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THE CONFORMATIONAL ANALYSIS OF 4-MONO- AND 4,5-DISUBSTITUTED CYCLOHEXENES

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Abstract—The conformational equilibrium of a number of deuterated 4-mono- and *trans*-4,5-disubstituted cyclohexenes has been studied by NMR spectroscopy and the values of ΔG_R for different R-substituted (at C_4) cyclohexenes determined. It is shown that the so-called "supra-annular effect" does not exist as a special kind of conformational interaction.

Until recently the conformational analysis of cyclohexenes has received little attention. The calculations predict a half-chair form as the preferred conformation for cyclohexene.[1,2] The study of the deuterium-labelled cyclohexene analogs shows that for two possible half-chair conformations the energy of ring inversion is only 5·3 kcal/mole[2] while for two chair conformations of cyclohexane the energy of inversion is 11 kcal/mole. The application of the NMR technique to 4-bromocyclohexene[3] gives the value of ΔG_{Br} as 0·07–0·10 kcal/mole. The value of ΔG_{CH_3} deduced from the kinetics of epoxidation of 4-alkyl- and 4,5-dialkylcyclohexenes, is about 1·1 kcal/mole.[4]

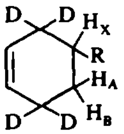
The conformational study of some substituted cyclohexenes by UV and IR spectroscopy[5] and molecular polarisability[6] has been attempted. Thus, the dipole moments of stereoisomeric methyl cyclohexene-4,5-dicarboxylates were measured[6] but unfortunately, no detailed calculation was given. The presence of two irregular —COOMe groups in these models is a great obstacle to any accurate calculation. The conformational analysis was also extended to some heterocyclic analogs of cyclohexene and to polyfunctional derivatives.[8]

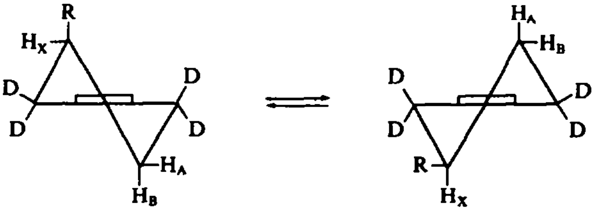
Recently an attempt was made to relate the conformations of the substituted cyclohexenes to the reactivity of the double bond towards electrophylic reagents. The strong deactivation of the double bond in 4-mono- and 4,5-disubstituted cyclohexenes with electronegative substituents is well known and has been demonstrated both by accurate kinetic studies[9] and by semi-quantitative estimations of the rates of addition for a large number of cyclohexene derivatives.[5,10]

This phenomenon was explained by the electrostatic influence of electronegative groups ("field effect").[9] However, in more recent times another interpretation was proposed and widely discussed.[5,10] It was assumed that the low reactivity of the double bond is of conformational origin: the interaction between the π-electrons of the double bond and the electronegative substituents (CHO, COOH, COOMe, NO_2 etc) at positions 4 and 5 should bring about the predominance of conformations with axial substituents.[5b] This kind of interaction was called "supra-annular effect". In the opinion of the authors of this concept, the "supra-annular effect" must be particularly evident in the case of *trans*-4,5-disubstituted cyclohexenes, giving rise to stable *trans*-diaxial conformations. The same concept postulates the stability of axial or diaxial conformations for a large series of cyclohexene derivatives.

RESULTS

The aim of this work was the conformational analysis of some 4-mono- and 4,5-disubstituted cyclohexenes by NMR methods. Preliminary study proved that the spectra of these systems are very complicated. In order to simplify them we prepared a series of 4-mono- and *trans*-4,5-disubstituted derivatives of 3,3,6,6-tetradeutero-cyclohexene (I and II). On the basis of the known evidence[1,2] it was assumed that all these compounds exist in half-chair conformations.

I




IA IB

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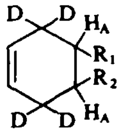
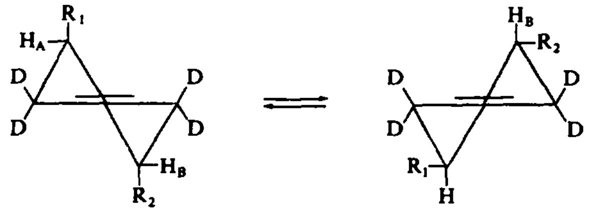




IIA IIB

In the spectra of *trans*-disubstituted cyclohexenes of type II the protons at C_4 and C_5 form an AB system from which J_{AB} can be obtained. The data of the corresponding NMR spectra are presented in Table 1. The value of the dihedral angles in cyclohexene[1] implies that the coupling constants for H_A and H_B must be nearly the same as in the cyclohexane series. Assuming $J_{aa} = 12$ c/s, $J_{ae} = 3{\cdot}5$ c/s and $J_{ee} = 3$ c/s[11] one may easily estimate the conformational equilibrium for the compounds of type II.

TABLE 1. *trans*-4,5-DISUBSTITUTED CYCLOHEXENES (II)

Compounds (type II)	Substituents		Solvent	Proton system	Chemical shifts in ppm (±0·1 ppm)		J_{AB} (±0·2 c/s)
	R_1	R_2			H_A	H_B	
III	COCl	COOMe	—	AB	3·2	2·8	10·3
IV	NO_2	C_6H_5	$CHCl_3$	AB	4·9	2·9	11·1
V	C_6H_5	CHO	$CHCl_3$	ABX $\|J_{AX} = 0\|$	2·4	2·9	10·6*

* $J_{BX} = 2$ c/s; however, the signal of H_B appears as a doublet with broad lines ($W_{\frac{1}{2}} = 5{\cdot}2$ c/s) while H_A gives $W_{\frac{1}{2}} = 2{\cdot}5$ c/s.

The high values of J_{AB} (see Table 1) are convincing proof of the *trans*-diaxial position of protons at C_4 and C_5 and hence the *trans*-diequatorial conformation for all compounds studied. It is to be noted these J_{AB} values are very close to the values of J_{aa} in konduritols.[8]

The saturated compound VI was also studied and found to exist in the diequatorial conformation (J_{AB} = 10·4 c/s, δ_A = 3·0 ppm and δ_B = 2·6 ppm). Since the J_{AB} values for III and VI nearly coincide, the close similarity of the H_A–H_B dihedral angles in both compounds is evident.

In the NMR spectra of 4-monosubstituted cyclohexenes of type I the protons at C_4 and C_5 form an ABX or ABC system. As an example the ABC part of the spectrum of acid VII is shown in Fig. 1. The theoretical spectrum of VII. calculated with the aid of a computing machine, is also given in Fig. 1. In the case of the ABX systems the values $|J_{AX} + J_{BX}|$ on which the conformational assignment was based, could be obtained directly from the spectrum. The corresponding data are given in Table 2.

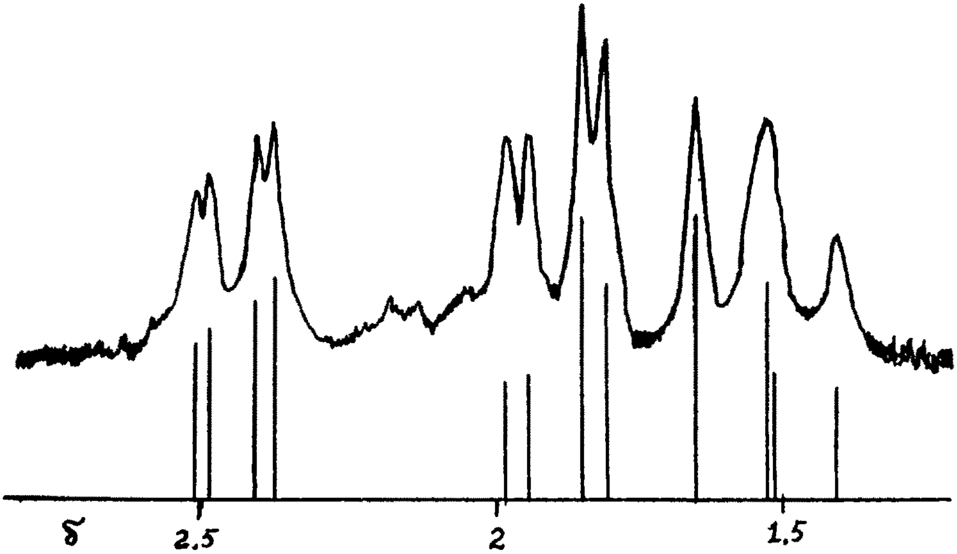
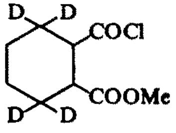
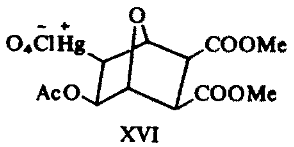


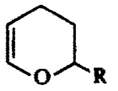
FIG. 1 The ABC-part in the NMR spectrum of VII at 100 Mc: (a) scan; (b) theory (computed).



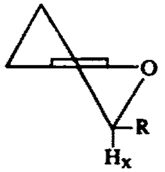
VI



XVI



XIII: R = CHO
XIV: R = COOMe



XV

TABLE 2. 4-MONOSUBSTITUTED CYCLOHEXENES (I)

Compound (type I)	R	Solvent	Proton system	Chemical shift δ ($\pm$0·05 ppm) A	B	C or X	$J_{AX} + J_{BX}$ c/s $\pm$ 0·3 c/s	% of IB	ΔG kcal/mole
VII	COOH	—	ABC	1·55	1·9	2·4	14·1	85	1
VIII	CHO	$CHCl_3$	ABCM*	1·6	1·9	2·5	12·6	70	0·4–0·5
IX	COOMe	$CHCl_3$	ABC	1·6	1·9	2·4	13·8	80	0·8–0·9
X	CN	$CHCl_3$	ABX	Narrow multiplet (1·5–2·1 ppm)		2·8	11·3	55	0·1
XI	NO_2	—	ABX	Narrow multiplet (1·9–2·3 ppm)		4·55	11·9	60	0·2–0·3
XII	COC_6H_5	C_6H_6	ABX	Narrow multiplet (1·5–1·9 ppm)		3·3	12·7	70	0·4–0·5

* $J_{CM} = 1$ c/s: $J_{AM} = J_{BM} = 0$

The position of the conformational equilibrium can be found from the following equation:[11, 12]

$$|J_{AX} + J_{BX}| = N\,\Sigma J_{IB} + (1 - N)\,\Sigma J_{IA} = (J_{aa} + J_{ae}) + (1 - N)(J_{ee} + J_{ae})$$

The main error in these calculations originates from the uncertainty of the standard values for J_{aa}, J_{ae} and J_{ee} and from the influence which the electronegativity of the substituent exerts on the coupling constants. However, calculations of this sort are commonly used for semi-quantitative estimations.[11, 12] We determined the positions of conformational equilibrium assuming $J_{aa} = 12$ c/s, $J_{ae} = 3{\cdot}5$ c/s and $J_{ee} = 3$ c/s:[11] the figures thus obtained and the values of ΔG are given in Table 2.

For comparison the conformational equilibrium of two 2-monosubstituted dihydropyrans (XIII and XIV) was studied. Considering the proton at C_2 as the X-part of an ABX system[13, 14] it is possible to estimate the position of the equilibrium in the same manner as above. In the spectrum of XIII the proton at C_2 gives a multiplet (δ 4·2–4·1 ppm) with band width of 11·5 c/s (outer lines); in the case of XIV it also gives a multiplet (δ 4·35–4·2 ppm) with band width of 11·2 c/s. Assuming, as in the case of tetrahydropyran derivatives,[13, 14] $J_{aa} = 12$ c/s, $J_{ae} = 3$ c/s and $J_{ee} = 2$ c/s the contribution of the equatorial conformation XV can be estimated at 60–70% as minimum.

DISCUSSION

As can be seen from Tables 1 and 2, in all cases studied the more stable conformers are those with equatorial substituents. This is especially evident in the case of *trans*-4,5-disubstituted cyclohexenes of type II. The non-occurrence of a stable conformation with an axial substituent fixedly overlapping with the double bond proves that the "supra-annular effect" does not exist as a special conformational effect.

A comparison of the ΔG values found for mono-substituted cyclohexenes (Table 2) with those in the cyclohexane series[6] shows that the contribution of the axial conformation in cyclohexenes is greater than in cyclohexanes. This fact is in agreement with the results obtained for bromocyclohexenes.[3] It seems to be due mainly to the fact that instead of two 1,3-diaxial hydrogen-substituent interactions in the axial conformation of a monosubstituted cyclohexane, in the case of the 4-monosubstituted cyclohexenes there is only one analogous interaction, namely, between the axial substituent and the quasi-axial hydrogen atom at C_6. When the substituents are non-polar or of low polarity, the situation is evident, but when they are polar, a possible dipole–dipole repulsion between the substituent and the double bond has to be taken into account.

As can be seen from the present work, the homoconjugation of the double bond with an electro-negative group at C_4 ("supra-annular effect") does not affect the conformational equilibrium in any tangible way. However, in principle it cannot be excluded that a sufficiently strong interaction between the substituent and the double bond will actually bring about the predominance of the axial conformation. The stabilization of the axial conformation by an intramolecular H-bond does not seem very likely since it was not observed in the case of the acid VII. The stabilization is possible either due to a dipole–dipole attraction or due to the strong co-ordination of the double bond with the substituents. A number of cases where the usually unstable conformations were stabilized by these forces are reported in the literature. Thus, in the case of N-(tetra-O-acetyl- α-D-glucopyranosyl)-4-methylpyridinium bromide the inversion of the stability order was attributed to dipole–dipole attraction.[17] In *trans*-(2-methoxy-3-tetrahydropyranyl)-mercurychloride the coordination between the O atom of the OMe group and the Hg atom was found to stabilize the otherwise unfavourable diequatorial conformation.[14]

For compounds III and IV one might expect the dipole–dipole repulsion of substituents leading to the destabilization of the diequatorial conformation. Such a kind of interaction is well known for 1,2-dihalocyclohexanes.[18] As can be deduced from the NMR spectra, such a repulsion is unimportant in the case of III and UV.

Our previous work[14, 19] as well as that of other authors[13, 20] showed that for a large number of 2-alkoxy-, 2-halo-, 2-alkylthiodihydro- and tetrahydropyrans the axial conformation is more stable. This phenomenon, which was called "anomeric effect"[21] seems to be caused by a dipole–dipole repulsion between the heteroatom and the substituent; it is common for many oxygen- and sulfur-containing heterocycles. The conformational equilibrium of XIII and XIV proves that it is the equatorial conformation which is more stable and therefore neither the "anomeric" nor "supra-annular" effect play any serious role in these two cases.

Since the "supra-annular effect" as a special kind of conformational effect does not exist in the cyclohexene systems, the low reactivity of the double bond should be explained in non-conformational terms. The factors affecting the reactivity of the double bond have been discussed.[9]

It remains to be noted that the introduction of electronegative substituents at C_4 involves not only a decrease in the nucleophilicity of the double bond but also a decrease in the rates of solvolysis, which was observed for some derivatives of cyclohexane, norbornane[22] and 7-oxabicyclo [2.2.1]-heptane.[23] Thus, a stable mercury-organic perchlorate XVI could be obtained,[23c] while in general such compounds are too labile to be isolated.[24] This implies that the difficulty of the electrophylic addition to the double bond in 4-substituted cyclohexenes with electronegative groups represents a particular case of carbonium ion formation in the 6-membered cycles bearing electronegative substituent in *meta*- and *para*-positions to the positively charged carbon. On the other hand, the concept of the "supra-annular effect" seems to be inapplicable to the understanding of solvolytic reactions.

EXPERIMENTAL

Compounds III–XII were prepared from 1,1,4,4-d_4-butadiene[25] and the corresponding dienophyles according to the known procedures. NMR spectra were recorded both on RS-60 and JNM-4H-100 spectrometers with HMDS as internal reference. The computing of the spectra was done on a M-20 computer.

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