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1,2-OXAZINE CHEMISTRY—III

CONFORMATIONAL EQUILIBRIA IN METHYL DERIVATIVES OF TETRAHYDRO-1,2-OXAZINE

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Abstract—The conformational equilibria of methyl groups on the four carbon atoms of the tetrahydro-1,2-oxazine ring are investigated. Correlation of these equilibria with the 1,3-transannular distances in this system shows that oxygen is a "softer" atom than nitrogen.

INTRODUCTION

We have previously described the synthesis[1] and X-ray crystallographic investigation[2] of some derivatives of tetrahydro - 1, 2 - oxazine. This paper deals with conformational aspects of the behaviour of some of these compounds, in particular, those carrying an N-Me group.

Axial Me groups on the four ring C atoms of the tetrahydro - 1, 2 - oxazine ring should suffer different types and magnitudes of non-bonded interactions.

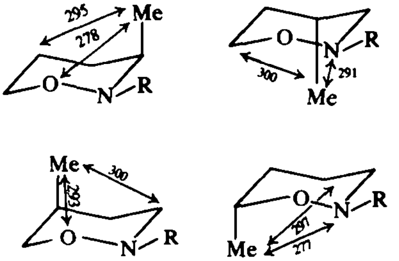


Fig 1. Transannular distances (calculated in Ref 2) for axial methyl groups.

Axial groups at C(3) and C(5) experience repulsions from axial C–H bonds, and the electron cloud of the ring O atom. The repulsions experienced by a C(5) axial Me are however expected to be less than those of a C(3) axial Me because the O–C(5) distance (*ca* 293 pm) is greater than that of O–C(3) (*ca* 278 pm)[2]. Similarly axial Me groups at C(4) and C(6) experience repulsions from an axial C–H bond and the axial electron pair on nitrogen. The axial C(4) Me is expected to be less hindered than the axial C(6) Me, because of the relative distances to nitrogen, *ca* 291 and 277 pm respectively.[2]

We thought it likely at the outset that we should find the hindrance to the axial groups forced against nitrogen to be greater than hindrance to the axial groups forced against oxygen. This is because it is known that the axial equatorial energy difference of a 5-Me group in N,N′,5-trimethylhexahydropyrimidine (**1**), with two Me-N interactions,[3,4] is greater than in 5 - methyl - 1, 3 - dioxan,[5,6] with two Me–O interactions, despite the presumed greater distance between the interacting centres in the nitrogen containing ring. It is in any case widely accepted that the van der Waals radius of oxygen (140 pm) is less than that of nitrogen (150 pm). As will be seen below our results confirm these ideas.

A suitable method for studying conformational equilibria in this ring system is low temperature NMR spectroscopy. It is known that nitrogen inversion in N-methyltetrahydro - 1, 2 - oxazine becomes slow on the NMR timescale below −10°.[7,8] This suggests that in various substituted derivatives those conformations separated by a nitrogen inversion barrier should be observable in the readily accessible region of about −35° to −40°.

The complete conformational inversion scheme for 2,6 - dimethyltetrahydro - 1,2 - oxazine, which will serve as a model for all the equilibria discussed in this paper, is shown in Fig 2. When nitrogen inversion is slow on the NMR timescale the spectrometer will 'see' the two time averaged pairs of conformations *cis* (**3a** + **3c**) and *trans* (**3b** + **3d**). However since it seems very likely that the N-Me group strongly prefers the equatorial orientation,[2] the observed species will be **3a** and **3d** and the equilibrium parameters will relate to the conformational equilibrium at C(6). The analogy between the above described method and the conventional method for conformational investigation involving chemical equilibration and the use of a conformation blocking group[9] is obvious. Moreover the same caveat, about relating the chemical equilibrium to the conformational equilibrium still applies.

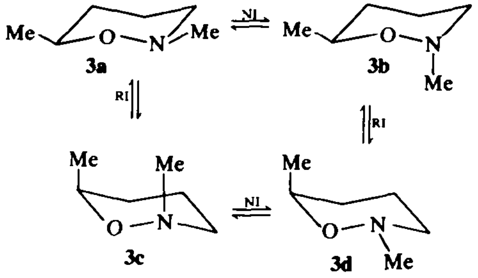


Fig 2. Conformational inversion scheme for 2,6-dimethyltetrahydro-1,2-oxazine.

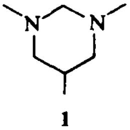
RESULTS AND DISCUSSION

(*a*) *Dimethyl-tetrahydro*-1, 2-*oxazines*. We first examined the low temperature spectra of the 2,6-, 2,5-, 2,4-, and 2,3-dimethyl-tetrahydro-1,2-oxazines (3–6). For all these compounds there is no change in their spectra even as low as −70° in methylene chloride solution except for the expected small amount of line broadening. This observation indicates that the equilibria for all these compounds are so far displaced towards the most stable conformations that the others cannot be detected by NMR spectroscopy in either the C- or N-Me regions. It seems very reasonable to suppose that the most stable conformation in each case has both Me groups equatorial.

An upper limit on the proportion of a second conformation can be set by the noise level of the spectrum. Since the noise was in general less than 5% of the magnitude of the N-Me signal there is probably less than 5% of any minor conformation present (barring accidental equivalence in both N- and C-Me regions). A lower limit to the free energy difference between the major and any minor conformation is thus 6·0 kJ mole^{-1} at −35°.

(*b*) *Trimethyltetrahydro*-1, 2-*oxazines*. We next turned our attention to the trimethyltetrahydro-1,2-oxazines described in the first paper of this series. The ^{1}H spectra of the *cis*-2,3,6-, *cis*-2,4,5- and *trans*-2,3,5-trimethyl derivatives are temperature dependent, whilst the spectra of the *trans*-2,3,6- and 2,4,5-isomers are not.

For *cis* - 2, 3, 6 - trimethyltetrahydro - 1, 2 - oxazine (7) at 60 MHz the higher field of the two C-Me doublets shown by spin decoupling to be the C-(3) Me broadens as the temperature is lowered, but resharpens by −50°. The N-Me signal remains a singlet during this temperature change, but both the C(3) and C(6) proton signals collapse and then sharpen again. At −50° the C(3) proton has a different splitting pattern than at room temperature.



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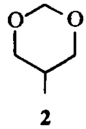

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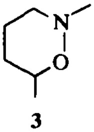

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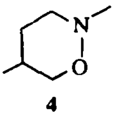

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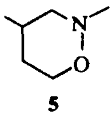

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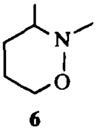

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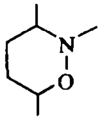

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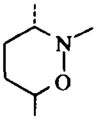

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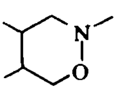

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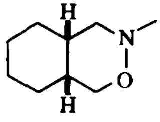

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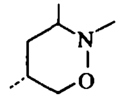

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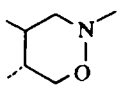

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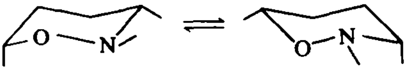
The two probable conformations for this compound are **7a** and **7b** and we interpret the spectra in terms of a predominance of **7a**. The splitting pattern for the C(3) and C(6) hydrogens are the X portions of ABX spectra, further split by the respective C-Me groups. From spectra of this sort one can only extract two pieces of coupling information: J_{XMe} and $J_{AX}+J_{BX}$. At room temperature the C(6) hydrogen shows $J_{XMe} = 6{\cdot}3$ Hz and $J_{AX}+J_{BX} = ca$ 12 Hz. At −50° the C(3) hydrogen shows $J_{XMe} = 6{\cdot}9$ Hz and $J_{AX}+J_{BX} = ca$ 6·4 Hz. The C(6) hydrogen however gives essentially the same pattern as at room temperature. Bearing in mind that the room temperature spectrum represents a time average of **7a** and **7b** whilst the low temperature spectrum only represents the predominant conformation this pattern suggests that **7a** is the dominant conformation. The splittings at the C(6) hydrogen in **7a** will be the sum of a *trans* (large) and a *gauche* (small) coupling, whereas the splittings at the C(3) hydrogen will both be *gauche* (small).



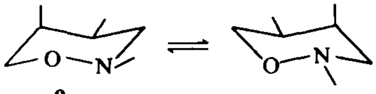
7b **7a**

This interpretation is confirmed by the spectrum of the *trans* isomer (**8**). The C(6) hydrogen, which here must be axial, shows a similar splitting pattern to that in the *cis* isomer. Moreover a preliminary investigation of the ^{13}C spectra of both isomers also supports this conformational assignment.

Since the N-Me group in **7** remained a singlet at low temperatures we were only able to estimate the relative amounts of **7a** and **7b** by the 100 MHz spectrum of the C-Me region at −35°, which shows two doublets in the ratio of 3(±1):1. Thus **7a** is 2·2±0·8 kJ mole^{-1} more stable than **7b** at −35°.

The ^{1}H NMR spectrum of *cis*- 2,4,5-trimethyltetrahydro-1,2-oxazine (**9**) changes markedly with temperature. Analogous changes are observed for *cis*-2-oxa-3-aza-3-methyldecalin (**10**). At −35° the N-Me signal is an unequal doublet, whilst well defined splitting patterns are observed for C(3) and C(6) hydrogens. At +60° the N-Me signal is a singlet and the C(3) and C(6) hydrogen patterns have altered.

The two probable conformations for the *cis*-2, 4, 5-trimethyl compound are **9a** and **9b**. We interpret the spectra in terms of a predominance of **9a** (K = 2 ± 0·5 in CH_2Cl_2, K = 3 ± 0·5 in CD_3OD at −35°)

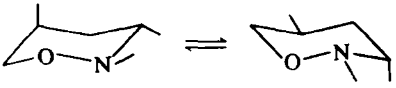


9a **9b**

Complete ABX analysis of the C(6) region in CD_3OD solution shows that the C(6) hydrogens in the major conformation have two small gauche couplings with the C(5) hydrogens (0 and 2·4 Hz at −35°) whilst the time averaged spectrum of these hydrogens (for both conformations) at +60° also displays two small couplings (4·9 and 3·5 Hz). Quite clearly conformation **9a** predominates. We estimate ΔG to be 1·4 ± 0·6 kJ mole^{-1} in methylene chloride solution at −35°.

The small increase in amount of the preferred conformation on changing from methylene chloride to the H-bonding solvent deuteriomethanol is also in accord with our assignment. H-bonding to the axial lone pair on nitrogen will be hindered in **9b** but not in **9a**.[8] Thus, as is observed, deuteriomethanol should increase the amount of **9a**.

Similar arguments to those advanced in the assignment of predominant conformations in the above cases can be used for the *trans* - 2, 3, 5 - trimethyl derivative (**11**). Here, for the C(6) hydrogens at ambient temperatures two small gauche vicinal couplings (3·3 and 4·6 Hz) remarkably similar to those of **8** are observed showing **11a** to predominate. The low temperature spectrum (CH_2Cl_2 solution) shows two N-Me peaks giving K = 3 ± 0·5, from which ΔG = 2·2 ± 0·4 kJ mole^{-1}.



11a **11b**

From the results detailed above for the three compounds **8**, **9** and **11** it is possible to construct a

Table 1. NMR Chemical shift data for Tetrahydro-1,2-oxazines +33·5° (τ scale)

Compound	Solvent	C(3)H	C(4, 5)H	C(6)H	N–CH_3	C(3)CH_3	C(6)CH_3	C(4, 5)CH_3
2,3-diMe (**6**)	None	7·70	8·50	6·30	7·70	9·07	—	—
	CH_2Cl_2	7·50	8·35	6·20	7·50	9·03	—	—
2,6-diMe (**3**)	None	7·70	8·50	6·30	7·70	—	8·98	—
	CH_2Cl_2	7·25	8·33	6·20	7·55	—	8·93	—
2,4-diMe (**5**)	None	7·30	8·50	6·20	7·55	—	—	9·07
	CH_2Cl_2	7·30	8·50	6·20	7·55	—	—	9·10
2,5-diMe (**4**)	None	7·30	8·50	6·20	7·55	—	—	9·17
	CH_2Cl_2	7·30	8·50	6·20	7·55	—	—	9·10
c 2,3,6-triMe (**7**)	CCl_4	7·25	8·50	6·17	7·60	8·98	8·87	—
	CH_2Cl_2	7·27	8·50	6·10	7·52	8·94	8·87	—
	CD_3OD	7·18	8·50	6·10	7·48	8·88	8·83	—
t 2,3,6-triMe (**8**)	CH_2Cl_2	7·67	8·50	6·50	7·52	9·05	8·94	—
c 2,4,5-triMe (**9**)	CCl_4	7·55	8·33	6·40	7·58	—	—	9·07, 9·07
	CH_2Cl_2	7·50	8·33	6·47	7·55	—	—	9·11, 9·20
	CD_3OD	7·55	8·33	6·17	7·47	—	—	9·07, 9·11
t 2,4,5-triMe (**12**)	CCl_4	7·50	8·75	6·50	7·55	—	—	9·10
	CH_2Cl_2	7·47	8·75	6·50	7·50	—	—	9·20
oxaza decalin (**10**)	CCl_4	7·52	8·55	6·40	7·60	—	—	—
	$CDCl_3$	7·40	8·52	6·17	7·45	—	—	—
	CH_2Cl_2	7·43	8·50	6·20	7·50	—	—	—
	CD_3OD	7·37	8·50	6·22	7·48	—	—	—
	C_6H_6	7·58	8·67	6·40	7·53	—	—	—
t 2,3,5-triMe (**11**)	CH_2Cl_2	7·27	8·40	6·29	7·42	8·99	—	8·99

C(3)H, C(4, 5)H and C(6)H resonances are multiplets; estimated error ±0·1 ppm.
N–CH_3 resonances are singlets; estimated error ±0·05 ppm.
C(3)CH_3, C(6)CH_3 and C(4, 5)CH_3 resonances are doublets or pairs of doublets; estimated error ±0·05 ppm.

table of the relative conformational preferences for Me groups on the tetrahydro - 1, 2 - oxazine ring (at − 35°)

C5a preferred to C4a by 1·40 ± 0·6 kJ mole^{-1};
C5a preferred to C3a by 2·2 ± 0·4 kJ mole^{-1};
C3a preferred to C6a by 2·2 ± 0·8 kJ mole^{-1}.

It is apparent that the order of hindrance to axial Me groups is $C_{5a} < C_{4a} < C_{3a} < C_{6a}$. If a direct measurement of the conformational equilibrium at any one position were available we could now estimate the conformational energy difference for Me groups at all four ring C atoms. In the absence of a direct measurement we shall assume that the free energy difference at C(5) is 6·0 kJ mole^{-1} (the minimum value estimated earlier), which gives the following free energy differences C(5) 6·0; C(4) 7·4 ± 0·6; C(3) 8·2 ± 0·4; C(6) 10·4 ± 1·2 kJ mole^{-1}.

Whilst the absolute values for these energy differences depend on the assumption of a value for C(5) their relative values are more soundly based. Moreover they fit well with the distances that we calculated in the previous paper in this series. The least hindered axial positions were found to be C(4) and C(5) and the most hindered positions C(3) and C(6). The sums of the calculated Me to ring atom distances illustrate this C(5), 593 pm; C(4), 591 pm; C(3), 573 pm; C(6), 574 pm.

The distances between axial Me groups and ring atoms fall neatly into three classes. There is a similarity between all the Me to carbon distances (295–300 pm). The C(5) and C(4) Me groups are practically equidistant from oxygen and nitrogen respectively (293 and 291 pm) whilst much shorter distances separate the C(3) and C(6) Me groups from the heteroatoms (278 and 277 pm). Whilst these latter pairs of distances are internally identical within experimental error, the pairs differ significantly from each other. Thus it is extremely interesting that although an axial Me group on C(5) pushed against oxygen, has practically the same transannular distances as the group on C(4) which is forced towards nitrogen, it is found to be less hindered. Similarly a C(3) axial group is less hindered than a C(6) Me group despite the similar distances involved. These results strongly suggest that at this part of the repulsive potential (277–293 pm) nitrogen is a "harder" atom than O by about 1·4 to 2·2 kJ mole^{-1}.

EXPERIMENTAL

The NMR spectra were recorded in *ca* 10% W/V solns on either a Perkin-Elmer R10 spectrometer or on a Varian HA100 spectrometer using standard variable temp equipment. Low temp spectra were measured for CH_2Cl_2 or CD_3OD solns. We thank Dr J. E. Anderson of University College London for the 100 MHz spectra.

Estimates of equilibrium constants were obtained from the low temp NMR spectra by integration of the N-Me region (**9** and **11**) or the C-Me region (**7**). Independent estimates of these constants obtained from coupling constant comparisons of low and high temp spectra were consistent with the values quoted.

REFERENCES

[1] F. G. Riddell and D. A. R. Williams, *Tetrahedron* **30**, 1083 (1974)
[2] F. G. Riddell, P. Murray-Rust and J. Murray-Rust, *Tetrahedron.*
[3] F. G. Riddell, unpublished observations
[4] F. G. Riddell and D. A. R. Williams, *Tetrahedron Letters* 2073 (1971)
[5] F. G. Riddell and M. J. T. Robinson, *Tetrahedron* **23**, 3417 (1967)
[6] E. L. Eliel and M. C. Knoeber, *J. Am. Chem. Soc.* **88**, 5347 (1966); *Ibid.* **90**, 3444 (1968)
[7] F. G. Riddell, J. M. Lehn and J. Wagner, *Chem. Comm.* 1403 (1968)
[8] F. G. Riddell, D. A. R. Williams, C. Hootele and N. Reid, *J. Chem. Soc* (B), 1739 (1970)
[9] F. G. Riddell, *Structure of molecules and internal rotation* (Edited by Orville Thomas) Wiley, in press