1,2-Oxazine Chemistry. Part 6.† Conformational Analysis of Cyclohexene and a Heterocyclic Analogue by ^{13}C Nuclear Magnetic Resonance Spectroscopy

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The ^{13}C n.m.r. spectra of twenty-six 3,6-dihydro-1,2-oxazines are reported. A multiple linear regression analysis of the substituent effects on the shifts of the ring carbon atoms gives results similar to those found with cyclohexene, suggesting conformational similarities between these ring systems. It is inferred from the results that alkyl groups at positions 3 and 4 in a cyclohexene-like system largely prefer the equatorial position.

MANY reports have appeared of the ^{13}C n.m.r. spectra of cyclohexane and its heterocyclic analogues.[1-6] The conformational behaviour of cyclohexane is well understood, [7,8] and this understanding has now extended into the saturated heterocyclic field.[9] Because of the relative rigidity of the chair form of cyclohexane, giving well defined spatial relationships inside the molecule, and the high relative free energy of the boat-twist forms,[10] ^{13}C n.m.r. spectra of cyclohexane derivatives are readily interpreted in terms of chemical shift substituent effects.[11,12] This approach has been extended by us into the heterocyclic field,[2,3] where the utility of ^{13}C spectra in detecting conformational abnormalities has been amply demonstrated. First, in the 1,3-dioxan series, where there is a large chair-twist free energy difference, we have demonstrated [2] an additivity of effects in conformationally locked systems qualitatively similar to those in cyclohexane. This then enabled us to pinpoint conformational abnormalities in molecules where exceptional

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† Part 5, F. G. Riddell and H. Labaziewicz, *Org. Magnetic Resonance*, 1974, **6**, 599.

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[1] D. K. Dalling and D. M. Grant, *J. Amer. Chem. Soc.*, 1967, **89**, 6612.

[2] G. M. Kellie and F. G. Riddell, *J. Chem. Soc. (B)*, 1971, 1030.

[3] E. L. Eliel, V. S. Rao, and F. G. Riddell, *J. Amer. Chem. Soc.*, 1976, **98**, 3583.

[4] A. J. Jones, E. L. Eliel, D. M. Grant, M. C. Knoeber, and W. F. Bailey, *J. Amer. Chem. Soc.*, 1971, **93**, 4772.

[5] E. L. Eliel, W. F. Bailey, L. D. Kopp, R. L. Willer, D. M. Grant, R. Bertrand, K. A. Christenson, D. K. Dalling, M. W. Duch, E. Wenkert, F. M. Schell, and D. W. Cochran, *J. Amer. Chem. Soc.*, 1975, **97**, 322.

[6] K. Pihlaja and P. Pasanen, *Suomen Kem.*, 1973, **B46**, 273.

[7] E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, 'Conformational Analysis,' Interscience–Wiley, New York, 1965.

[8] M. Hanack, 'Conformation Theory,' Academic Press, New York, 1965.

[9] F. G. Riddell, *Quart. Rev.*, 1967, **21**, 364.

[10] G. M. Kellie and F. G. Riddell, *Topics Stereochem.*, 1974, **8**, 225.

[11] N. K. Wilson and J. B. Stothers, *Topics Stereochem.*, 1974, **8**, 2.

[12] J. B. Stothers, 'Carbon-13 N.m.r. Spectroscopy,' Academic Press, New York, 1972.

strain forces them to adopt twist conformations. Secondly, in 1,3-dithians, where much less strain is required to force a molecule into a twist conformation, we have been able to show additivity of substituent effects when low energy twist conformations, as well as chair conformations, are taken into account.[3] ^{13}C N.m.r. is thus an extremely sensitive indicator of abnormal conformational behaviour in heterocyclic systems.

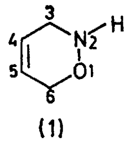
Although a substantial body of data is now available concerning ^{13}C spectra of saturated six-membered rings, much less is to be found dealing with cyclohexene and its analogues. In our current work on the 3,6-dihydro-1,2-oxazine system (1) a large number of compounds were available for ^{13}C spectral investigation as heterocyclic analogues of cyclohexene. Because these spectra would provide data useful in their own right, and also possibly yield some conformational insights into cyclohexenoid systems, we proceeded with this investigation. We present here the spectral results obtained, our spectral assignments, the substituent effects derived from a multiple linear regression analysis, and our conformational interpretation of these results.

TABLE 1

^{13}C Chemical shifts * of 3,6-dihydro-1,2-oxazines

Subst.	C-3	C-4	C-5	C-6	N·C	N·C·*C*	5-Me	6-Me	Ph
None	47.19	124.53	125.71	67.73					
2-Me	56.62	123.49	125.83	68.47	45.98				
2-Et	54.85	123.69	126.22	68.67	52.95	12.00			
2-Pr^i	51.72	124.01	126.28	68.86	56.75	19.32			
5-Me	47.00	119.48	132.49	71.13			18.56		
2-Et-5-Me	54.51	117.75	133.45	71.82	52.80	12.09	18.00		
2-Pr^i-5-Me	51.38	118.02	133.56	71.99	56.61	19.48	17.97		
6-Me	46.87	124.12	130.49	72.42				19.32	
2-Pr^i-6-Me	51.56	123.66	131.30	73.39	56.58	19.16		19.83	
5-Ph	47.23	120.32	137.45	69.05					
2-Me-5-Ph	56.72	119.72	136.10	69.64	45.92				136.53(C-1)
2-Pr^i-5-Ph	51.78	120.21	136.51	69.97	56.74	19.37			139.07(C-1)
4-Ph	48.70	134.48	121.18	68.05					
2-Me-4-Ph	58.23	134.24	121.85	68.43	46.06				
2-Pr^i-4-Ph	53.29	134.83	122.45	68.70	56.74	19.37			137.61(C-1)
6-Ph	47.00	125.23	128.49	77.76					139.12, 128.57, 128.22, 127.90
2-Me-6-Ph	56.39	124.23	128.87	79.46	46.14				139.66, 128.55, 128.25, 127.95
2-Et-6-Ph	54.56	124.47	129.14	79.49	52.86	12.01			139.69, 128.44, 128.06
2-Pr^i-6-Ph	51.48	124.82	129.25	79.73	56.64	19.72 19.05			139.69, 128.44, 128.11
5-Methyl-6-Ph	47.23	120.61	133.56	81.38			19.67		138.04, 129.16, 128.60
2,5-Me$_2$-6-Ph	56.73	119.67	135.00	83.39	46.00		18.76		138.70, 128.90, 128.38
2-Et-5-Me-6-Ph	54.72	119.87	135.32	83.45	52.58	11.89	18.74		138.76, 128.98, 128.33
2-Pr^i-5-Me-6-Ph	51.59	120.25	135.43	83.68	56.27	19.83 18.99	18.66		138.88, 129.06, 129.25
5-Ph-6-Me	47.43	121.65	141.25	73.41				18.30	139.07(C-1), 128.51, 127.40, 126.07
2-Et-6-Me	55.07	120.97	142.19	74.51	52.60	12.12		18.59	139.10(C-1), 128.47, 127.27, 126.23
2-Pr^i-6-Me-5-Ph	52.05	121.29	142.16	74.57	56.44	19.73 19.28		18.40	139.10(C-1), 128.44, 127.24, 126.27

* In p.p.m. (±0.05 p.p.m.) relative to Me_4Si.



(1)

The chemical shift data and spectral assignments are presented in Table 1. Assignment of the resonances was largely trivial, save for the case of *N*-isopropyl derivatives where off-resonance decoupling identified the N·C signals from the ring (triplet) and from the isopropyl group (doublet). The only other difficulty was encountered in differentiating the C-5 resonance of the 5-phenyl derivatives from the resonance of C-1 in the phenyl group. Since both these resonances lack any appreciable nuclear Overhauser effect they are both of low intensity, and they are not amenable to the off-resonance technique. The assignments given are based on a comparison of the way the C-5 resonance changes as NH is changed to NPr^i in a series without a 5-phenyl group with the possible assignments in both series containing a 5-phenyl group. The tentative assignments arrived at in this way were then checked for consistency by calculating the effect of a 6-methyl group and confirming this effect by evaluating differences between the chemical shifts in the 5-phenyl and 5-phenyl-6-methyl series. Reversal of the assignments of C-5 and the phenyl C-1 considerably worsens the fit in the regression analysis, further confirming their validity.

Assumption of additivity of substituent effects is customary in systems such as this. The chemical shift of the *x*th ring carbon atom in the *n*th compound (Δxn) is given by equation (1), where Δxp is the shift of the *x*th

$$\Delta xn = \Delta x\mathrm{p} + \sum_{\mathrm{u}}^{\mathrm{v}} \mathrm{E}_x^y + \mathrm{k} \qquad (1)$$

carbon atom in the parent and the terms E_x^y are the *y* effects of substituents on the chemical shift of carbon atom *x*. The constant k is usually arbitrarily set at 0.*

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* For this work we chose not to set k = 0.

One thus obtains an overdetermined set of linear equations from which the substituent effects E can be evaluated by multiple linear regression analysis. Our derived substituent effects are presented in Table 2. For comparison, Table 3 presents the effects of substitution in the related systems cyclohexene, cyclohexane, piperidine, and 1,3-dioxan.

TABLE 2

Substituent effects on chemical shifts * (p.p.m.)

Ring atom	Substituent								
	2-Me	2-Et	2-Pr^i	5-Me	6-Me	4-Ph	5-Ph	6-Ph	Constant
C-3	9.46 ±0.09	7.60 ±0.09	4.49 ±0.08			1.67 ±0.10	0.29 ±0.07		−0.11
C-4	−0.73 ±0.26	−0.61 ±0.25	−0.33 ±0.22	−4.89 ±0.22	0.62 ±0.26	11.05 ±0.31	−3.12 ±0.25	1.43 ±0.22	−0.71
C-5	0.21 ±0.32	0.83 ±0.31	0.78 ±0.27	6.45 ±0.28	4.82 ±0.32	−4.30 ±0.38	10.63 ±0.31	2.40 ±0.28	0.09
C-6	1.07 ±0.21	1.16 ±0.21	1.29 ±0.18	3.61 ±0.18	4.74 ±0.21	0.21 ±0.26	1.29 ±0.20	10.96 ±0.18	−0.33

* A positive effect indicates a shift to low field, *i.e.* an increase in the shift difference from Me_4Si.

Electron diffraction [13] and microwave [14] spectroscopy show that cyclohexene has a half-chair conformation of symmetry C_2. The barrier to ring inversion in cyclohexene, just measurable by n.m.r. spectroscopy,[15] is *ca.* 5.3 kcal mol^{-1} at −164 °C, although the mechanism of ring inversion remains a matter of dispute.[16]

TABLE 3

Comparison of substituent effects in dihydro-oxazines, cyclohexenes, cyclohexanes, and piperidine (p.p.m.)

Parameter [a]	Oxazines	Cyclohexenes [b]	Cyclohexanes [c]	Piperidines [b]
α5Me5	6.45	7.1		
α6Me6	4.74	7.1	5.6 *eq* 1.1 *ax*	
α5Ph5	10.63	9.0		
β2Me3	9.46	9.4	8.9 *eq* 5.2 *ax*	9.2
β2Et3	7.60	6.2		
β5Me4	−4.89	−4.9		
β5Me6	3.61	6.0		
β6Me5	4.82	6.8	8.9 *eq* 5.2 *ax*	
β4Ph5	−4.30	−3.0		
β5Ph4	−3.12	−3.0		
β6Ph5	2.40	2.9		

[a] The nomenclature α5Me5 refers to the α-effect of a 5-Me group on C-5. [b] Data from ref. 12. [c] Data from ref. 1.

Axial-like and equatorial-like positions occur on carbon atoms 3(6) and 4(5) in the cyclohexene ring. Low-temperature n.m.r. measurements [17] suggest that fluorine, chlorine, and bromine marginally prefer to be equatorial at C-4 but that iodine marginally prefers to be axial. Few data are available concerning equilibria at C-3 or equilibria of alkyl and aryl groups at C-3 or -4, although it has been suggested that bulky substituents at C-3 prefer the axial position.[18,19]

An interesting substituent effect on ^{13}C chemical shifts found in cyclohexane and in saturated six-membered heterocycles is the γ-axial effect. This is a shielding of 5—10 p.p.m. experienced by a ring carbon atom from a γ-axial methyl group. The effect appears in a variety of systems and consideration of its magnitude *versus* conformational strain (Table 4) involved suggests that it is largely due to molecular geometry and not to steric compression as has been suggested.[1-6] There is no large γ-effect observed in either the oxazines or cyclohexene. The effects of a 2-alkyl substituent on C-4 or of a 6-alkyl or -aryl substituent on C-4 are small (between −0.8 and 1.5 p.p.m.). Now the observed effects in the dihydro-oxazines will be an average of axial and equatorial effects weighted according to conformer population. We can therefore conclude that, if there is a γ-axial effect in cyclohexenoid systems of (say) 4 p.p.m. or more, alkyl substituents prefer to be equatorial. This argument, which probably holds best for C-4 substituents in cyclohexene (*N*-substituents in the oxazines) where the geometry is more cyclohexane-like than for C-3 substituents (C-6 in the oxazines), is reinforced by two other observations. The β-effect of an *N*-alkyl group on C-3 (+9.46) is closer to the β-effect of an equatorial methyl group in cyclohexane (+8.9) than an axial group (+5.2).[1] Moreover it is satisfactorily close

TABLE 4

γ-Axial effect *versus* conformational free energy difference for some six-membered rings

Ring	ΔG/ kcal mol^{-1}	Ref.	γ-Effect (p.p.m.)	Ref.
Methylcyclohexane	1.7	7, 8	−5.4	1
2-Methyl-1,3-dioxan	4.0	*a*	−9.0	2
4-Methyl-1,3-dioxan	2.9	*b*	−7.3, −5.3	2
2-Methyl-1,3-dithian	1.9	*c*	−9.4	3
4-Methyl-1,3-dithian	1.6	*c*	−5.5, −6.5	3

[a] F. W. Nader and E. L. Eliel, *J. Amer. Chem. Soc.*, 1970, **92**, 3050. [b] K. Pihlaja and S. Luoma, *Acta Chem. Scand.*, 1968, **22**, 2401. [c] K. Pihlaja, *J.C.S. Perkin II*, 1974, 890.

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[13] J. F. Chiang and S. H. Bauer, *J. Amer. Chem. Soc.*, 1969, **91**, 1898.

[14] L. H. Scharpen, J. E. Wollrab, and D. P. Ames, *J. Chem. Phys.*, 1968, **49**, 2368.

[15] F. A. L. Anet and Z. L. Haq, *J. Amer. Chem. Soc.*, 1965, **87**, 3147.

[16] J. E. Anderson and J. D. Roberts, *J. Amer. Chem. Soc.*, 1970, **92**, 97.

[17] F. R. Jensen and C. H. Bushweller, *J. Amer. Chem. Soc.*, 1969, **91**, 5774.

[18] E. W. Garbisch, jun., *J. Org. Chem.*, 1962, **27**, 4249.

[19] E. Shakashita, *Nippon Kagaku Zasshi*, 1960, **81**, 49.

to the β-equatorial effect of an *N*-methyl group in piperidine (+9.2).[12] The alternative, though in our opinion much less likely, is that if there is a substantial axial population at C-3 the γ-axial effect in cylohexene is small.

The overall similarities between the values shown in Table 3 for the dihydro-oxazines and the cyclohexenes suggest considerable conformational similarities between these systems. This complements, in these unsaturated systems, the qualitative similarities in conformational behaviour between cyclohexane and its hetero-analogues.[9]

We draw attention to the similarities of the α-phenyl effects at C-4, -5, and -6 (11.05, 10.63, and 10.96, respectively). The magnitude of the effect is unaffected by the nature of the carbon atom carrying the phenyl group.

Another observation relates to β-substituent effects on olefinic carbon atoms. If the β-substituent is on the adjacent olefinic carbon the effect is negative (*ca.* −4 p.p.m.), whereas if the β-substituent is on the allylic carbon atom the effect is positive (+4 p.p.m.).

EXPERIMENTAL

The compounds were prepared by Diels–Alder addition of 1-chloro-1-nitrosocyclohexane to the appropriate diene and subsequent alkylation of the resulting dihydro-oxazine. Details will be presented in a forthcoming paper.[20] As in previous work, the 4-phenyl and 5-phenyl derivatives were run as mixtures, whose composition was readily determined from the proton n.m.r. spectra.[21]

Spectra were recorded for solutions in $CDCl_3$ (*ca.* 20% w/v) with a Bruker WH90 instrument at McMaster University. Computations were performed with the Stirling University computer using the regression part of the package SPSS.

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[20] H. Labaziewicz and F. G. Riddell, in preparation.

[21] F. G. Riddell and H. Labaziewicz, *Org. Magnetic Resonance*, 1974, **6**, 599.