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THE CONFORMATIONS OF HYDROXYLAMINE DERIVATIVES

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CONTENTS

INTRODUCTION

Organic chemists get into a fixed rut when thinking about the conformations of organic molecules. So deeply ingrained is the concept of the three-fold barrier to rotation in ethane, that many chemists automatically assume that *trans*- and *gauche*-conformations must inevitably be involved and that perfectly staggered conformations are invariably energy minima whenever there is a rotation about a single bond in an organic molecule. We can even extrapolate this thinking from carbon–carbon to carbon–heteroatom bonds, because molecules such as methylamine, methanol and their higher homologues also show similar threefold periodicity in their bond rotation behaviour.

The importance of the conformational analysis of hydroxylamine derivatives is that it forces us to get out of this rut. Both molecular orbital calculations and experiments on hydroxylamine and its derivatives show a completely different conformational picture. Hydroxylamine has two maxima and two minima on its potential function for N–O bond rotation, and the barrier is several times larger than in ethane and related compounds. Hydroxylamine derivatives thus form an excellent series of compounds for testing how a grossly different potential function for bond rotation alters the conformational behaviour of organic compounds.

Furthermore, the presence of oxygen next to nitrogen raises the barrier to nitrogen inversion considerably. This effect has proved very valuable in nmr studies of these compounds and has also been used to shed considerable light on the factors that influence rates of nitrogen inversion.

Hydroxylamine derivatives therefore have a distinctive place in conformational analysis. Their unique properties have led to their use in investigating several types of interesting and otherwise difficult conformational problems, and the anomalies that have been observed have helped to shed light on the behaviour of other "more normal" systems. It is the purpose of this article to review these aspects of the chemistry of organic derivatives of hydroxylamine.

ACYCLIC COMPOUNDS

Preferred conformations

Molecular orbital calculations give the best available evidence for the conformational behaviour of hydroxylamine itself. In 1967 Pedersen and Morukama,[1] and Fink, Pan and Allen[2] published the results of MO calculations. Their results were similar and showed the molecular energy to vary with N–O bond rotation as shown in Fig. 1. The barriers to rotation were calculated to be 11.95 kcal mol^{-1} and 1.16 kcal mol^{-1}.[2] The two conformations were calculated to be 10.79 kcal mol^{-1} apart.[2] The stable conformation is seen to be **1a** with the lone pairs and bonds formally eclipsed, in complete contrast to our intuitive ideas extrapolated from ethane, methanol and methylamine. The less stable conformation (**1b**) has the formal bonds and lone pairs staggered. The other staggered arrangement (**1c**) does not occupy a potential energy minimum.

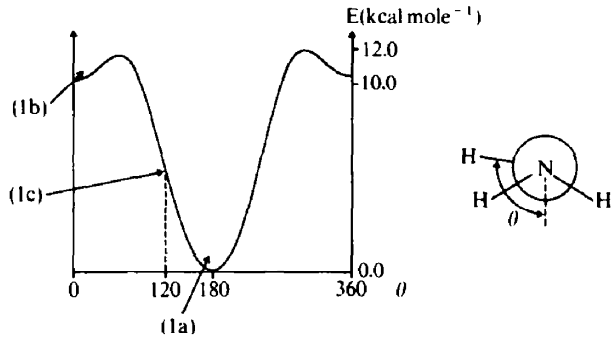
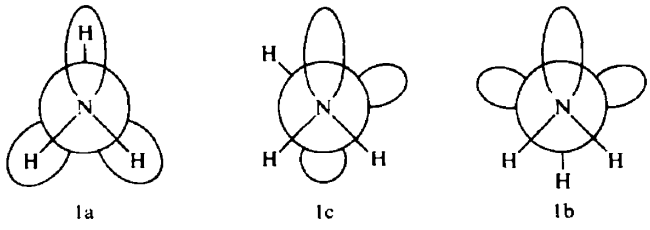


Fig. 1. Barrier to rotation about the N–O bond in hydroxylamine from MO calculations (ref 2).

In 1972 Radom, Hehre and Pople[3] reported their results of calculations on hydroxylamine and both monomethyl derivatives. By and large, their calculations agree with those of the earlier workers. The shape of the barrier is qualitatively similar. The higher barrier to rotation was calculated to be 11.72 kcal mol^{-1} and the energy difference between the conformations to be 8.01 kcal mol^{-1}. Calculations on the Me derivatives indicated that methylated derivatives have an almost identical rotation barrier, but that the energy difference is about 1 kcal mol^{-1} lower (OMe, 6.71; NMe, 6.95 kcal mol^{-1}).

Experimental evidence on hydroxylamine itself qualitatively confirms the result of the MO calculations. The IR study by Giguere and Liu,[4] and the microwave investigation by Tsunekawa[5] are both in accord with the *trans* conformation (**1a**) being strongly preferred for the parent compound.

For methylated derivatives dipole moment data suggest that there is a substantial proportion of the *trans* conformation present.[6] The best evidence on methylated derivatives however comes from an electron diffraction study which reveals the presence of two conformations for the N,O-dimethyl and the trimethyl derivatives.[7] For the trimethyl derivative, comparison of R values shows that the major conformation is **2a**, that there is a 98 % probability that there is a second conformation present, and that the probability that the minor conformation is **2b** rather than **2c** is 85 %. For the di- and trimethyl compounds the *trans* conformation (**2a**) is *ca.* 0.6 kcal mole^{-1} more stable than the other. This value is considerably lower than the predictions of Pople *et al.*[3] for the N- and O-monomethyl derivatives. Structural parameters for the methylated hydroxylamines derived from this work are presented in Table 1.



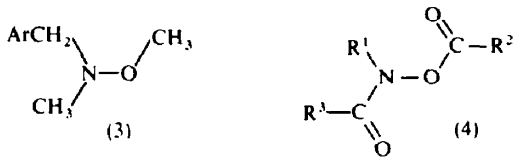


Table 1. Structural parameters for methylated hydroxylamine derivatives (ref 7)

	H_2NOH^a	MeNHOH	H_2NOMe	MeHNOMe	Me_2NOMe
r(C–N)/pm	—	143.8(17)	—	143.7(12)	144.7(4)
r(C–O)/pm	—	—	138.9(2)	138.1(7)	137.2(6)

[a] value from reference 3.

Rotational and inversional processes†

The NMR spectra of many derivatives of hydroxylamine show a temperature dependence attributable either to N–O bond rotation or to inversion at nitrogen. Griffith and Roberts[8] studied the process observed in **3** Ar=Ph) and ascribed it to nitrogen inversion without explicitly considering slow bond rotation. Their evidence was the lowering of the barrier as solvent polarity is increased. The Arrhenius activation energy fell by 3.0 kcal mol^{-1} along the series of increasingly polar solvents: n-hexane, carbon disulphide, chloroform, methylene chloride, and the barrier was not observable in the more polar solvents acetone and methanol. They pointed out that the transition state for nitrogen inversion, with a planar N atom, should be more polar than the ground state; thus, increasing the solvent polarity should increase the stabilisation of the transition state and lower the barrier.

This view was questioned by Raban and Kenney[9] and by Walter and Schaumann.[10] These workers, with the earlier sets of MO calculations[1,2] to refer to, pointed out that the total inversion pathway is as in Fig. 2. The observed conformers a and a* are enantiomeric and therefore the methylene hydrogens in the benzyl group become diastereotopic when either nitrogen inversion (NI) or bond rotation (BR) becomes slow on the NMR time-scale. They observed a small steric retardation of the rate-limiting process which was consistent with it being bond rotation.

Fletcher and Sutherland found support for nitrogen inversion as the origin of the observed process.[11] They noted that the observed barrier changed very little when the size of the O-substituent was reduced from alkyl or acyl to hydrogen. Such changes would be expected to cause substantial variations in the barrier were it due to N–O bond rotation. These views were also supported by a subsequent publication from Roberts' group.[12]

The most recent work on trialkyl hydroxylamines also comes down firmly on the side of nitrogen inversion being a slower process than bond rotation.[13] The series of compounds (**3**) with varying substitution patterns on the aromatic ring was studied. *Ortho* substituents were found to cause a steric acceleration of the observed process, a result that is consistent with N-inversion being the rate limiting step.

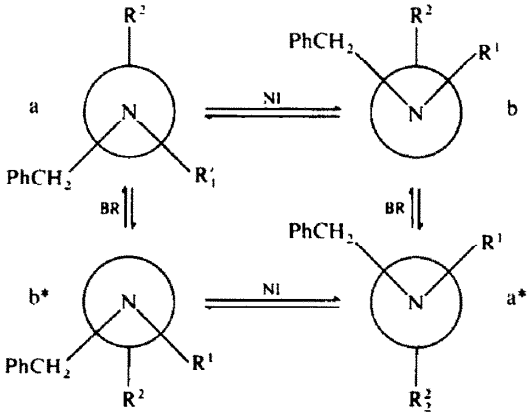
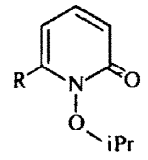


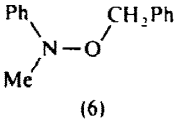
Fig. 2. Bond rotation and nitrogen inversion pathways in N-benzyl-N,O-dialkylhydroxylamines.

† As will be seen later in the text, whenever $\Delta S^{\ddagger}$ has been reliably determined for a nitrogen inversion process in a hydroxylamine derivative, its value has always been found to be close to zero. $\Delta G_c^{\ddagger}$ values at widely differing coalescence temperatures are therefore probably a reasonably reliable means of comparing nitrogen inversion barriers, since they correspond closely to $\Delta H^{\ddagger}$ values.

Although the above results for trialkyl derivatives point strongly to a slow nitrogen inversion process, inclusion of the nitrogen atom in a conjugated system such as an amide, a urethane or a pyridone causes N–O bond rotation to become the rate-limiting step. Price and Sutherland found barriers of *ca.* 10 kcal mol^{-1} for the compounds (**4**)[14] whilst Raban and Kost found a barrier of 10 kcal mol^{-1} for **5a** and estimated barriers of 8–9 kcal mol^{-1} for **5b** and **6**.[15] The most recent work on N–O bond rotation barriers comes from Riddell and Turner who found barriers of *ca.* 15 kcal mol^{-1} for compounds of type **7** and demonstrated that steric effects were important in increasing the barrier.



(5) a R = Cl
b, R = H



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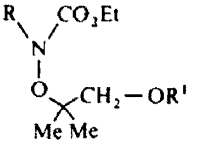

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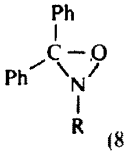

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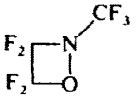

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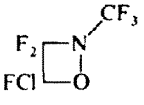

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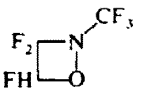

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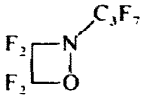

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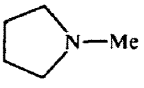

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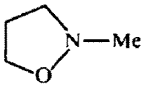

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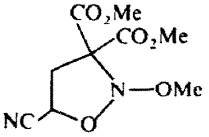

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CYCLIC DERIVATIVES

In cyclic derivatives of hydroxylamine, nitrogen inversion becomes the dominating slow rate process.

3-Membered rings

Oxidation of imines with optically pure peracids such as (+)-peroxycamphoric acid gives rise to optically active oxaziridines such as **8**.[17,18] These compounds are optically active because nitrogen inversion is slowed both by the adjacent O atom and by inclusion in a 3-membered ring.[19] It proved possible to study the rate of inversion of the N atom by following the racemisation of **8** at elevated temperatures.[17] The rate of the inversion process is appreciably more rapid when R = t-Bu ($\Delta H^{\ddagger}$ 27.7 kcal mol^{-1}) than when R = Me ($\Delta H^{\ddagger}$ = 34.1 kcal mol^{-1}), a result attributed to steric hindrance in the ground state of the t-Bu derivative raising its energy and lowering the barrier.

4-Membered rings

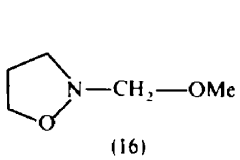
Lee and Orrell studied the nitrogen inversion process in the fluorinated oxazetidines (**9–12**).[20] The ^{19}F NMR spectra showed coalescences at *ca.* −30° from which free energies of activation of *ca.* 10 kcal mole^{-1} were deduced. From comparison with other species it can be shown that the fluoroalkyl groups tend to increase the rate of nitrogen inversion and lower the barrier.[19]

5-Membered rings

Interest in 5-membered rings containing the N–O bond has largely centred around measurements of rates of the nitrogen inversion process and defining the effects of substituents on this process. The

effect of α-O atoms in raising the barrier to the nitrogen inversion process and thus slowing its rate is dramatically illustrated by comparing the barriers in **13** $\Delta G^{\ddagger}$ *ca.* 8.1 kcal mol^{-1};[22] **14** $\Delta G^{\ddagger}$ *ca.* 15.6 kcal mol^{-1};[23] and **15** E_a *ca.* 29.2 kcal mole^{-1}.[24] In the former cases the barrier is between two equi-energetic conformations. In the latter two diastereoisomeric forms are involved. The rate of nitrogen inversion is observed to decrease when the Me in **14** is replaced by the bulkier isopropyl group.[25] The rate is also lowered by the β-O atom in **16** ($\Delta G^{\ddagger}$ *ca.* 10.3 kcal mole^{-1})[25].

Conformational studies on some N-trimethylsilyloxyisoxazolidines (**17**) have been reported.[26]



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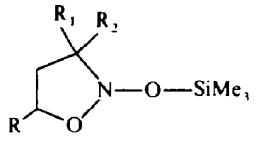
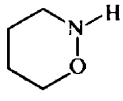


(17) R = CO_2Me, Me
R_1 = CO_2Me, Me, H
R_2 = CO_2Me, Ph



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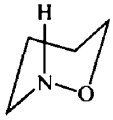

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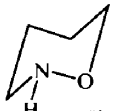

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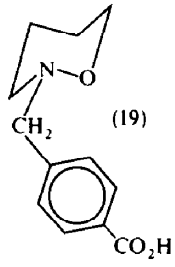

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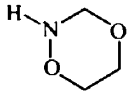

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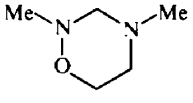

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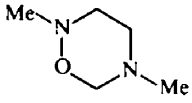

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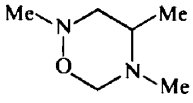

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6-Membered rings

(i) *Tetrahydro-1,2-oxazine* (**18**). The parent 6-membered ring system containing the N–O bond is tetrahydro-1,2-oxazine, which has been extensively investigated by the groups in Stirling[23,27–32] and Norwich.[31–34]

An X-ray crystallographic investigation of the derivative **19** showed that the ring has a well-defined chair conformation. The conformation of the ring can be considered in two parts (CNOC) and (CCCC). The first has the shorter bond lengths and greater internal torsion angles, whilst the second is more nearly cyclohexane-like in character with normal C–C bond lengths and torsion angles of *ca.* 55°.

The torsion angle about the N–O bond, whose length is 145.6 pm, is 67° and is the largest in the ring. In an ideal cyclohexane chair, the torsion angles are exactly 60° yet in the real molecule internal forces in the molecule reduce this to 55°. From our knowledge of the torsional behaviour of acyclic compounds containing N–O bonds (Fig. 1) we can see that at this sort of torsion angle there would be

considerable residual torsional strain. This strain is in some measure relieved by opening the ring internal torsion angle to 67°.

Further evidence of the importance of torsional strain about the N–O bond in this system is obtained from studies of axial-equatorial equilibria of groups on nitrogen. Whereas in piperidine and many other saturated heterocyclic systems there is evidence for the N–H axial conformation being appreciably populated,[35] or even the most abundant conformation,[36] the N–H group is almost exclusively equatorial in tetrahydro-1,2-oxazine.[33,34] Similarly, from ^{1}H NMR spectral data there is absolutely no evidence for an axial N–Me group in the 2-Me derivative at temperatures where both nitrogen and ring inversion would be expected to be slow.[28] There is thus a very strong tendency for N-substituents to be equatorial in tetrahydro-1,2-oxazine derivatives. This arises because the axial conformation (**18a**) has the same rotational arrangement about the N–O bond as **1b** which is in the higher energy minimum on the N–O rotation pathway. The equatorial conformation (**18b**) on the other hand corresponds to **1c** which is certainly lower in energy than **1b** even though it does not occupy a potential energy minimum (Fig. 1). The torsional potential about the N–O bond is here contributing substantially to the conformational preference of the compound. The above argument applies even more strongly for N-Me (or alkyl) derivatives where non-bonded interactions across the top of the ring will raise the energy of the axial conformation even more. However, in compounds such as the tetrahydro-1,4,2-dioxazines (**20**), where these syn-diaxial interactions are minimised and there are favourable anomeric interactions, the energy of the axial conformation is lowered sufficiently for it to be observed.

The presence of the O atom adjacent to N in the tetrahydro-1,2-oxazine ring slows down the rate of nitrogen inversion to such an extent that its rate becomes readily measurable by NMR spectroscopy at temperatures of around 0°.[23,27] Observed activation parameters are $\Delta H^{\ddagger}$ 15.1 $\pm$ 0.4 kcal mol^{-1}, $\Delta S^{\ddagger}$ 2.3 $\pm$ 1.5 cal mol^{-1} K^{-1}.[27] This has two useful consequences. Firstly, 6-membered rings containing an N–O bond and a further heteroatom have proved very valuable for examining the effects of heteroatoms at various positions on the rates of nitrogen inversion in 6-membered rings.[37] Secondly, because of the high conformational free energy difference of the N-Me group, freezing out of N-Me inversion is a very convenient way of obtaining slow conformational exchange. This results in the observation of mixtures of *cis* and *trans* isomers with equatorial N-Me groups, allowing observations to be made of individual conformers and of the positions of conformational equilibria.

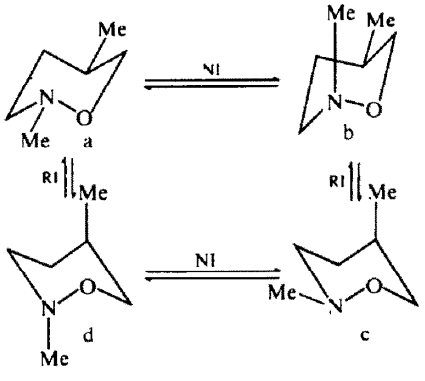


Fig. 3. Ring and nitrogen inversion in 2,5-dimethyltetrahydro-1,2-oxazine.

This latter method has been used to examine the conformational equilibria of C–Me groups in tetrahydro-1,2-oxazines. For example, the 2,5-dimethyl derivative whose conformational route map is shown in Fig. 3 has been examined.[33] Slowing of the nitrogen inversion processes in this compound separates conformations **a** and **d** from **b** and **c**. At low temperatures (*ca.* −40°) two sets of signals are observed which are assigned to the diequatorial conformation **a** (major component) and the N-equatorial-5-axial conformation **c**. Conformations **b** and **d** with axial N–Me groups will not contribute significantly to the equilibria. The observed free energy difference, which corresponds to the equatorial-axial change of a 5-Me group is 1.36 $\pm$ 0.1 kcal mol^{-1}. Analogous experiments allowed the determination of the free energy differences of Me groups at all four ring C atoms. (Fig. 4).[31]

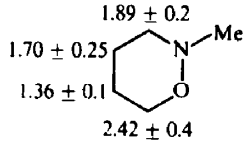


Fig. 4. Free energy differences (kcal mol^{-1}) of methyl groups at positions 3, 4, 5 and 6 in the tetrahydro-1,2-oxazine ring.

From the X-ray crystallographic work discussed earlier[30] it had proved possible to estimate the distances between axial C-Me and other atoms on the ring causing steric hindrance (Fig. 5). Me groups at C(4) and C(5) are seen to be at almost identical distances from the hindering atoms yet experimentally the C(5) axial Me is found to experience smaller interactions. Presumably this arises because the O atom against which the C(5) axial group is forced has a smaller van der Waals radius than the N atom which hinders the C(4) axial group. Similar comparison of positions 3 and 6 in the ring also reveals the same trend with the group forced into oxygen being less hindered than the group forced into nitrogen despite almost identical trans-annular distances. For axial substituents at 3 and 6 the hindrance to the axial position is expected to be greater than for positions 4 and 5 because of the closer proximity of the hindering groups. This is found experimentally. These experiments provide a clear cut example of the importance of the relative size of O and N atoms in determining conformational preferences.

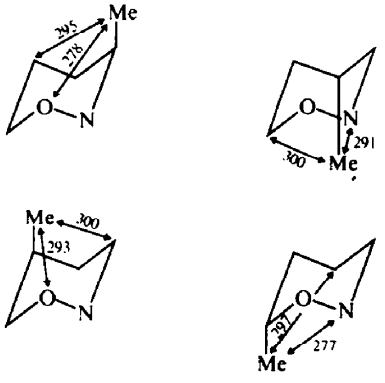


Fig. 5. Distances separating methyl carbon atoms from other ring atoms in tetrahydro-1,2-oxazine (pm).

(ii) *Tetrahydro*-1,4,2-*dioxazine*. In the tetrahydro-1,4,2-dioxazine ring (**20**) the conformational behaviour of the ring is modified compared to the 1,2-oxazine ring by the introduction of an additional O atom β to the N. The ring thus displays a fascinating fusion of the conformational properties of the tetrahydro-1,2- and 1,3-oxazine rings.[38-40]

NMR spectral evidence on derivatives of the basic ring system shows that there are two distinct inversion phenomena observable: nitrogen inversion ($\Delta G^{\ddagger}$ 11.4 ± 0.2 kcal mol^{-1}) and ring inversion ($\Delta G^{\ddagger}$ 10.9 ± 0.2 kcal mol^{-1}).[40] The barrier to inversion of an equatorial N–Me group is clearly intermediate between the barriers in the 1,2-oxazine and 1,3-oxazine rings ($\Delta G^{\ddagger}$ *ca.* 14.4 kcal mol^{-1} and 7.6 kcal mol^{-1} respectively). The effect of the β-O atom is clearly to lower the barrier to inversion of the equatorial N–Me group, and the effect of the α-O atom is clearly seen to raise this barrier.

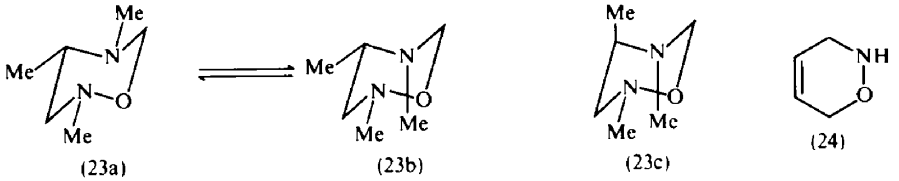
The conformational free energy difference of a Me group on N in the 1,3-oxazine ring is *ca.* 0.0 kcal mol^{-1}, because of lower non-bonded interactions on the axial Me group and a favourable anomeric interaction,[41] giving roughly equal amounts of axial and equatorial conformations. In the 1,2-oxazine ring only the equatorial conformation can be detected. In the tetrahydro-1,4,2-dioxazine ring this free energy difference is *ca.* 1.0 kcal mol^{-1} allowing ready detection of the axial conformation. This value is again intermediate between the two model systems.

(iii)*Tetrahydro*-1,2,4-*oxadiazine*. In this series of compounds the conformational properties represent a compromise between those of the two reference systems, tetrahydro-1,2-oxazine and hexahydropyrimidine. A detailed conformational analysis has been made for the 2,4-dimethyl derivative (**21**) by making use of a combination of ^{1}H and ^{13}C NMR results.[42,43] Two nitrogen

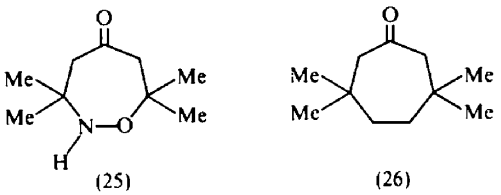
inversion barriers are observed. The barrier to inversion of the equatorial 4-Me group is *ca.* 7.4–7.9 kcal mol^{-1}, very similar to that observed for N,N'-dimethylhexahydropyrimidine.[44] The barrier to inversion of the equatorial 2-Me group is *ca.* 12.7–13.1 kcal mol^{-1}. This value is higher than in the previously discussed 1,2,4-dioxazines but again is lower than in the 1,2-oxazine series. This reflects the fact that the β-N atom lowers the N-inversion barrier, but by a lesser amount than a β-O atom. The barrier to ring inversion is found to be 12.7 kcal mol^{-1}.

(iv) *Tetrahydro-1,2,5-oxadiazine.* For this series of compounds the reference ring systems are tetrahydro-1,2- and 1,3-oxazine. In the ^{1}H NMR spectrum of the dimethyl derivative (**22**) a kinetic process is observed with activation parameters very similar to those for 2-methyltetrahydro-1,2-oxazine ($\Delta H^{\ddagger}$ 14.4 ± 0.1, 15.1 ± 0.4 kcal mol^{-1}, $\Delta S^{\ddagger}$ 1.2 ± 0.4, +2.3 ± 1.5 cal mol^{-1} K^{-1} respectively).[42,45,46] This similarity in parameters suggests as a common origin inversion of the N(2) centre, and furthermore it implies that the effect of the γ-N atom on this N-inversion barrier is negligible.

On freezing out of N(2) inversion in the 2,4,5-trimethyl derivative (**23**) several interesting points emerge.[47] Below coalescence the ^{1}H spectra show resonances associated with a major conformational set (**23a** and **23b**) and a minor conformation (**23c**). In the major set which has the 4-Me group equatorial, the 5-Me group equally populates the equatorial and axial positions. This agrees with the known behaviour of the 1,3-oxazine component if the *gauche* interactions about the 4,5-bond are roughly equal for axial and equatorial N–Me groups. In the minor conformation, the C-4 and C-5 Me groups are both axial. In this case the N–Me group goes axial in the 1,3-oxazine-like end of the ring at minimal expense in energy, to avoid the gauche butane repulsion it would experience were it equatorial.



(23a) (23b) (23c) (24)



(25) (26)

(v) *Dihydro-1,2-oxazines.* Just as the retardation of the nitrogen inversion rate in the hydroxylamine moiety of the saturated cyclohexane-like rings discussed above has proved valuable in their conformational analysis, so the same effect has proved valuable in the study of the cyclohexene analogue, 3,6-dihydro-1,2-oxazine (**24**). Indeed these results are perhaps more valuable because, despite the enormous amount of conformational data available on cyclohexane and saturated heterocyclic 6-membered rings,[48] there is a paucity of data on cyclohexene and related systems. Inclusion of the slowly inverting N atom of hydroxylamine function into a cyclohexene ring allows observation of equilibrium mixtures of both *cis* and *trans* isomers in the NMR spectrum and permits conformational assignments to be made.

^{13}C NMR measurements[49] showed that alkyl substituents on nitrogen and at position 6 were substantially equatorial confirming an earlier report.[50] Observation of *cis* ⇌ *trans* equilibria in a wide variety of substituted dihydro-1,2-oxazines[51] then allowed the following equatorial preferences to be quantified: N-Me and Et *ca.* 1.0 kcal mol^{-1}, N-iPr > 1.3 kcal mol^{-1}; 6-phenyl *ca.* 1.3 kcal mol^{-1}. These results support Rickborn's contention that a 4-equatorial Me group in cyclohexene is *ca.* 1.0 kcal mol^{-1} more stable than when axial,[52] but run counter to some other suggestions that bulky substituents at position 3 (or 6) in a cyclohexene ring prefer to be axial.[53,54]

Larger rings

The most striking example of a hydroxylamine fragment having a marked conformational effect upon a ring of more than 6 atoms arises from a comparison of the rates of conformational interchange found in the 7-membered rings (**25** and **26**).[55] For the hydroxylamine (**25**) a process with $\Delta G^{\ddagger}$ 19.5 $\pm$ 0.5 kcal mol^{-1} at *ca.* 100° was observed which was *ca.* 10 kcal mol^{-1} greater than in the hydrocarbon (**26**). This very large increase in activation energy possibly arises because the presence of the *gem*-dimethyl groups in the ring restricts the number of possible conformations on the pseudorotation circuit thus placing the N–O bond rotation into the rate-determining step considerably raising the barrier.

CONCLUSION

In this review we have seen that hydroxylamine derivatives have contributed considerably to our knowledge of the conformational analysis of both acyclic and cyclic systems. The high inversion barrier to nitrogen inversion and the usual two-fold barrier to rotation about the N–O bond have both shown their influence on the conformational properties of these compounds, and have permitted clarification of several otherwise intractable conformational problems.

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