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RESTRICTED ROTATION OF SUBSTITUENTS (OTHER THAN METHYL) IN CYCLOHEXANOID SYSTEMS.

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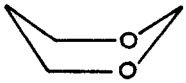
The conformation of 1,3-dioxanes is relatively unknown. I.R. studies have proved the conformational homogeneity of 1,3-dioxane itself(4), and dipole moment measurements indicate that the most stable conformation is the chair form(5). The barrier to ring inversion of 1,3-dioxane and of 5,5-dimethyldioxane has been carefully determined(6,7). English workers have studied some 5-substituted-1,3-dioxanes(5). Electron diffraction or X-ray data for 1,3-dioxanes seem to be inexistent, but a recent study by these methods on 2-phenyl-1,3-dithiane has established the chair conformation for this ring system(8).

On the basis of the rotational barrier in methanol (1,1 kcal) the enthalpy difference between the chair and the "boat" form of 1,3-dioxanes is estimated at 2,2 kcal(5) and the prediction is made : ..."substituted derivatives may well have stable flexible forms". For the boat form of 1,3-dioxane, the two forms α and β should be considered. These are classical boat forms, but an energy minimum will be obtained by a slight rotation to the "twist-boat" conformation. The cited estimation of 2,2 kcal applies to form α.


α


β

Of all boat forms, arising by pseudorotation, only the α form has a plane of symmetry. Very recently a boat conformation has been advanced for 4-tert.butyl-4-methyl-1,3-dioxane(9).

We have now prepared a number of 5,5-disubstituted-1,3-dioxanes (see table I) and recorded their P.M.R. spectra at various temperatures. Fig. 1 shows the P.M.R. spectrum of 5-methyl-5-ethyl-1,3-dioxane at about -100°, well below the coalescence temperature. The striking feature of the low temperature spectrum is that in the region where the protons

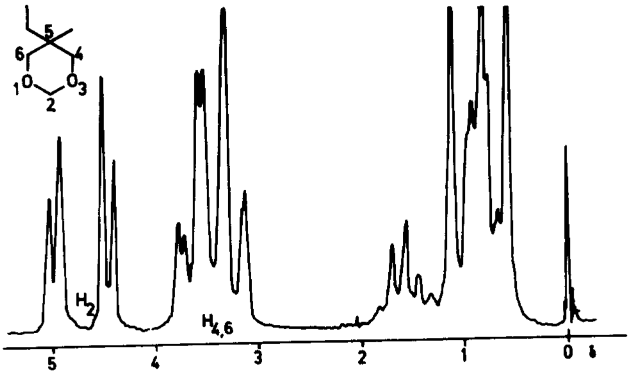


FIGURE 1

of C_4 and C_6 absorb (denoted in the following text as H_4 and H_6) two partially overlapping AB systems can be detected. This low temperature feature is common to all the compounds studied, except for 5,5-dimethyl-, 5,5-diethyl- and 5-ethyl-5-n.butyl-1,3-dioxane.

The two overlapping AB systems could be explained by assuming that the molecules take up boat conformation. In substituted 1,3-dioxanes boat forms do not have a plane of symmetry - thus rendering H_4 and H_6 non-identical (the one exception, the classical boat form α, is energetically unfavourable, because of the strong repulsion between the hydrogen on the C_2 atom and the alkyl substituent of the C_5 atom). On this basis however, it would not be possible to explain the single AB system in the three above mentioned compounds. The hypothesis of predominant boat conformations in the compounds studied may also be rejected on theoretical grounds. The boat conformations become energetically attractive if excessive strain in the chair conformation is effectively relieved by adopting the boat conformations. We estimate that an axial methyl (or any non-tertiary alkyl group) in the 5 position of 1,3-dioxane introduces but little strain. The magnitude of this strain may be crudely estimated at 0.7 kcal from the $-\Delta G_{a \rightarrow e}$ value for OMe in methoxycyclohexane (0.7 kcal)(10); in both cases the strain is due to a clinal O — CH_2 interaction of a skew butane type unit.

This small strain is but very incompletely releaved by taking up the boat conformation. This is confirmed on inspection of a model of these compounds. Chair conformations like in fig. 2 are therefore more probable for 5,5-dialkyldioxanes. The two partially overlapping AB systems in some of the compounds, and their absence in some others can be explained using the Newmann projection formulas of the two inverting chair conformations I and II viewed along the C_4-C_5 axis.

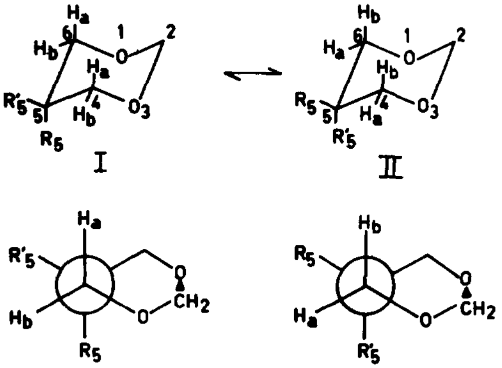


FIGURE 2

In I proton H_a is clinal with respect both to R'_5 and C_5-C_6, while H_b is in the different surroundings of R'_5 and R_5. Conformation I thus gives an AB pattern for these protons. The axial proton H_b in II is now differently surrounded than H_a is in I, for R'_5 has been substituted for R_5. At first sight the equatorial proton H_a in II seems to be identically surrounded as H_b is in I, and therefore we expect that the second visible AB pattern (coming from conformation II) should overlap with the first (from conf. I) in its equatorial part$^{(11)}$. This is not so. Unlike with 5-hydroxy-1,3-dithianes$^{(12)}$, the equatorial H_4 and H_6 protons in 1,3-dioxanes behave$^{(1)}$ like similar protons in carbon hexacycles, nl. the equatorial protons absorb at lower field values than the axial ones. It is indeed clear from the spectra (see also table, where Δ_e is to

be compared with Δ a : Δ e$\rangle\Delta$a) that the two visible AB patterns are more differentiated in the low field portion (Δe) : that is in their equatorial parts. Inspection of the Newmann projections (fig. 2) gives a rational explanation. Suppose that R'_5 = Me and R_5 = higher alkyl group. A difference in the immediate environment of H_a in I and on the other hand of H_b in II, is to be expected if the rotation of R_5 is hindered. The more pronounced non-identity of H_b in I corresponding to H_a in II, illustrates that axial groups have a more restricted rotation than equatorial groups.
The C_α-C_β bond in the R_5 sidechain of I is thus preferentially turned away from the cycle, pointing into the direction of H_b, the latter thus being shifted (i.e. upfield) from H_a in II, where now R_5 is equatorial.

It is obvious then that the effect will not be found when $R_5 = R'_5$ and also that it will not be pronounced when both R'_5 and R_5 are different from methyl.
In connection with the actual situation, where groups are planted in a (C)-C-(C) moiety, it has also been found that unequal rotamer population can also be demonstrated for groups in the (C)-C-(O) moiety of the molecule(13).

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TABLE.

Shifts and coupling Values (in cps at 56.4 Mc) for the (two) AB Patterns of 4 and 6 Protons in 5,5-disubstituted-1,3-Dioxanes at low Temperature (ca -100°C).

Substituents	Me, Me	Et, Et	Et, n.Bu	Me, Et	Me, n.Pr	Me, i.Pr	Me, n.Pe
J_1 / $(\nu_o\delta)_1$	10.8 / 12.4	11.3 / 29.5	11.2 / 30.0	10.8 / 18.0	10.8 / 17.7	10.9 / 26.0	11.1 / 18.9
J_1 / $(\nu_o\delta)_2$	-	-	-	11.1 / 24.0	11.0 / 24.0	11.1 / 42.5	(a)
Δ_e / Δ_a (b)	-	-	-	4.0 / 1.9	4.1 / 2.2	9.5 / 7.1	$\Delta_e \gtrsim \Delta_a$

Substituents	Me, cyclo-Pe	Me, cyclo-Hex
J_1 / $(\nu_o\delta)_1$	10.8 / 16.8	10.5 / 26.0
J_2 / $(\nu_o\delta)_2$	11.2 / 29.4	10.8 / 48.2
Δ_e / Δ_a	7.0 / 5.6	11.1 / 11.1

(a) Qualitatively the equatorial part shows an inflection of the lowest field peak. The peaks in this case are however very broad so that precise data cannot be obtained.

(b) Δe refers to the shift difference between the equatorial protons of the two AB systems corresponding to the conformations of fig. 2.

Δa refers to the same difference between the axial protons.

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(10) This is the recommended value, see ref. (4).

(11) The intensities of the two overlapping AB systems are about the same, as the two conformations I and II have, in this particular case, nearly the same free energy.

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