a geminal coupling constant of ~7.5 Hz has the opposite orientation of the lone pair. The chemical shifts of the C2 protons in the conformer (type **A**) (Scheme 2) are also reversed, *i.e.* the axial protons appeared downfield. Conformers **C**, **F**, **G** and **H** with a staggered orientation around the N–O bond, and **B** and **D** with a C6 axial substituent will not have adequate populations as far as NMR detection is concerned. The conformational network would involve several nitrogen inversion ($\mathbf{N}_i$), ring inversion ($\mathbf{R}_i$) and N–O bond rotation ($\mathbf{B}_r$) processes. Slowing of only one or two of the three orthogonal conformational processes in Scheme 2 will not lead to any spectral change since all conformers may still interconvert rapidly. All three orthogonal conformational processes must be slowed down on the NMR time-scale to observe the presence of two conformers (say **A** and **E**).

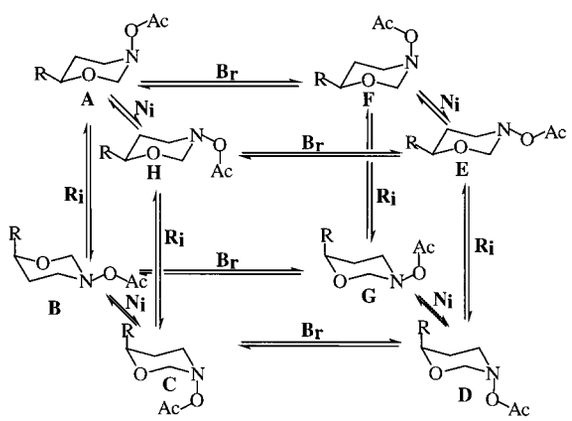
The composition of conformers along with energy barriers

Table 2 ^{13}C NMR chemical shifts[a] of compounds **5**



Compound	Conformer	C-2	C-4	C-5	C-6	$COCH_3$	CO	Others[b]
5a	Major	83.84	51.55	20.66	66.83	19.87	169.85	
5b	Major	83.72	51.57	22.59	76.72	19.84	169.84	$SiMe_2$ −5.35; CH_2 65.99; SiC 18.45; 3-Me 25.85
5c	Major	88.29	52.67	19.50	67.24	19.63	170.44	Me 18.71
	Minor	92.42	52.67	26.53	67.24	19.63	169.92	18.71
5d	Major	78.08	47.47	24.91	71.87	19.81	169.71	Me 16.34; OAc, 21.13; CH_2 71.24; CO 171.28
	Minor	78.63	48.15	26.57	71.87	19.81	169.71	25.96 63.73
5e	Major	88.57	47.73	19.03	60.26	19.73	170.16	Me 21.77; Me 26.83
5f	Major	88.85	53.19	26.37	78.71	19.60	170.44	Me 18.68; ^{i}141.0; ^{o}126.02; ^{p}127.97; ^{m}128.53
	Minor	92.27	55.67	33.83	79.39	19.60		18.68
5g	Major	79.43	61.12	30.07	73.06	20.03	169.77	Me 11.55; CH_2 23.76; ^{i}141.18; ^{o}125.87; ^{p}127.94; ^{m}128.50
	Minor	78.71	58.37	29.74	72.11	19.67	170.25	Me 10.30; CH_2 26.01; ^{i}138.15; ^{o}126.33; ^{p}127.46; ^{m}128.82
5h	Major	89.10	64.33	31.32	78.68	19.15	171.14	Me 18.05; CH_2 26.11; Me 10.60; ^{i}141.14; ^{o}126.03; ^{p}127.92; ^{m}128.52
	Minor	91.95	66.09	38.13	79.18	19.15	170.50	17.34 25.33 9.41; ^{i}140.50; ^{o}124.30; ^{p}125.50; ^{m}127.2
5i	Major	80.11	57.29	38.66	74.07	19.63	170.22	Me 28.21; Me 24.37; ^{i}141.19; ^{o}125.86; ^{p}127.93; ^{m}128.50

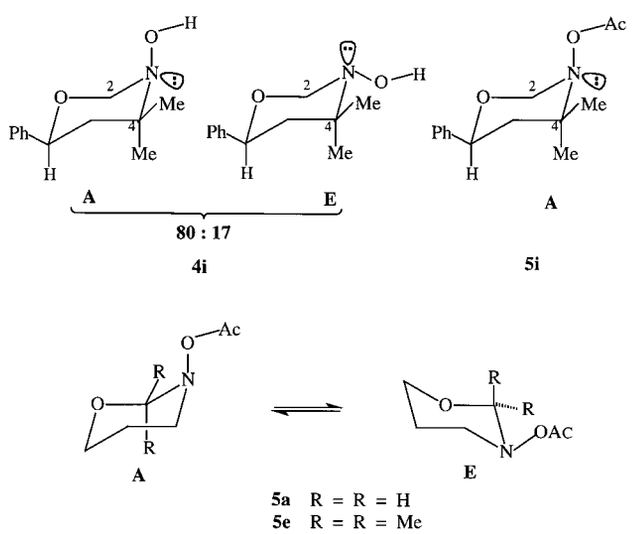
[a] In ppm relative to internal TMS. [b] i, o, p and m refer to *ipso*, *ortho*, *para* and *meta* carbons of the phenyl group, respectively.



Scheme 2 N_i = nitrogen inversion, R_i = ring inversion, B_r = N–O bond rotation.

($\Delta G^{\ddagger}$) for the rate limiting process in the conformational equilibria of the compounds **5** are given in Table 1. The low temperature ^{1}H NMR data are incorporated in the Experimental section. The ^{13}C NMR chemical shifts are given in Table 2. Compounds **5a**, **5b**, **5e** and **5i** existed as a single conformer in each case; even at −95 °C (CD_2Cl_2) no minor conformer was detected in the ^{1}H and ^{13}C NMR spectra. Geminal coupling constants in the range 12.1–12.5 Hz ($^{2}J_{2a,2e}$) clearly demonstrate the presence of a single conformer of type **A** (Scheme 2) with axial orientation of the acyloxy group. A strong anomeric effect thus dictates the selection of the preferred conformer. The substituent at C6 for compounds **5b** and **5i** occupies an equatorial position as expected. The axial nature of the C6-H was conformed by the large values for the vicinal coupling constants ($^{3}J_{5a,6a}$ > 12 Hz).

While the hydroxy compound **4i** has been shown[10] to have conformer types **A** and **E** in a respective ratio of 83 : 17, the absence of the minor form **E** in **5i** could be attributed to the augmented *gauche* interaction a sterically more demanding acyloxy group must experience with the 4,4-dimethyl groups (Scheme 3). A similar explanation can be put forward for the exclusive presence of the conformer **A** for the compound **5e**. While the conformers **A** and **D** are a diastereomeric pair for compounds **5b** and **5i**, they become enantiomers for the parent (**5a**) and the 2,2-dimethyl compound (**5e**) (Scheme 2). As such,

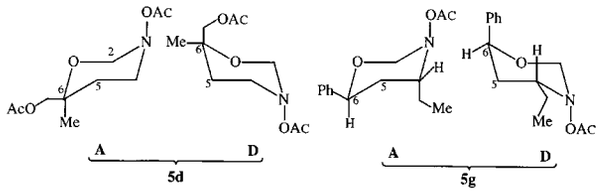


Scheme 3

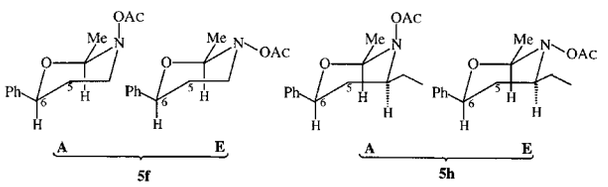
degenerate racemization at higher temperature led to the collapse of the AB quartet (C2-H_2 of **5a**) and the two singlets (C2-Me_2 of **5e**) into a singlet in each case. For the latter compounds (**5a**, **5e**), the minor conformers (type **B** or **E**), if present, may not be detected by NMR spectroscopy since they may be interconverting with the conformers **A** or **D** by a very fast chair inversion process, even at −95 °C (CD_2Cl_2).

The ^{1}H NMR analysis clearly demonstrated the presence of the diastereomeric pair **A** and **D** for the compounds **5d** and **5g**. The $^{2}J_{2a,2e}$ value of 12.5 Hz in each of the four conformers in Scheme 4 confirms the presence of axially-oriented acyloxy groups. Various *J* values and ^{13}C NMR chemical shifts indicated the major conformer as **A** in each case. For instance, the axial and equatorial orientation of C6-H for compound **5g** in conformation type **A** and **D**, respectively, is clearly demonstrated by coupling constants. For the compounds **5f** and **5h**, the $J_{5,6}$ values confirm the presence of conformers **A** and **E**, with both having axially-oriented hydrogen at C6 (Scheme 5). A strong anomeric effect is expected to favour isomer **A** in each of these compounds.

The ^{13}C NMR signals of the ring carbons were assigned unequivocally by general chemical shift arguments and DEPT



Scheme 4



Scheme 5

analysis and are included in Table 2. The C2 and C5 atoms were assigned the lowest and highest field signals, respectively, because of the former being adjacent to two electronegative atoms whereas the latter is adjacent to none. Of the remaining two carbons, the C6, being adjacent to a more electronegative oxygen, was assigned the lower field signal. For the compounds **5c**, **5f** and **5h** the most significant difference in chemical shift was observed for the C5 atom, a downfield shift of about 7 ppm for the minor isomer indicating the equatorial orientation of the acyloxy substituent at the nitrogen. The upfield shift of C5 in the major isomer is attributed to the γ-*gauche* effect[16] of the axially oriented acyloxy group. The ^{13}C NMR spectra gave further credence to the assignment, based on the ^{1}H NMR spectral analysis, that the acyloxy groups in compounds **5d** and **5g** occupy axial positions in both the major and minor invertomers. As such, while the difference in C5 chemical shift in **5d** is not so significant, the axial CH_3 in **5d-A** and axial CH_2O in **5d-D** appeared upfield by 9.6 and 7.5 ppm, respectively. Similar observations were made for C5 and the CH_2 carbon of the ethyl group in compound **5g**. The C2-methyl group in both the major (**A**) and minor (**E**) conformers of **5c**, **5f** and **5h** remained in the equatorial position as demonstrated by the chemical shift values of around 18 ppm. A similar observation was made for the related *N*-methyl-1,3-oxazinanes.[2]

The energy barriers (Table 1) for the overall interconversion process for compounds **5a** and **5d** were similar in magnitude, however it is less by about 3 kJ mol^{-1} for compounds **5e** and **5g**. The latter compounds have a more crowded environment around nitrogen than the former, hence the decrease of the energy barrier with the increase of steric crowding points toward the nitrogen inversion as the rate-limiting process.[3] Steric crowding raises the ground state energy, and the extended CNC angle of 120 °C at the sp^2-hybridized planar transition state can tolerate the bulky environment better and as such the transition state energy is decreased.[13] Had the N–O rotation been the rate limiting process, then compounds **5e** and **5g** would have higher energy barriers than **5a** and **5d** since a crowded environment impedes rotation. Several of the corresponding *N*-hydroxy compounds[9] **4** do not exist in the cyclic form; they remain in the acyclic nitrone form **3**. However we were able to compare the barrier for the acyloxy compound **5h** ($\Delta G^{\ddagger}$ 71.0 kJ mol^{-1}) with that of the corresponding hydroxy derivative **4h** ($\Delta G^{\ddagger}$ = 72.7 kJ mol^{-1}).[10] The steric acceleration[13] of the inversion process in **5h** (in comparison to **4h**) indicates the nitrogen inversion as the rate limiting process in the interconversion potential energy diagram. Among the acyloxy derivatives studied, **5h** is found to have the highest energy barrier for the overall inversion process. The presence of alkyl substituents in **5h** at both the positions adjacent to nitrogen presumably increases the N–O rotational contribution to the overall inversion process which is mainly controlled by nitrogen inversion.[13]

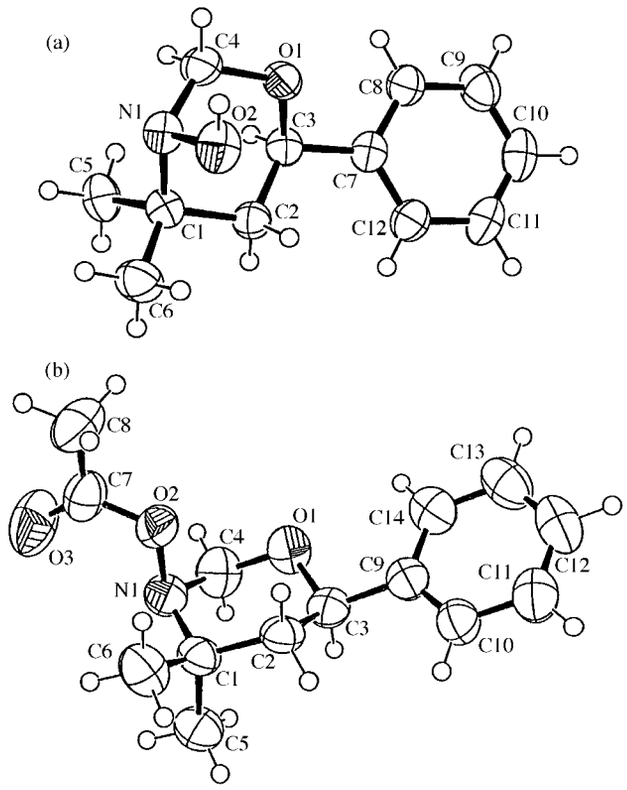


Fig. 1 (*a*) X-Ray structure of 3-hydroxy-4,4-dimethyl-6-phenyl-1,3-oxazinane (**4i**). (*b*) X-Ray structure of 3-acyloxy-4,4-dimethyl-6-phenyl-1,3-oxazinane (**5i**).

In order to compare (and also confirm) the NMR results, X-ray structures of compounds **4i** and **5i** were determined, and the ORTEP drawings of the two compounds are given in Fig. 1. As is evident from the drawing of **5i**, the N–O and C=O bonds are in a *cis* planar arrangement as expected,[17] with a N(1)–O(2)–C(7)–O(3) dihedral angle of 2.1°. The dihedral angles C(1)–N(1)–O(2)–C(7) and C(4)–N(1)–O(2)–C(7) are −124.9 and 117.9°, respectively. Assuming the lone pair on N(1) is symmetrically disposed with respect to C(1) and C(4), the O(2)–C(7) bond of the oxygen substituent was found to be within 3.5° of eclipsing the nitrogen lone pair. In the crystalline state compound **5i** adopts a chair conformation with an axially-oriented acyloxy group, showing a similarity of structure in both solution and the solid state.

Even though the hydroxylamine **4i** adopts a chair conformation in the crystalline state, it is interesting to note that the substituents and lone pairs around the N(1)–O(2) bond are not formally eclipsed, remaining instead in a staggered orientation. The dihedral angles C(1)–N(1)–O(2)–H(C2) and C(4)–N(1)–O(2)–H(C2) were found to be −179.8 and 61.7°, respectively. The (x, y, z) fragment is related to the (2 − x, −y, 1 − z) fragment through a center of inversion. The hydrogen attached to O(2) is hydrogen bonded to N(1) in the other fragment with a O(2)–H(C2)···N(1) distance of 2.835 Å representing a strong hydrogen bond. The position of the hydrogen atom H(C2) is thus clearly determined by intermolecular hydrogen bonding rather than any intramolecular interactions. However, as in the case of acyloxy derivative **5i**, the hydroxy substituent in **4i** also occupies an axial position owing to anomeric stabilization. While the dihedral angles in compound **5i** around C(4)–N(1), C(4)–O(1), O(1)–C(3) were found to be −56.2, −61.3, −57.2°, respectively, the dihedral angles around N(1)–C(1), C(1)–C(2) and C(2)–C(3) were found to be +48.7, −49.6, −53.3°. The chair conformation is thus found to be somewhat flattened in the carbon moiety, whereas the part containing the heteroatoms is more puckered.

Experimental

The variable temperature ^{13}C NMR spectra were recorded on a JEOL Lambda-500 NMR spectrometer, operating in the Fourier transform mode, with a digital resolution of 0.31 Hz at 125.65 MHz. The spectra were recorded in $CDCl_3$ and in CD_2Cl_2 with TMS as internal standard; *J* values are given in Hz. The spectra were obtained in the usual way with wide band proton decoupling, and multiplicities of signals were determined using DEPT experiments. The temperature was calibrated using standard chemical shifts of methanol and glycol for low and high temperatures respectively. The temperatures were accurate to ±0.5 °C. ^1H NMR spectra were recorded at 500.00 MHz on the above instrument and assignments of proton chemical shifts were confirmed by decoupling experiments.

The exchange-affected ^1H NMR spectra were recorded at 500 MHz over a temperature range of −20 to +50 °C. The C(2) protons of **5a** showed an AB pattern at low temperature and a singlet at high temperature. This exchange can be depicted as AB ⟺ BA, and the simulations of spectra were carried out using a computer program ABSHAPE.[18] For compounds **5d** and **5g**, the C(2) proton signals, which showed two AB patterns of unequal populations at low temperature, were utilized for the exchange studies. This exchange can be depicted as AB ⟺ A′B′, and the simulations of spectra were carried out using the computer program ABEX. The C(2) methyls of compound **5e** gave a doublet at low temperature and a singlet at high temperature. This case was treated as a simple A ⟺ X system with equal populations, and the simulations were carried out using the computer program AXEX.[18] For compounds **5f** and **5h**, both the signals of the benzylic proton at C(6) and the proton at C(2) were utilized. The C(6) proton region showed two dd [coupling to protons at C(5)] of unequal population at low temperature, whereas the C(2) proton showed two 1:3:3:1 quartets due to coupling to the methyl group at C(2). Simulations of exchange-affected spectra of **5f** and **5h** were carried out using a modification[18] to the library program AXEX[19] for the non-coupled two-site exchange. The first order couplings of the protons were assumed to be giving overlapping two-site exchanges with the same population ratio and equal rates of exchange.

The matching of simulated and experimental spectra was carried out by eye to yield the rate constants. The activation parameters $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ were calculated from plots of ln (*k*/*T*) *vs.* 1/*T*. It is well known[20] that NMR bandshape fitting frequently gives rather large but mutually compensating systematic errors in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$, and these are not reported here. However, bandshape fitting is viewed as a method of obtaining rather accurate values (probable to within ±0.3 kJ mol^{-1} for $\Delta G^{\ddagger}$ in the vicinity of the coalescence temperature). The $\Delta G^{\ddagger}$ values calculated are shown in Table 1.

All melting points are uncorrected. Elemental analyses were performed on a Fisons instruments Elemental Analyser 1108, IR spectra were recorded on a Nicolet 5 DXB FTIR and are reported in wavenumbers (cm^{-1}). Silica gel chromatographic separations were performed with flash silica gel (Baker Chemicals Co). The procedure for the preparation of individual compounds along with their characterization and low temperature NMR data (at 500 MHz) of the compounds are as follows.

General procedure for the preparation of acetyl derivatives

The acetyl compounds **5a**, **5b**, **5h** and **5i** were prepared from the corresponding 3-hydroxy-1,3-oxazinanes[9] **4a**, **4b**, **4h** and **4i** as described below. Acetic anhydride (1.2 mmol) was added to a solution of the hydroxylamine **4** (1.0 mmol) in CH_2Cl_2 (3 cm^3) at 0 °C and the mixture stirred at 0 °C for 1 h. After removal of solvent and excess acetic anhydride the product was purified by passing through a short column of silica using Et_2O–hexane (5:1) as the eluant to give the acetate **5** in 70–85% yield.

The compounds **5c** and **5g** were produced from the corresponding equibrating mixtures of **3c** ⟺ **4c**, and **3g** ⟺ **4g**, respectively, using the above procedure. Compounds **5d** and **5f** were prepared from the corresponding mixtures of **2d** + **3d** ⟺ **4d** and **2f** + **3f** ⟺ **4f**, respectively. Finally the nitrone **3e** was acetylated to afford the compound **5e**. The isolated yields of the acetylated compounds **5** were in the range 45–65% based on the amount of **3** ⟺ **4** in a mixture of **2** + **3** ⟺ **4**.

For the present work 2,5-dimethyl-5-hydroxymethylisoxazolidine **6** was prepared by the reaction of *N*-methylmethyleneamine *N*-oxide with methallyl alcohol in 90% yield as colourless liquid using a procedure reported earlier[21] (Found: C, 55.0; H, 9.9; N, 10.6. $C_6H_{13}NO_2$ requires C, 55.04; H, 9.96; N, 10.66%); ν_{max}(neat)/cm^{-1} 3416, 2989, 2931, 2871, 2853, 1458, 1404, 1375, 1309, 1056, 881 and 790; *m*/*z* 131 (M^+ 100%). The ^1H NMR signals at ambient temperature were broad due to nitrogen inversion: δ_H 1.27 (3 H, s), 2.02 (2 H, m), 2.49 (2 H, m), 2.70 (3 H, s), 3.31 (1 H, br s, OH), 3.55 (2 H, m).

The isoxazolidine **6** (6.0 mmol) in CH_2Cl_2 (5 cm^3) on treatment with acetic anhydride (8.0 mmol) at 25 °C (2 h) afforded the compound **1d** as a colourless liquid in almost quantitative yield. An analytical sample of **1d** was prepared by passing through a short silica gel column using 5:1 hexane–Et_2O as eluant (Found: C, 55.5; H, 8.7; N, 8.0. $C_8H_{15}NO_5$ requires C, 55.47; H, 8.73; N, 8.09%); ν_{max}(neat) 2974, 2946, 2872, 2846, 2776, 1740, 1458, 1372, 1308, 1238, 1040, 952, 890 and 810; *m*/*z* 173 (M^+ 24.6%). The ^1H NMR signals at ambient temperature were broad due to nitrogen inversion: δ_H 1.33 (3 H, s), 2.10 (3 H, s), 1.95–2.30 (2 H, m), 2.52 (1 H, m), 2.70 (3 H, s), 3.25 (1 H, m), 4.02 (2 H, m).

Compound **1d**, on peracid-induced ring opening,[9] afforded a mixture of isomers **2d**, **3d** ⟺ **4d** in almost quantitative yield. Solutions of the acetates **5** should not be warmed since heating leads to decomposition. Samples were kept in the freezer to avoid decomposition.

3-Acyloxy-1,3-oxazinane (5a). Colourless liquid (Found: C, 49.6; H, 7.55; N, 9.7. $C_6H_{11}NO_3$ requires C, 49.64; H, 7.64; N, 9.65%); ν_{max}(neat)/cm^{-1} 2984, 2930, 1768, 1658, 1440, 1366, 1208, 1156, 1072, 1016, 942, 886 and 808; *m*/*z* 145 (M^+, 10.1%); δ_H(Major) (−30 °C) 1.40 (1 H, br d, *J* 12.3 Hz, C5-H_{eq}), 2.17 (3 H, s), 2.40 (1 H, app q, *J* 12.3 Hz, C5-H_{ax}), 3.37 (1 H, dt, *J* 3.4, 13.8 Hz, C4-H_{ax}), 3.48 (1 H, app d, *J* 14.6 Hz, C4-H_{eq}), 3.81 (1 H, dt, *J* 2.2, 12.1 Hz, C6-H_{ax}), 4.13 (1 H, app d, *J* 11.9 Hz, C6-H_{eq}), 4.57 (1 H, d, *J* 12.1 Hz, C2-H_{eq}), 4.78 (1 H, d, *J* 12.1 Hz, C2-H_{ax}).

3-Acyloxy-6-*tert*-butyldimethylsiloxymethyl-1,3-oxazinane (5b). Colourless liquid (Found: C, 53.8; H, 9.3; N, 4.7. $C_{13}H_{27}SiNO_4$ requires C, 53.96; H, 9.41; N, 4.84%); ν_{max}(neat)/cm^{-1} 2954, 2928, 2856, 1762, 1670, 1472, 1464, 1362, 1252, 1206, 1102, 1078, 1050, 1006, 938, 838 and 778; *m*/*z* 290 [$(M + 1)^+$, 10.8%]; δ_H(Major) (−30 °C) 0.09 (3 H, s), 0.10 (3 H, s), 0.91 (9 H, s), 1.47 (1 H, d, *J* 12.6 Hz, C5-H_{eq}), 1.99 (1 H, dq, *J* 3.7, 13.4 Hz, C5-H_{ax}), 2.15 (3 H, s), 3.35 (1 H, dt, *J* 3.5, 13.4 Hz, C4-H_{ax}), 3.54 (1 H, app dd, *J* 2.0, 15.0 Hz, C4-H_{eq}), 3.61 (1 H, m, C6-H_{ax}), 3.74 (2 H, m), 4.58 (1 H, d, *J* 12.4 Hz, C2-H_{eq}), 4.86 (1 H, d, *J* 12.4 Hz, C2-H_{ax}).

3-Acyloxy-2-methyl-1,3-oxazinane (5c). Colourless liquid (Found: C, 52.8; H, 8.3; N, 8.7. $C_7H_{13}NO_3$ requires C, 52.81; H, 8.23; N, 8.80%); ν_{max}(neat)/cm^{-1} 2992, 2961, 2919, 2846, 1760, 1145, 1394, 1366, 1254, 1204, 1150, 1108, 1082, 1001, 957, 918, 861 and 835; *m*/*z* 159 (M^+, 78%); δ_H(Major) (−30 °C) 1.32 (3 H, d, *J* 5.8 Hz, and 1 H, overlapping, C5-H_{eq}), 2.19 (3 H, s, and an overlapping 1 H, m, C5-H_{ax} at 2.23), 3.38 (1 H, dt, *J* 3.7, 14.0 Hz, C4-H_{ax}), 3.52 (1 H, br d, *J* 14.0 Hz, C4-H_{eq}), 3.86 (1 H, dt, *J* 2.3, 11.6 Hz, C6-H_{ax}), 4.16 (1 H, ddd, *J* 2.3, 3.4, 11.6 Hz,

C6-H_{eq}), 4.55 (1 H, q, *J* 5.8 Hz, C2-H_{eq}). Non-overlapping peaks for minor conformer appeared at 1.75 (1 H, br d, *J* 13.8 Hz, C5-H_{eq}), 2.75 (1 H, m), 3.57 (1 H, m), 3.99 (1 H, m), 4.11 (1 H, q, *J* 5.2 Hz, C2-H_{ax}).

3-Acyloxy-6-methyl-6-acyloxymethyl-1,3-oxazinane (5d). Colourless needles, mp 40–41 °C (Et_2O–hexane) (Found: C, 51.8; H, 7.35; N, 6.0. $C_{10}H_{17}NO_5$ requires C, 51.94; H, 7.41; N, 6.06%); ν_{max}(neat)/cm^{-1} 2980, 2942, 2867, 1750, 1650, 1440, 1370, 1234, 1042, 1008, 938 and 814; *m*/*z* 232 [(M + 1)$^+$, 5.6%]; δ_H(Major) (−50 °C) 1.21 (1 H, app d, *J* 13.4 Hz; at −10 °C it becomes ddd, *J* 1.9, 3.0, 13.2 Hz, C5-H_{eq}), 1.41 (3 H, s), 2.18 (3 H, s), 2.21 (3 H, s), 2.24 (1 H, dt, *J* 5.6, 13.1 Hz, C5-H_{ax}), 3.42 (1 H, m, overlapping with other signals, C4-H_{eq}), 3.48 (1 H, dt, *J* 3.7, 12.1 Hz, C4-H_{ax}), 4.02 (1 H, d, *J* 11.5 Hz), 4.10 (1 H, d, *J* 11.5 Hz), 4.73 (2 H, AB, *J* 12.5 Hz, C2-H_2). Non-overlapping peaks for minor conformer appeared at, 1.35 (3 H, s), 1.47 (1 H, ddd, *J* 2.0, 3.5, 14.3 Hz, C5-H_{eq}), 2.19 (6 H, s), 4.06 (1 H, d, *J* 11.6 Hz), 4.45 (1 H, d, *J* 11.6 Hz), 4.62 (1 H, d, *J* 12.5 Hz, C2-H_{eq}), 4.79 (1 H, d, *J* 12.5 Hz, C2-H_{ax}).

3-Acyloxy-2,2-dimethyl-1,3-oxazinane (5e). Colourless liquid (Found: C, 55.5; H, 8.7; N, 8.0. $C_8H_{15}NO_3$ requires C, 55.47; H, 8.73; N, 8.09%); ν_{max}(neat)/cm^{-1} 2994, 2958, 2868, 1762, 1680, 1440, 1392, 1368, 1246, 1202, 1162, 1138, 1076, 1002, 970 and 804; *m*/*z* 174 [(M + 1)$^+$, 12.3%]; δ_H(Major) (−30 °C) 1.35 (1 H, app d, *J* 13.6 Hz, C5-H_{eq}), 1.39 (3 H, s), 1.59 (3 H, s), 2.18 (3 H, s), 2.21 (1 H, m, C5-H_{ax}) 3.29 (1 H, ddd, *J* 2.1, 4.1, 15.0, Hz, C4-H_{eq}), 3.68 (1 H, dt, *J* 3.8, 12.1 Hz, C4-H_{ax}) 3.91 (1 H, dd, *J* 5.1, 12.1 Hz, C6-H_{eq}), 4.08 (1 H, dt, *J* 2.6, 12.1 Hz, C6-H_{ax}).

3-Acyloxy-2-methyl-6-phenyl-1,3-oxazinane (5f). Colourless liquid (Found: C, 66.2; H, 7.3; N, 5.9. $C_{13}H_{17}NO_3$ requires C, 66.36; H, 7.28; N, 5.96%); ν_{max}(neat)/cm^{-1} 3021, 3008, 2993, 2889, 2360, 1760, 1494, 1448, 1366, 1304, 1206, 1104, 1060, 1002, 950, 892, 800, 754 and 700; *m*/*z* 235 (M$^+$, 21%); δ_H(Major) (−30 °C) 1.40 (3 H, d, *J* 6.0 Hz), 1.62 (1 H, d, *J* 13.7 Hz, C5-H_{eq}), 2.20 (3 H, s), 2.25 (1 H, dq, *J* 4.2, 13.1 Hz, C5-H_{ax}), 3.54 (1 H, dt, *J* 3.5, 13.0 Hz, C4-H_{ax}), 3.64 (1 H, ddd, *J* 1.6, 4.2, 13.0 Hz, C4-H_{eq}), 4.74 (1 H, dd, *J* 2.1, 11.5 Hz, C6-H_{ax}), 4.76 (1 H, q, *J* 6.0 Hz, C2-H_{ax}), 7.29–7.45 (5 H, m). Non-overlapping peaks for minor conformer appeared at 4.30 (1 H, q, *J* 5.3 Hz, C2-H_{ax}), 4.56 (1 H, dd, *J* 2.1, 11.6 Hz, C6-H_{ax}).

3-Acyloxy-4-ethyl-6-phenyl-1,3-oxazinane (5g). Colourless liquid (Found: C, 67.5; H, 7.6; N, 5.6. $C_{14}H_{19}NO_3$ requires C, 67.44; H, 7.68; N, 5.62%); ν_{max}(neat)/cm^{-1} 3027, 3018, 2981, 2925, 1760, 1496, 1452, 1366, 1210, 1048, 1000, 936, 824, 752 and 700; *m*/*z* 249 (M$^+$, 24%); δ_H(Major) (−30 °C) 1.09 (3 H, t, *J* 7.3 Hz), 1.63 (1 H, app d, *J* 13.7 Hz, C5-H_{eq}), 1.78 (1 H, quintet of doublet, *J* 7.3, 15.3 Hz, C4-CH), 1.98 (1 H, app septet, *J* ~7.4 Hz, C4-CH), 2.17 (3 H, s), 2.41 (1 H, ddd, *J* 5.4, 13.7, 14.5 Hz, C5-H_{ax}), 3.30 (1 H, app q, *J* ~6.8 Hz, C4-H_{eq}), 4.77 (1 H, dd, *J* 1.9, 11.9 Hz, C6-H_{ax}), 4.80 (1 H, d, *J* 12.5 Hz, C2-H_{eq}), 4.90 (1 H, d, *J* 12.5 Hz, C6-H_{ax}), 7.32–7.45 (5 H, m); (Minor) 0.97 (3 H, t, *J* 7.3 Hz), 1.43 (1 H, app septet, *J* ~7.1 Hz, C4-CH), 1.61 (1 H, m, overlapping, C4-CH), 2.13 (1 H, app d, *J* 14.1 Hz, C5-H_{eq}), 2.20 (3 H, s), 2.50 (1 H, dt, *J* 5.6, 12.8 Hz, C5-H_{ax})), 2.97 (1 H, m, C4-H_{ax}), 4.52 (1 H, d, *J* 12.5 Hz, C2-H_{eq}), 4.68 (1 H, d, *J* 12.5 Hz C2-H_{ax}), 5.26 (1 H, d, *J* 5.2 Hz, C6-H_{eq}), 7.32–7.45 (5 H, m).

3-Acyloxy-4-ethyl-2-methyl-6-phenyl-1,3-oxazinane (5h). Colourless liquid (Found: C, 68.2; H, 8.0; N, 5.2. $C_{15}H_{21}NO_3$ requires C, 68.41; H, 8.04; N, 5.32%); ν_{max}(neat)/cm^{-1} 3018, 2994, 2964, 1766, 1496, 1452, 1366, 1304, 1204, 1150, 1082, 996, 938, 884, 756 and 702; *m*/*z* 263 (M$^+$, 9.8%); δ_H(Major) (−30 °C) 0.98 (3 H, t, *J* 7.5 Hz), 1.39 (3 H, d, *J* 6.1 Hz, and 1 H overlapping, C5-H_{eq}), 1.72 (2 H, m), 1.86 (1 H, q, *J* 12.3 Hz, C5-H_{ax}), 2.20 (3 H, s), 3.26 (1 H, m), 4.69 (1 H, dd, *J* 2.0, 11.3 Hz, C6-H_{ax}), 4.76 (1 H, q, *J* 6.1 Hz, C2-H_{ax}). Non-overlapping peaks for minor appeared at 0.89 (3 H, t, *J* 7.5 Hz), 2.90 (1 H, m), 4.30 (1 H, q, *J* 5.4 Hz, C2-H_{ax}), 4.57 (1 H, d, *J* 11.3 Hz, C6-H_{ax}).

3-Acyloxy-4,4-dimethyl-6-phenyl-1,3-oxazinane (5i). Colourless needles, mp 55–56 °C (Et_2O–hexane); (Found: C, 67.3; H, 7.5; N, 5.6. $C_{14}H_{19}NO_3$ requires C, 67.44; H, 7.68; N, 5.62%); ν_{max}(KBr)/cm^{-1} 3066, 3053, 3027, 3008, 2990, 2975, 2943, 2922, 2871, 2850, 1755, 1497, 1378, 1238, 1206, 1189, 1130, 1088, 1067, 1054, 1029, 996, 936, 757 and 701; *m*/*z* 249 (M$^+$, 30.6%); δ_H(Major) (−30 °C) 1.22 (3 H, s), 1.49 (3 H, s), 1.57 (1 H, dd, *J* 2.2, 13.7 Hz, C5-H_{eq}), 2.19 (1 H, t, *J* 12.8 Hz, C5-H_{ax} and 3 H, s overlapping), 4.81 (1 H, d, *J* 12.0 Hz; dd at 23 °C, *J* 2.3, 12.0 Hz, C6-H_{ax}), 4.82 (1 H, d, *J* 12.5 Hz, C2-H_{eq}), 5.04 (1 H, d, *J* 12.5 Hz, C2-H_{ax}), 7.30–7.42 (5 H, m).

X-Ray crystal analysis of 4i and 5i †

Compound 4i. *Crystal data.* $C_{14}H_{19}NO_3$, *M* = 249.3, monoclinic, *a* = 15.071(6), *b* = 6.133(3), *c* = 14.918(6) Å, *β* = 93.07(3)°, *V* = 1376.9(5) Å^3 (by least-squares refinement on diffractometer angles for 25 automatically centred reflections, *λ* = 0.71073 Å), space group *P*2(1)/*c* (No. 14), *Z* = 4, D_x = 1.203 Mg m^{-3}; colourless, air/moisture-stable crystals, 0.60 × 0.40 × 0.20 mm, *μ*(Mo-K*α*) = 0.084 mm^{-1}.

Data collection and processing. Crystal quality was checked using film techniques, Siemens P4 diffractometer, *ω*/2*θ* mode with *ω*, graphite-monochromated Mo-K*α* radiation; 2418 reflections measured [(2.73 < *θ* < 25.05), (−12 ≤ *h* ≤ 12, −7 ≤ *k* ≤ 7, −17 ≤ *l* ≤ 0)], 1273 unique (merging *R* = 0.0265), 1272 with $I \geqslant 2\sigma(I)$ classed as observed. Data were corrected for Lorentz and polarization effects but not for absorptions, max. and min. transmission: 0.8979 and 0.9231.

Structure analysis and refinement. Direct methods (all non-H atoms) followed by difference maps to recover the positions of all hydrogen atoms. All hydrogen atoms were located from a difference Fourier map. Full-matrix least-squares refinement based on F^2; non-hydrogen atoms anisotropic, hydrogen atoms isotropic, refined in riding mode with the atoms to which attached. 1272 observations and 164 variables, including an isotropic extinction coefficient [final value = 0.035(5)]. Weighting scheme: $w = 1/[s^2(F_o^2) + (0.0632P)^2 + 0.2688P]$ where $P = (F_o^2 + 2F_c^2)/3$. Final *R* and *wR* values are 0.0495 and 0.0792, with goodness-of-fit = 1.042. Largest diff. peak and hole = 0.119 and −0.127 e Å^{-3}.

Compound 5i. *Crystal data.* $C_{12}H_{17}NO_2$, *M* = 207.27, Monoclinic, *a* = 6.9582(14), *b* = 12.532(3), *c* = 12.885(3) Å, *β* = 97.70(3)°, *V* = 1113.5(4) Å^3 (by least-squares refinement on diffractometer angles for 25 automatically centred reflections, *λ* = 0.71073 Å), space group *P*2(1)/*c* (No. 14), *Z* = 4, D_x = 1.236 Mg m^{-3}, 1.20 × 0.60 × 0.30 mm, *μ*(Mo-K*α*) = 0.084 mm^{-1}.

Data collection and processing. Crystal quality was checked using film techniques, Siemens P4 diffractometer, *ω* mode with *ω* scan, graphite-monochromated Mo-K*α* radiation; 2113 reflecions measured (2.28 < *θ* < 24.99, 0 ≤ *h* ≤ 8, 0 ≤ *k* ≤ 14, −15 ≤ *l* ≤ 15), 1944 unique (merging *R* = 0.0226) 1272 with $I > 2\sigma(I)$ classed as observed. Data were corrected for Lorentz and polarization effects but not for absorptions, max. and min. transmission: 0.9753 and 0.9061.

Structure analysis and refinement. Direct methods (all non-H atoms) followed by difference maps to recover the positions

† Full crystallographic details, excluding structure factor tables, have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details of the deposition scheme, see 'Instructions for Authors', *J. Chem. Soc., Perkin Trans. 2*, available *via* the RSC web page (http://www.rsc.org/authors). Any request to the CCDC for this material should quote the full literature citation and the reference number 188/155.

of all hydrogen atoms. Full-matrix least-squares refinement based on F^2; non-hydrogen atoms anisotropic, hydrogen atoms isotropic. 1944 observations and 137 variables, including an isotropic extinction coefficient [final value = 0.029(4)]. Weighting scheme: $w = 1/[s^2(F_o^2) + (0.0632P)^2 + 0.2688P]$ where $P = (F_o^2 + 2F_c^2)3$. Final R and wR values are 0.0415 and 0.0964, with goodness-of-fit = 1.015. Largest diff. peak and hole = 0.375 and −0.351 e Å^{-3}.

Computer programs used. Data collection, cell refinement: Siemens XSCANS (SIEMENS, 1995);[22] data reduction and structure solution, refinement, graphics, publication material: Siemens SHELXTL.[23]

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