The Conformational Equilibria in a Cyclohexene-like System: 3,6-Dihydro-1,2-oxazine

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Low-temperature n.m.r. spectra of some 3,6-dihydro-1,2-oxazines show peaks due to *cis*- and *trans*-isomers. Peak-area measurements by planimetry show that 2-methyl and -ethyl substituents prefer to be equatorial by *ca.* 1.0 kcal mol^{-1} (1 cal = 4.184 J), a 2-isopropyl group has a larger equatorial preference (>1.3 kcal mol^{-1}), and a 6-phenyl group prefers to be equatorial by *ca.* 1.3 kcal mol^{-1}. There are substantial solvent effects upon the equilibria.

DESPITE the enormous amount of conformational data now available on cyclohexane [1] and its heterocyclic derivatives [2,3] there is a paucity of information on cyclohexene and related systems. This arises for two main reasons. First, cyclohexene has a very low barrier to ring inversion, *ca.* 5.3 kcal † mol^{-1} at −164 °C, [4] making studies of conformational equilibria by low temperature n.m.r. methods almost impracticable, although these methods can be widely employed for cyclohexane derivatives.[5] Secondly, chemical equilibration as a method for investigating conformational equilibria [6] has not been employed for lack of suitably authenticated conformation-holding groups and possibly also even suitable equilibration reactions.

An answer to these problems may be found by the inclusion of a slowly inverting nitrogen atom in the ring. At temperatures where nitrogen inversion is slow on the n.m.r. time scale both *cis*- and *trans*-isomers may then be observed in the n.m.r. spectrum. We have previously employed this technique in the tetrahydro-1,2-oxazine series,[7] and report here its application in the dihydro-1,2-oxazine series,

The data on conformational equilibria in cyclohexenoid systems are sparse and confusing. It is known that cyclohexene possesses a half-chair conformation of symmetry C_2.[8,9] In this conformation there are axial-like and equatorial-like positions on carbons 3(6) and 4(5). Low-temperature n.m.r. measurements suggest that fluorine, chlorine, and bromine marginally prefer to be equatorial at C-4 but that iodine has a very slight axial preference.[10] Some work by Rickborn suggests that a 4-equatorial methyl group is *ca.* 1.0 kcal mol^{-1} more stable than a 4-axial.[11] Few data are available concerning equilibria at position 3 although it has been suggested that bulky substituents prefer the axial position.[12,13]

Because of the situation outlined above we decided to investigate the conformational equilibria in 3,6-dihydro-1,2-oxazines. In this system the rate of nitrogen inversion is retarded by the adjacent oxygen atom,[14] rendering both *cis*- and *trans*-forms of suitable derivatives visible in the n.m.r. spectrum at readily accessible temperatures (*ca.* − 40 °C). Shortly after this work had commenced Katritzky and his co-workers reported on the conformational equilibrium in two 6-phenyl-3,6-dihydro-1,2-oxazines.[15] The investigations we report here, covering a more extensive set of compounds, by and large confirm Katritzky's conclusions,[15] but point out several important areas where further investigation would seem appropriate.

† 1 cal = 4.184 J.

EXPERIMENTAL

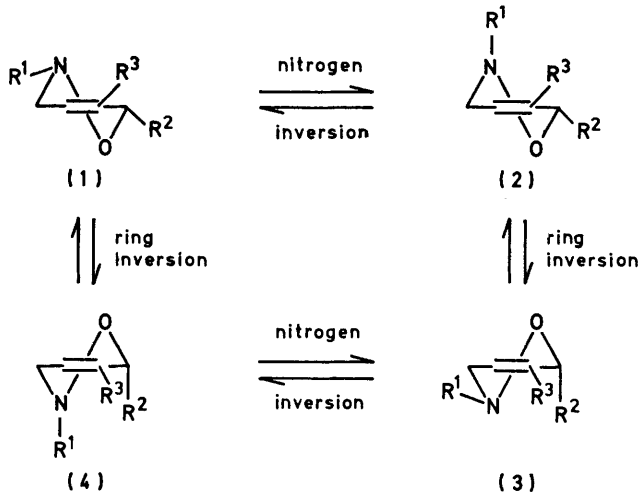
The compounds were prepared by the Diels–Alder reaction of 1-chloro-1-nitrosocyclohexane with the appropriate diene.[16] N.m.r. spectra were obtained for 10% w/v solutions on a Perkin-Elmer R32 spectometer operating at 90 MHz in Stirling or on a Varian A60 spectrometer in McMaster University, Hamilton, Ontario, Canada, using a sufficiently low r.f. field to avoid saturation of resonances. The relative amounts of *cis*- and *trans*-isomers were determined by planimetry of appropriate parts of the low-temperature spectra. In some cases planimetry was performed on spin-decoupled resonances to resolve overlap of the multiplets due to each isomer. The results are recorded in the Table.

DISCUSSION

In our work on the ^{13}C n.m.r. spectra of dihydro-1,2-oxazines [17] we were able to conclude that substituents on nitrogen and position 6 largely prefer equatorial positions. A similar conclusion was reached by Katritzky.[15] Although quantitatively his dipole-moment results were at variance with his more accurate n.m.r. measurements their qualitative significance is that the *N*-equatorial conformation (1) predominates. Given this conclusion we can proceed to interpret our results in terms of the Scheme.

It is accepted that nitrogen inversion is a slower process than ring inversion in these dihydro-oxazines.[14,15] Therefore the *cis*–*trans*-equilibrium frozen-out in the n.m.r. spectrum will be (1 + 4) ⇌ (2 + 3). If we eliminate (4) as a participant on the left hand side the observed equilibrium will be (1) ⇌ (2 + 3). In the results for the *cis* ⇌ *trans* equilibrium of the 6-methyl, 6-phenyl, and 5-methyl-6-phenyl series in $CDCl_3$ solutions, it is seen that the position of the equilibrium varies to a far greater extent with the N-substituent than with the C-substituent. This suggests that the main contribution to the *cis* ⇌ *trans* equilibrium is (1) ⇌ (2). In view of this we can suggest that as a first approximation the *cis*–*trans* energy difference in the *N*-methyl compounds

of 0.8—1.0 kcal mol^{-1} represents the free-energy difference of equatorial and axial *N*-methyl groups. With a free-energy difference of this size for methyl it is likely that the



free-energy difference for *N*-t-butyl would be much greater. We are thus led to agree with Katritzky's conclusion that the equilibrium in *N*-t-butyl-6-phenyldihydro-1,2-oxazine (ΔG = 1.3 kcal mol^{-1}) [15] is largely recalculation of the free-energy difference for *N*-methyl as 1.00 kcal mol^{-1}. Similar calculations for the *N*-ethyl group give its conformational free-energy difference as 0.96 kcal mol^{-1}. The *cis–trans* free-energy difference in *N*-isopropyl-6-phenyldihydro-1,2-oxazine (1.3 kcal mol^{-1}) is very close to that of the *N*-t-butyl derivative, suggesting that *N*-isopropyl substituents exist almost exclusively in the equatorial position ($\Delta G > 1.3$ kcal mol^{-1}) and that the observed equilibrium is of the 6-phenyl group.

Why should the conformational free-energy of an axial *N*-isopropyl group be so much greater than for a methyl or ethyl group? Part of the answer may be associated with possible entropy of mixing present in the ethyl derivative due to rotation about the N–C bond. This will be lost for the isopropyl group as there should be only one permitted conformation with C–H *endo* to the ring (two are permitted for ethyl). This will, however, only contribute $<RT\ln 2$ to the free energy difference (<0.3 kcal mol^{-1}), so clearly some other more important factor is operating. This may also be seen in the conformational equilibria of cyclohexane derivatives (Me, 1.7; Et, 1.7; Pr^i *ca.* 2.5 kcal mol^{-1}).[18] The free-energy difference for *N*-isopropyl may therefore be as much as 0.8 kcal mol^{-1} higher than for *N*-methyl.

If we now accept that an *N*-isopropyl group prefers to be almost exclusively equatorial (say $\Delta G > 2.0$ kcal mol^{-1}) we can turn to the conformational equilibria in the 5-methyl-6-phenyl series. From the result for the *N*-isopropyl compound ΔG for the 6-phenyl is calculated to be 1.0 kcal mol^{-1}. If this value is now applied to the N-Me and N-Et compounds the ΔG values of NMe and

Conformational free energy differences ($-\Delta G$) for 3,6-dihydro-1,2-oxazines (determined by areas method) for *trans* ⇌ *cis*

C-substituent (R^2,R^3)	N-substituent (R^1)	Solvent/temp. (°C)	K	$-\Delta G$/kcal mol^{-1}	% Less stable conformer(s)	Resonance observed	Chemical shifts (δ) of peaks integrated Major	Minor
6-Me	Me	$CDCl_3$ (−45)	8.81 ± 1.8	0.98 ± 0.10	10.7 ± 2	6 Me	1.21	1.39
6-Me	Et	$CDCl_3$ (−40)	5.06 ± 0.74	0.75 ± 0.07	16.5 ± 2	6 H Me decoupled	4.60	4.40
6-Ph	Me	$CDCl_3$ (−45)	6.14 ± 1.0	0.82 ± 0.07	14.0 ± 2	6 H	5.53	5.27
6-Ph	Et	$CDCl_3$ (−40)	5.66 ± 2.0	0.80 ± 0.14	15.0 ± 4	6 H	5.50	5.27
6-Ph	Pr^i	$CDCl_3$ (−50)	20.2 ± 4.7	1.32 ± 0.10	4.7 ± 1	6 H	5.61	5.37 (60 MHz)
5-Me, 6-Ph	Me	$CDCl_3$ (−38)	5.49 ± 0.42	0.79 ± 0.03	15.4 ± 1	6 H	5.37	4.96
						N Me	2.76	2.56
						5 Me	1.43	1.69
		CD_3CN (−40)	2.42 ± 0.1	0.41 ± 0.02	29.2 ± 1	6 H	5.24	4.89
						N Me	2.59	2.39
						5 Me	1.35	1.57
		CD_3OD (−44)	9.52 ± 1.1	1.02 ± 0.09	9.5 ± 1	6 H	5.31	4.92
						N Me	2.67	2.46
						5 Me	1.37	1.58
		C_5D_5N (−40)	2.76 ± 0.28	0.47 ± 0.02	26.6 ± 2	N Me	2.72	2.48
						5 Me	1.37	1.54
		$CFCl_3$ (−40)	2.71 ± 0.14	0.46 ± 0.02	26.9 ± 1	6 H	5.18	4.73
						N Me	2.57	2.40
						5 Me	1.37	1.58
5-Me, 6-Ph	Et	$CDCl_3$ (−51)	5.94 ± 0.98	0.78 ± 0.06	14.4 ± 2	6 H	5.42	5.10 (60 MHz)
5-Me, 6-Ph	Pr^i	$CDCl_3$ (−54)	10.49 ± 2.8	1.02 ± 0.1	8.7 ± 2	6 H	5.38	5.05 (60 MHz)
5-Ph, 6-Me	Me	$CDCl_3$ (−41)	1.63 ± 0.2	0.22 ± 0.1	38.0 ± 3	6 Me	1.15	1.42
5-Ph, 6-Me	Et	$CDCl_3$ (−35)	1.16 ± 0.1	0.07 ± 0.1	46.3 ± 2	6 H Me decoupled	5.26	5.08
5-Ph, 6-Me	Pr^i	$CDCl_3$ (−35)	1.31 ± 0.1	0.13 ± 0.1	43.3 ± 2	6 H Me decoupled	5.30	5.12

between (1) and (3). Thus the free-energy difference of a 6-phenyl group is *ca.* 1.3 kcal mol^{-1}. Given this value we can recalculate the proportions of (1), (2), and (3) present in the equilibrium of the *N*-methyl-6-phenyl compound and arrive at the following figures: (1) = 86%; (2) = 9.5%; (3) = 4.5%. This now allows

NEt groups are found to be *ca.* 1.1 kcal mol^{-1}. The values found for *N*-methyl and *N*-ethyl groups in this series agree well with those in the 6-phenyl series. The lower value for the conformational free-energy difference of the 6-phenyl group (1.0 *vs.* 1.3 kcal mol^{-1}) is presumably due to torsional strain between the 5-methyl and 6-phenyl groups in 6-phenyl equatorial arrangement.

It is difficult to draw conclusions about the conformational equilibrium of a 6-methyl group in the absence of data from the 2-isopropyl-6-methyl derivative. From the data obtained for the other two compounds it is clear that it has an equatorial preference as large as, if not larger than, a 6-phenyl group.

The series with 5-phenyl-6-methyl-substituents is obviously anomalous when compared with the three other series studied. The equlibrium is almost evenly balanced between *cis* and *trans* and does not vary with the N-substituent. This suggests that the equilibrium (1) $\rightleftharpoons$ (2) is not important for this compound. In conformations (1) and (2) there will be strain due to partial eclipsing of phenyl and methyl along the C(5)–C(6) bond. In these conformations the tendency of the phenyl to become coplanar with the double bond will be resisted by the 6-methyl group. Only in (3) and (4) can the phenyl go freely into conjugation with the double bond, although the latter is unlikely to contribute much to the conformational equilibrium. Thus the energy of (3) in the 5-phenyl-6-methyl series will be lowered, with respect to (3) in the other series. The main equilibrium is therefore probably between (1), with the phenyl out of conjugation, and (3) with the phenyl group conjugated with the double bond. Although we presume that (1) predominates, it is not clear that this is correct.

We investigated the solvent dependence of the equilibrium for 2,5-dimethyl-6-phenyldihydro-1,2-oxazine. The equilibrium is very solvent dependent. In the strongly hydrogen-bonding solvent CD_3OD and the very weak hydrogen-bonding solvent $CDCl_3$ the free-energy differences are larger than in the non-hydrogen-bonding solvents, CD_3CN, pyridine, and $CFCl_3$. These latter solvents all give very similar free-energy differences. In this ring system solvation will be important both at the hydroxylamine and at the olefinic sides of the molecule. This solvent dependence may partly explain the discrepancy between Katritzky's n.m.r. ($CDCl_3$; $CFCl_3$) and dipole moment (cyclohexane) results.[15] Further investigation is clearly called for.

* Katritzky *et al.* propose a value of 1.9 kcal mol^{-1}.[19] Careful consideration of their work, however, suggests this to be a lower limit and in our opinion the value is probably considerably higher than this.

CONCLUSIONS

The results we find are very similar to those of Katritzky and his co-workers.[15] A 2-methyl or -ethyl group prefers to be equatorial by *ca.* 1.0 kcal mol^{-1}, a similar value to that found for 4-methylcyclohexene but considerably lower than the value for 2-methyltetrahydro-1,2-oxazine.* A 6-phenyl group prefers to be equatorial by *ca.* 1.3 kcal mol^{-1}, although this value drops to *ca.* 1.0 kcal mol^{-1} in the presence of a 5-methyl group. This is contrary to earlier suggestions that bulky substituent at position 3 in cyclohexene prefers the axial position. Finally solvent effects, particularly where hydrogen bonding is involved, are shown to be very important in influencing conformational equilibria in this series.

We thank the Chemistry Department of McMaster University, for providing the facilities for some of this work.

[9/854 *Received, 4th June,* 1979]

REFERENCES

[1] See for example: E. L. Eliel, N. L. Allinger, S. J. Angyal, and C. A. Morrison, 'Conformational Analysis,' Interscience, New York 1965; M. Hanack, 'Conformation Theory,' Academic Press, New York, 1955.
[2] F. G. Riddell, *Quart. Rev.*, 1967, **21**, 364.
[3] J. B. Lambert and S. I. Featherman, *Chem. Rev.* 1975, **75**, 611.
[4] F. A. L. Anet and Z. L. Haq, *J. Amer. Chem. Soc.*, 1970, **92**, 97.
[5] H. Booth, in 'Progress in N.M.R. Spectroscopy,' eds. J. Emsley, J. Feeney, and L. H. Sutcliffe, Pergamon, Oxford, 1969, ch. 3.
[6] F. G. Riddell, in 'Internal Rotation in Molecules,' ed. W. Orville Thomas, Wiley, London, 1974, p. 19.
[7] F. G. Riddell and D. A. R. Williams, *Tetrahedron*, 1974, **30**, 1097.
[8] J. F. Chiang and S. H. Bauer, *J. Amer. Chem. Soc.*, 1969, **91**, 1898.
[9] L. H. Scharpen, J. E. Wollrab, and D. P. Ames, *J. Chem. Phys.*, 1968, **49**, 2368.
[10] F. R. Jensen and C. H. Bushweller, *J. Amer. Chem. Soc.*, 1969, **91**, 5774.
[11] B. Rickborn and S.-Y. Lwo, *J. Org. Chem.*, 1965, **30**, 2212.
[12] E. W. Garbisch, jun., *J. Org. Chem.*, 1962, **27**, 4249.
[13] E. Sakashita, *Nippon Kagaku Zasshi*, 1960, **81**, 49.
[14] F. G. Riddell and H. Labaziewicz, *J.C.S. Chem. Comm.*, 1975, 766.
[15] R. A. Y. Jones, A. R. Katritzky, and S. Saba, *J.C.S. Perkin II*, 1974, 1737.
[16] F. G. Riddell and H. Labaziewicz, *J.C.S. Perkin I*, 1979, 2926.
[17] H. Labaziewicz, F. G. Riddell, and B. G. Sayer, *J.C.S. Perkin II*, 1977, 619.
[18] B. J. Armitage, G. W. Kenner, and M. J. T. Robinson, *Tetrahedron*, 1964, **20**, 747.
[19] R. A. Y. Jones, A. R. Katritzky, S. Saba, and A. J. Sparrow, *J.C.S. Perkin II*, 1974, 1554.