Atropisomerism of Cyclohexane Compounds

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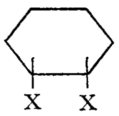
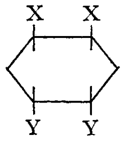
A *cis*-1,2-disubstituted cyclohexane [*e.g.*, (I)] exhibits atropisomerism[1] since the *ax*, *eq* $\rightleftarrows$ *eq*, *ax* transformation converts an asymmetric compound into its mirror image.[2] Resolution of atropisomers is held to be feasible at ordinary temperatures if the activation energy for racemization is greater than 16 kcal./mole.[3] A compound of type (I) is then unresolvable unless this minimum energy barrier to ring inversion can be arranged.

Most of the experimental data on the ring inversion of cyclohexane compounds have been obtained by n.m.r. For the parent compound there is still disagreement about the magnitudes of the activation parameters,[4] an unfortunate situation in view of the central position of cyclohexane in conformational analysis. We believe that the development of a nonspectral method for the study of ring inversion would be of value and that the simplest of these would involve measurement of the racemization of an atropisomeric system. We describe results which show that the approach is tractable.

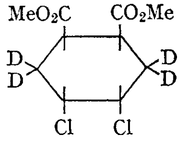
We expected that a *cis*-1,2-disubstituted cyclohexane would invert less rapidly than its epimer because in the *cis*-compound the substituents must pass each other. This expectation was incorrect. *cis*- and *trans*-1,2-Disubstituted [3,3,6,6-$^{2}H_{4}$]cyclohexane compounds did show the expected[5] differing temperature dependence of their n.m.r. spectra, but $\Delta G^{\ddagger}$ values calculated[6] from the coalescence temperatures and chemical shifts of the low-field signals were the same, *i.e.*, 10·7—11·0 kcal./mole.



(I)



(II)



(III)

The spectral results shown in Figure 1 are typical. This Figure shows the n.m.r. spectrum of *cis*-1,2-bismethoxycarbonyl[3,3,4,5,6,6-$^{2}H_{6}$]-cyclohexane at various temperatures. This compound was synthesized in order to facilitate analysis of the temperature dependence of both sets of ring protons. At room temperature, the protons geminal to methoxycarbonyl and to deuterium appear as single peaks at 2·8 and 1·5

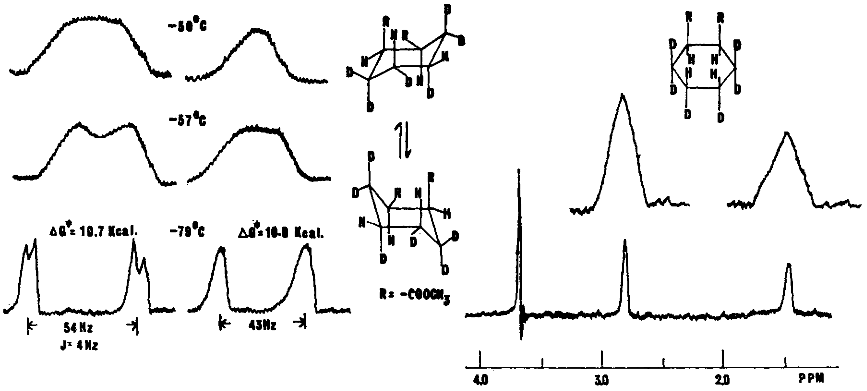


FIGURE 1. *The n.m.r. spectrum of* cis-1,2-*bismethoxycarbonyl*[3,3,4,5,6,6-$^2H_6$]*cyclohexane at various temperatures shown at* 500 *and* 50 *c./sec. sweep widths. The stereochemistry at* C-4 *and* C-5 *is indicated.*

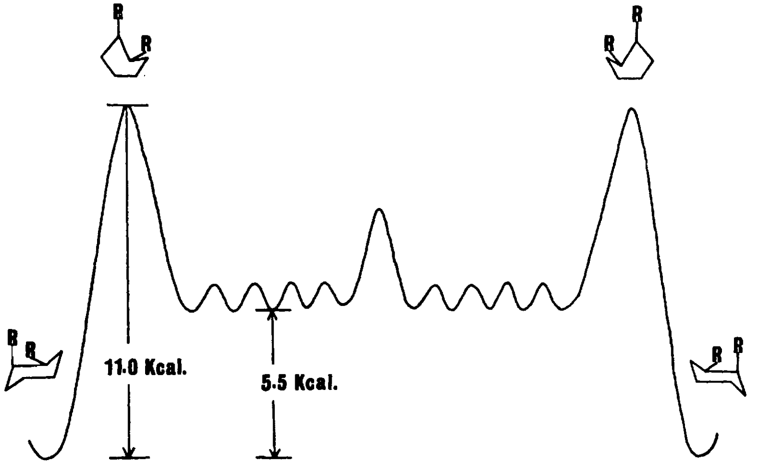


FIGURE 2. *The energy profile for the ring inversion of a* cis-1,2-*disubstituted cyclohexane.*

p.p.m., respectively. As the temperature is decreased two separate coalescence temperatures are observed; one, at —50°, for the protons geminal to methoxycarbonyl, and the other, at —57°, for the protons geminal to deuterium. Two coalescence temperatures are seen because there are two limiting chemical-shift differences: 54 c./sec. for the protons geminal to methoxycarbonyl and 43 c./sec. for the protons geminal to deuterium. The calculated $\Delta G\ddagger$ values are the same, 10·7—10·8 kcal./mole. For this compound, then, a single process leads to exchange of protons on both sides of the ring. Since, from the data quoted above, the rate is the same for both a *cis-* and a *trans*-isomer and does not differ significantly from that observed for cyclohexane[4] or monosubstituted cyclohexanes,[7] the pseudorotation being measured by the n.m.r. method cannot involve the carbon atoms which carry the substituents.

The meaning of these observations is that cyclohexane compounds invert *via* the half-chair transition state of lowest energy. So long as the molecule contains four adjacent CH_2 groups these will become coplanar in the half chair. Because the passing interaction in the *cis*-1,2-disubstituted compounds is unobservable, this must occur from the twist conformation. The energy profile for the ring inversion of a *cis*-1,2-disubstituted cyclohexane then has the form shown in Figure 2.[8] Since the energies of the half-chair and the twist conformations are about 10·8[4] and 5·5[9] kcal./mole above that of the chair, the passing interaction would be unobservable unless it amounted to more than 6 kcal./mole. For resolution to be possible the passing interaction would have to exceed 11 kcal./mole. Thus, in a practical sense, a *cis*-1,2-disubstituted cyclohexane is unresolvable.

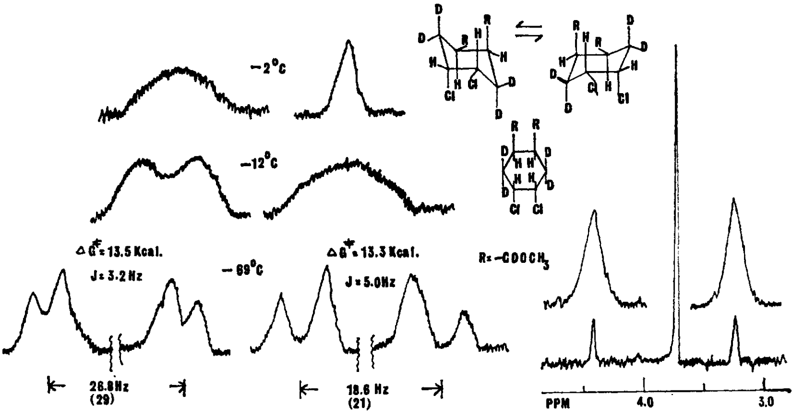


FIGURE 3. *The n.m.r. spectrum of* cis,anti,cis-4,5-*dichloro*-1,2-*bismethoxycarbonyl*[3,3,6,6-$^2H_4$]*cyclohexane at various temperatures.*

The energy of the transition state in the inversion of a substituted cyclohexane would be raised if the substituents were forced to be coplanar in the half chair. A compound such as (II) fulfils this requirement and at the same time retains the property of atropisomerism. The rate of inversion of (II) should be appreciably slower than that of (I), because in (II) either two X's or two Y's must be coplanar in the transition state.

Figure 3 shows the data obtained for such a compound, *viz.*, *cis,anti,cis*-4,5-dichloro-1,2-bismethoxycarbonyl[3,3,6,6-$^2H_4$]cyclohexane (III). At room temperature the tertiary protons geminal to chlorine and to methoxycarbonyl appear as sharp peaks at 5·2 and 4·4 p.p.m., respectively. As the temperature is decreased coalescence is now observed at −2° and −12°. Below −69° two AB quartets are seen with limiting chemical shifts of 29 and 21 c./sec. for the protons geminal to chlorine and methoxycarbonyl. As expected, the $\Delta G\ddagger$ values are the same, 13·3—13·5 kcal./mole, higher by approximately 3 kcal/mole than before.

Since the half-chair conformation with two chlorine atoms coplanar lies more than 13·8 kcal./mole above the chair,[10] compound (III) is considered to invert *via* the half-chair in which the methoxycarbonyl groups are coplanar. It is clear that by a proper choice of X and Y a compound of type (II) can be synthesized which will be resolvable. We are actively exploring such combinations.

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[7] Summarized by F. A. Bovey, E. W. Anderson, F. P. Hood, and R. L. Kornegay, *J. Chem. Phys.*, 1964, **40**, 3099.

[8] For a somewhat similar treatment, see Figure 2 of J. T. Gerig and J. D. Roberts, *J. Amer. Chem. Soc.*, 1966, **88**, 2791.

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