Conformational Analysis. Part 10.[1] A Theoretical and Nuclear Magnetic Resonance (Lanthanide-induced Shift) Study of the Conformation of Cyclohex-2-enone

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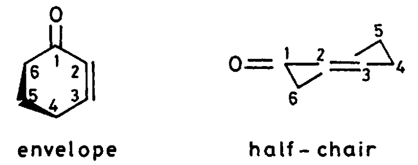
A combined study of the conformational behaviour of cyclohex-2-enone has been carried out using theoretical methods (MNDO, MMPI, STO-3G) and the lanthanide-induced shift (l.i.s.) n.m.r. technique. The theoretical results are all consistent with a predominant envelope conformation (pucker angle 22—26°), the most stable half-chair conformer (torsion angle *ca.* 15°) is *ca.* 0.5—1.5 kcal mol^{-1} less stable. The results of l.i.s. analysis give excellent agreement with both the half-chair and envelope conformations. In this not very well determined system this technique cannot differentiate between these very similar conformers.

In previous parts[2,3] of this series, we have shown that the simultaneous use of ^1H and ^{13}C lanthanide-induced shift (l.i.s.) techniques can provide information on conformations and conformational energies for a wide variety of molecules. In this work we have tried to combine this proven technique with theoretical methods for predicting molecular conformations. Semiempirical and force-field calculations are now able to predict primary molecular structures accurately. However, the determination of torsion angles, *i.e.* conformations in a complex cyclic molecule such as cyclohexenone, is not an easy task even for today's sophisticated theoretical methods; and the combination of the determination of the primary structure by theory and the secondary structure by l.i.s. is one possible approach to determining the precise conformation of such molecules in solution.

We hoped to use this combined procedure to deduce the conformations of cyclohexenone and related unsaturated ketones in solution. These compounds are of particular interest owing to the presence of two opposing forces: the carbonyl and olefinic groups will prefer a coplanar conformation while the methylene groups will try to adopt a staggered arrangement; these interactions are important in view of the role proposed for the conformation of ring *A* in steroidal hormones in relation to their activity[4]. We describe here our work on cyclohexenone.

The conformation of cyclohexenone in solution is not known with any certainty, although microwave studies[5] and Raman spectra[6] have suggested an envelope as opposed to a half-chair conformation in the gas phase (see Figure 1). The microwave study concluded that the cyclohexenone structure is nonplanar, but the model used to reproduce the rotational constants was not refined; on the other hand, the low-frequency Raman spectrum is in accord with a vibrational motion involving primarily the motion of the C-5 through the (approximate) plane of the remaining ring atoms. The geometry used in this case (envelope with a pucker angle 5432† equal to 22.6°) was obtained from MMPI calculation.

For the closely related 5-methylcyclohex-2-enone, earlier c.d.[7] and n.m.r.[8] studies suggested an envelope conformation, whilst a more recent c.d. investigation[9] proposed a half-chair conformation as more stable with the methyl group equatorial in hydrocarbon solvents (*ca.* 80%).



envelope half-chair

Figure 1. Conformations of cyclohexenone

The general technique of l.i.s. has been well documented[10] and used with $La(fod)_3$ to remove the ^{13}C diamagnetic complexation shifts; the pseudo-contact shifts obtained can then be used quantitatively to determine conformations in solution.

Experimental

The ^1H and ^{13}C spectra were all obtained with a Bruker WM 250 MHz spectrometer at *ca.* 25 °C. All solutions were in $CDCl_3$, previously stored over molecular sieves and passed through a dried Al_2O_3 column immediately before use. Lanthanide shift reagents were used as commercial samples dried *in vacuo* over P_4O_{10} for 24 h. A commercial sample of cyclohexenone was used without further purification.

The assignments of ^{13}C shifts were taken from previous results.[11]

For l.i.s. experiments the incremental weighing method was employed, with molar ratios (ρ) in the range 0.0—0.20 and four additions of lanthanide shift reagent ($\rho = [L]/[S]_0$).

Computer calculations were performed by use of the University of Liverpool VAX 11/780 and IBM 3083 computers.

Theoretical Calculations

The geometries used to determine the conformations in solution were obtained from two different theoretical methods: semiempirical *via* the computer program MNDO,[12] and Allinger's force-field through the MMPI[13] program.

In the MMPI calculations, when all the atoms were free and only the motion for C-5 is restricted by the torsion angle 5432 to obtain the different envelope forms, the energy was not minimised for those forms that have a torsion angle 5432 lower than 14°, because the program tended to give a conformation near to a half-chair but with the π-system non-planar and then the VESCF sequence did not converge. A similar procedure in

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† Here and elsewhere, torsion angles are denoted by position locants only, *i.e.* 5432 ≡ C(5)C(4)C(3)C(2).

Table 1. Heats of formation (a) and steric energies (b) for cyclohexenone (in kcal mol^{-1})^a

Half-chair			Envelope		
θ(5432)^b	(a) MNDO	(b) MMPI	θ(5432)^c	(a) MNDO	(b) MMPI
0°	−33.46	10.55	0°	−33.46	10.55
2°	−33.60	10.07	2°	−33.49	10.38
6°	−34.40	7.75	6°	−33.76	9.34
10°	−35.28	5.51	10°	−34.24	7.89
14°	−34.95	4.37	14°	−34.79	6.40
18°	−31.62	5.07	18°	−35.22	5.10
22°	−23.20	8.23	22°	−35.28	4.14
26°	−8.80	14.29	26°	−34.70	3.68
30°	10.16	15.74	30°	−33.13	3.85
34°	30.85	*d*	34°	−30.15	4.77

^{a} 1 kcal = 4.184 kJ. ^{b} θ(6123) = θ(5432). ^{c} Atoms 1, 2, 3, 4, and 6 in the plane. ^{d} SCF calculations do not converge.

Table 2. GAUSSIAN energies for the most stable forms from MNDO- and MMPI-optimised geometries

Conformer	Geometry	θ^a	Energy^b	ΔMNDO^b	ΔMMPI^b
Half-chair	MNDO	10°	−568.56	−5.64	
	MMPI	14°	−567.86		−6.62
Envelope	MNDO	22°	−569.99	−7.07	
	MMPI	26°	−568.84		−7.60
Planar	MNDO	0°	−562.92	0.000	
	MMPI	0°	−561.24		0.000

^{a} Pucker or twist angle. ^{b} In kcal mol^{-1} from −302.00 a.u.

Table 3. Observed shifts (δ), l.i.s. values (Δ*M*), diamagnetic shifts (Δ*D*), and pseudo-contact shifts (Δ*M* − Δ*D*) for cyclohexenone

	C=O	C-2	C-3	C-4	C-5	C-6
δ^a	200.22	130.44	151.20	26.21	23.18	38.63
Δ*M*^{b}	208.87	85.84	47.10	27.77	34.87	83.12
Intercept	200.28	130.47	151.23	26.24	23.22	38.65
Δ*D*^{c}	10.05	0.00	7.57	0.00	0.00	−1.34
Δ*M* − Δ*D*	198.82	85.84	39.53	27.77	34.87	84.46
	H-2	H-3	H-4	H-5	H-6	
δ^a	6.02	7.01	2.36	2.03	2.44	
Δ*M*^{b}	68.68	22.82	20.48	26.49	63.92	
Intercept	6.01	7.01	2.36	2.02	2.43	

^{a} $[S]_0 \simeq 1.0$M in Cl_3CD. ^{b} From four additions of $Yb(fod)_3$, ρ = 3.20, 6.70, 9.50, and 13.5 × 10^{-2}; all correlation coefficients >0.998, ^{c} From four additions of $La(fod)_3$, ρ = 6.00, 9.80, 15.7, and 21.3 × 10^{-2}; correlation coefficients 0.999 (C=O), 0.999 (C-3), and 0.972 (C-6).

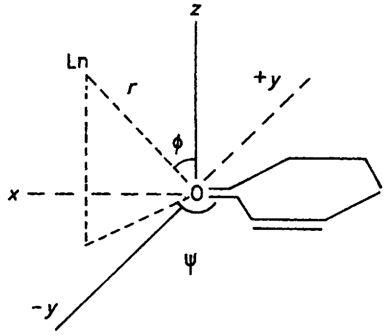

Figure 2. Complexation geometry used for the program HARDER

the MNDO calculation gave conformations with very similar energies without a significant minimum, because the energy gained from the movement of C-5 is compensated by a loss of planarity of O, C-1, C-2, and C-3.

For these reasons, in order to obtain symmetrised geometries, it was necessary to impose some restrictions on the optimisation methods, *e.g.* to put the carbon atoms in a plane except those which are implicated in the variation of pucker or twist angles in the envelope or half-hair conformations, and in this way to avoid the tendency of theoretical methods to give a final conformation which is neither an envelope nor a half-chair conformation but an intermediate one of lower symmetry. Thus these arbitrary restrictions are imposed in order to simplify the description of the molecular conformation.

Table 1 shows the MNDO-calculated heat of formation together with the steric energies from the MMPI calculations as the angle of pucker or twist is varied. The MNDO calculations give a minimum in both conformations: at a torsion angle of 22° for the envelope form and at 10° in the half-chair conformation, while in the MMPI calculations the most stable envelope conformation is predicted when the torsion angle 5432 is 26°, and the lowest energy for the half-chair conformation was found at torsion angles 5432 and 6123 of 14°.

In order to confirm these results, we carried out GAUSSIAN 76 calculations[14] over the most stable forms from MNDO and MMPI geometries in both conformers. The results are displayed in Table 2. In this case the order of energies is in the same sense as in the semiempirical and force-field methods, giving the envelope form as the most stable. In every case the lower (STO-3G) energy was obtained from the MNDO-optimised geometry; the reason for this situation may be the better consideration of π-systems in the MNDO method than in the simpler SCF procedure used in the force-field method. Similarly the 'hardness' of the protons is much greater in the MMPI method owing to the van der Waals component and the torsional term.[15] which gives a more staggered disposition for the aliphatic protons in the optimised geometries, although the carbon skeletons are very similar in the two cases. For all these reasons we conclude that the MMPI method does not afford as good results when we must employ a predefined geometry or restrict the motion of some atoms in the molecule.

When we use both theoretical geometries in the GAUSSIAN 76 calculations, we obtain differences of 1.42 or 0.97 kcal mol^{-1} between the envelope and half-chair conformations, *i.e. ca.* 90 and 80% population for the envelope conformer, in agreement with the experimental result from the microwave and Raman studies,[5,6] which suggested only an envelope form in the vapour phase. The theoretical calculations predict a pucker angle of 22—26° for the envelope conformation and 10—14° for the half-chair.

Results

The observed l.i.s. values (Δ*M*) with $Yb(fod)_3$ are given in Table 3 together with the unperturbed chemical shifts (δ), the extrapolated values (intercept) from the linear regression analysis of the data, and the ^{13}C diamagnetic complexation shifts (Δ*D*) from the corresponding experiments with $La(fod)_3$. The correlation coefficients (all ⩾0.998) demonstrate the accurate linearity of these plots.

The pseudo-contact contributions (Δ*M* − Δ*D*) were analysed using the program HARDER[16] to obtain the required conformational information. This program assumes the co-ordination geometry shown in Figure 2, where the co-ordination centre is placed at the origin. The HARDER

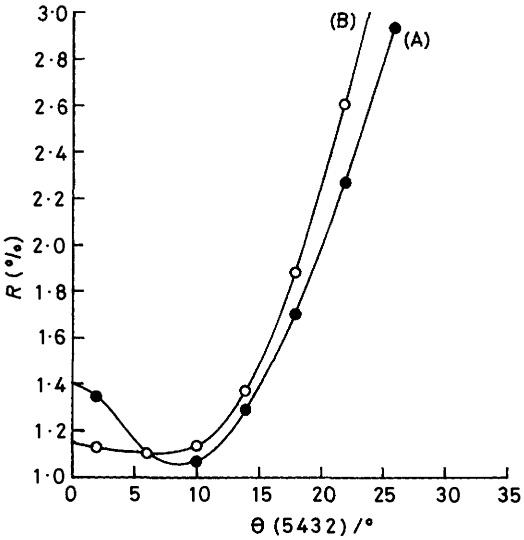

Figure 3. $R(\%)$ *versus* torsion angle 5432 (= 6123) in cyclohexenone half-chair: (A) MMPI geometry; (B) MNDO geometry

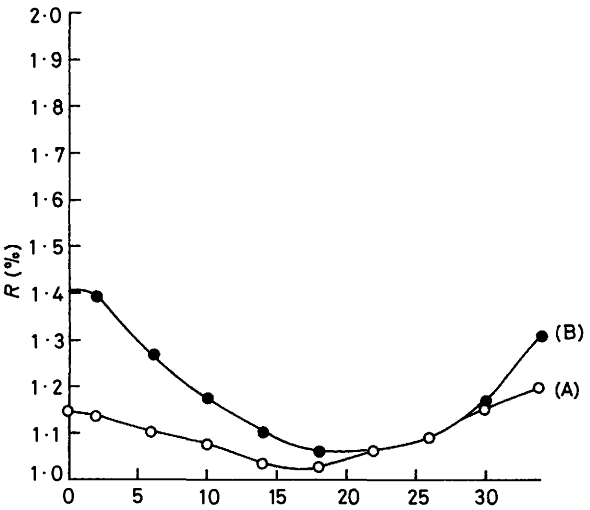

Figure 4. $R(\%)$ *versus* torsion angle 5432 in cyclohexenone envelope: (A) MMPI geometry; (B) MNDO geometry

program is fully described elsewhere[16] and is an extension of the LIRAS-3[3] programme. It performs the same calculations except for one major difference: whereas LIRAS-3 allows for co-ordination on the '$+y$' and '$-y$' sides (Figure 2) by reflection of the lanthanide ion in the *xz* plane, HARDER has a separate co-ordination geometry for the '$+y$' side, *i.e* a second set of polar co-ordinates r, ψ, and φ which can be varied independently of the first, in the '$-y$' side. This means that we can allow for different co-ordination geometries on the '$+y$' and '$-y$' sides and vary the population between them, according to differences in substrate geometry from one side to the other, as occur in the case of cyclohexenone.

However, although this allows for more reasonable co-ordination geometries, it also means that we have eight unknowns: two sets of r, ψ, and φ, plus a percentage population and the normalisation factor in the McConnell-Robertson equation. As a consequence of this, more data are required to ensure over-determined solutions and hence good results. A second problem for this method is the greatly increased computing time required, typically of the order of 1 h as compared with 2—3 min for LIRAS-3.

We have used this model with four-site lanthanide ion complexation in which the lanthanide position is reflected in the *xy* plane from the two independent sites, and the lanthanide ion position is allowed to vary over a chemically acceptable range,[17] according to the spatial disposition of the lone pairs of the carbonyl oxygen, of r = 2.50—3.50 Å, φ = 0—90°, and ψ = 120—160°. In addition, the geometries obtained by the different theoretical methods were required. These were analysed using the l.i.s. results. In Figures 3 and 4 are displayed representations of the agreement factor $R(\%)$ *versus* the angles of pucker and twist, respectively. The half-chair conformation shows a minimum at *ca.* 5—10° (R = 1.1%) for both MMPI and MNDO geometries. In view of the very good agreement factor in both cases, we may regard these minima as both well within the range of acceptability, *i.e.* giving essentially the same result.

In the envelope form both geometries (MNDO and MMPI) give a mimimum at the same pucker angle of 18° (Figure 4), but in this case the minima have a flatter shape than with the half-chair. Over the entire range of puckering angle considered (0—30°), the agreement factor is well within the range of acceptability ($< 5\%$). Thus these curves demonstrate that in this case the l.i.s. method cannot differentiate between the different conformations. The reason for the difference with the half-chair conformation is easy to see. In the envelope form the orientation of the complexing group (C=O) and the ring does not change; only C-5 varies (and therefore H-5 and also H-4 and -6). In the half-chair conformation the orientation of the carbonyl group *is* a function of the ring conformation, and the l.i.s. analysis will reflect this dependence.

The l.i.s. parameters for the minimum in the envelope conformation are: r_{-y} = 2.70 Å, φ_{-y} = 46°, ψ_{-y} = 160 °, r_{+y} = 2.74 Å, φ_{+y} = 60°, ψ_{+y} = 160°, and the population for the '$+y$' side is 54%. For the half-chair, the best result was with r_{-y} = 2.89 Å, φ_{-y} = 36°, ψ_{-y} = 160°, r_{+y} = 2.61 Å, φ_{+y} = 69°, ψ_{+y} = 160°, and the population for the '$+y$' side is 54%.

Conclusions

Of the theoretical methods used, MNDO gave equal energies for the envelope (θ = 22°) and half-chair forms (θ = 10°). Results from MMPI and STO-3G are in agreement with a predominant envelope conformation, with a pucker angle of *ca.* 22—26°. The energy difference between this conformation and the most stable half-chair conformation varies from 0.68 (MMPI) to *ca.* 1.4 kcal mol^{-1} (STO-3G).

The reason for the identical energies found in the MNDO calculations could be the underestimation of conjugation: in the envelope conformer the π-system is more planar than in the half-chair conformation.

The l.i.s. analysis gives an excellent agreement factor with both a half-chair conformation with a pucker angle of *ca.* 10° and an envelope conformation with any reasonable angle of pucker (0—30°). In this particular case the system is insufficiently well determined to allow a more precise analysis by the l.i.s. method.

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References

1 Part 9, R. J. Abraham, D. J. Chadwick, and F. Sancassan, *J. Chem. Soc., Perkin Trans. 2*, 1988, 169.

2 R. J. Abraham, H. A. Bergen, and D. J. Chadwick, *J. Chem. Res. (S)*, 1983, 118; *J. Chem. Soc., Perkin Trans. 2*, 1983, 1161; R. J. Abraham, D. J. Chadwick, and F. Sancassan, *Tetrahedron*, 1982, **38**, 3245.

3 R. J. Abraham, D. J. Chadwick, and F. Sancassan, *Tetrahedron*, 1982, **38**, 1485.

4 J. Gawronski, *Ser. Chem. Uniw. Adama Mickiewicza Poznaniv.*, 1976, **21**, 106.

5 S. A. Manley and J. K. Tyler, *Chem. Commun.*, 1970, 382.

6 L. A. Carreira and T. G. Towns, *J. Chem. Phys.*, 1979, **70**, 2273.

7 J.-J. Barieux, J. Gore, and M. Subit, *Tetrahedron Lett.*, 1975, 1835.

8 J.-J. Barieux, J. Gore, and J. Richer, *Bull. Soc. Chim. Fr.*, 1974, 1020.

9 J. K. Gawronski, *Tetrahedron*, 1982, **38**, 3.

10 O. Hoffer, *Top. Stereochem.*, 1976, **9**, 111.

11 D. J. Chadwick and D. H. Williams, *J. Chem. Soc., Perkin Trans. 2*, 1974, 1202; G. Hofle, *Tetrahedron*, 1976, **32**, 1431.

12 M. J. S. Dewar, *J. Am. Chem. Soc.*, 1977, **99**, 4899, 4907; QCPE no. 428.

13 N. L. Allinger and Y. H. Yuh, QCPE nos. 395 and 400 (1980).

14 J. S. Binkely, R. A. Whitesid, P. C. Hariharan, R. Seeper, J. A. Pople, W. J. Hehre, and M. D. Newton, QCPE no. 368 (1978).

15 C. Jaime and E. Osawa, *Tetrahedron*, 1983, **39**, 2769.

16 R. J. Abraham, D. J. Chadwick, F. Sancassan, and P. E. Smith, in preparation.

17 R. J. Abraham, D. J. Chadwick, and F. Sancassan, *Tetrahedron*, 1981, **37**, 1081.

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