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220 Mc/s NMR SPECTRA AND GEOMETRY OF SOME 2-SUBSTITUTED 1,3-DIOXANES

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The geometrical features of saturated five- and six-membered hetero rings in terms of the ring torsional angles, obtained from X-ray or electron diffraction data, and the relation between ring geometry and various physical properties (dipole moments, spectroscopical features) have been reviewed in detail (1). It appears that most six-membered hetero rings occur in the chair conformation; however, the exact geometry is strongly dependent on the nature of the hetero atom or atoms. This feature is illustrated in Fig. 1 for 1,3-dioxanes and 1,3-dithianes.

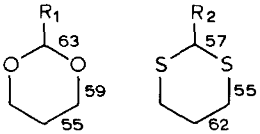

FIG.1. Ring torsional angles (from X-ray analysis (2,3)) in an equatorially 2-substituted 1,3-dioxane and -dithiane (R_1 = p-chlorophenyl, R_2 = phenyl).

However, for many heterocyclic systems no diffraction data on the unsubstituted ring are available, so the question arises whether an equatorial substituent at C_2 as shown in Fig.1 influences the ring geometry and, if so, whether such influence depends on the nature (e.g. size) of the substituent. Since our research groups, during the last few years, have extensively studied the conformational features of 1,3-dioxane derivatives (4-7) and carried out calculations of ring torsional angles from vicinal proton coupling constants in six-membered rings having a $-CH_2-CH_2-$ fragment (8-10), we have now undertaken a nuclear magnetic resonance study so as to determine the influence, if any, of an equatorial substituent at C_2 on the geometry in the C_4-C_5-C_6 part of the 1,3-dioxane ring. The following compounds were investigated: 2-methyl- (I), 2-i-propyl- (II), 2-t-butyl- (III) and 2-phenyl-1,3-dioxane (IV). The NMR data of 2-p-chlorophenyl-1,3-dioxane (V), published elsewhere (11), are also included, since X-ray analysis has been carried out on this particular compound (Fig.1), as are those of the unsubstituted 1,3-dioxane ring (12). The conformational preference of 2-substituents for the equatorial position in 1,3-dioxanes is very large (e.g. 4.0 kcal/mole for 2-methyl (4,5)), so that the contribution of the axial conformer may be neglected.

The synthesis of these compounds is described in ref.4. The NMR spectra were recorded at 220 Mc/s (Varian HR-220 spectrometer) in carbon tetrachloride solutions (ca. 10%).

Results

The analysis of the NMR spectra in the region of the protons in the C_4-C_5-C_6 moiety of the ring (Fig.2) is rather straightforward, as at 220 Mc/s the chemical shifts of the various protons in the ABCDB'A' system are very large with respect to the coupling constants. A detailed description of the analysis of this type of NMR spectra is presented elsewhere (11,13). The signals due to H_1,H_2,H_5 and H_6 are complicated by a significant long-range coupling: the best agreement between the observed and the calculated spectra was obtained by assigning a value of 2.5 - 3 c/s to the long-range coupling between the equatorial protons on C_4 and C_6 (J_{25}). No long-range couplings with H_7 could be detected. The chemical shifts and the coupling constants are collected in Table 1.

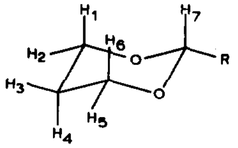

FIG.2

I R = methyl (Me)
II R = i-propyl (i-Pr)
III R = t-butyl (t-Bu)
IV R = phenyl (Ph)
V R = p-chlorophenyl (p-Cl-Ph)

From the vicinal coupling constants the ring torsional angle about the bonds C_4-C_5 and C_5-C_6 ($\psi_{45} = \psi_{56}$) can be calculated by means of the R-value method, introduced originally by Lambert (15) and made into a quantitative device by one of us (8,10), i.e.

$$R = (J_t + J_t')/(J_c + J_c') = (J_{14} + J_{23})/(J_{13} + J_{24}) = (3 - 2\cos^2\psi)/4\cos^2\psi \quad ....(1)$$

for a particular *$-CH_2-CH_2-$ fragment where ψ is the ring torsional angle in that fragment.* The results for about 30 compounds (8,10) indicate a very good agreement between ψ values obtained from R and those from diffraction data. The R values and the resulting ψ values are also listed in Table 1. From this Table the following features are evident:

(i) The values of the individual vicinal coupling constants do not show significant variation in the six compounds, from which it may be immediately concluded that no significant geometrical differences in the C_4-C_5-C_6 region occur in these compounds.

(ii) As a result, the R-values yield practically the same value for the ring torsional angles ψ_{45} and ψ_{56}. Of course, the decimal (third digit) is not significant, but it is included in order to show that no trend in ψ is evident at all upon change of the substituent at C_2 (e.g. there is no dependence of ψ on substituent size).

(iii) As concluded earlier (10), in the 2-p-chlorophenyl derivative the calculated torsional angle is in excellent agreement with that found (2) by X-ray: 55.1°.

Discussion

Bulky equatorial substituents such as t-butyl are often used as holding groups in six-membered rings so as to obtain a conformationally homogeneous system (16). Use of such a technique requires the assumption that the holding group has but negligible influence at long distance (17) (e.g. in cyclohexanes a 4-t-butyl group should not exert a polar or steric effect at the 1- or 1,2-positions and should produce only negligible distortion of the ring). Direct experimental support for this assumption (18) was obtained for the cis- and trans-2-halogeno-4-t-butylcyclohexanones from the linear relationship between the squares of the dipole moments and the vicinal coupling constants in the $-CH_2-CHX-$ moiety. For the cyclohexanes, molecular mechanics calculations (19)

TABLE 1. Chemical shifts (ppm from TMS), coupling constants[a] (c/s), R-values and ring torsional angles for various 1,3-dioxanes in carbon tetrachloride.

	Unsubstituted	2-Me (I)	2-*i*-Pr (II)	2-*t*-Bu (III)	2-Ph (IV)	2-*p*-Cl-Ph (V)
ν_1	Av:	3.61	3.60	3.60	3.83	3.83
ν_2	3.80	3.95	3.99	4.01	4.14	4.14
ν_3	Av:	1.23	1.24	1.24	1.35	1.34
ν_4	1.68	1.95	1.96	1.96	2.14	2.11
ν_7	4.70	4.50	4.09	3.95	5.32	5.30
ν_{subst}		CH_3 1.15	CH_3 0.84 H 1.65	CH_3 0.81	Ar 7.23	Ar 7.25
J_{12}	Diff:	-11.7	-11.6	-11.6	-11.7	-11.5
J_{34}	1.6	-13.3	-13.2	-13.2	-13.3	-13.2
J_{14}	Sum:	12.4	12.5	12.4	12.4	12.3
J_{23}	13.4	1.3	1.3	1.3	1.3	1.3
J_{13}	Sum:	2.6	2.6	2.6	2.6	2.6
J_{24}	7.6	5.0	5.0	5.0	5.0	4.9
R	1.76_3	1.80_3	1.81_6	1.80_2	1.80_2	1.81_3
ψ	$54._9$	$55._2$	$55._3$	$55._2$	$55._2$	$55._3$

a. In I the coupling J_{7-Me} = 5.0 c/s. In II the couplings in the *i*-propyl group are: J_{7-H} = 4.75 c/s, J_{H-CH_3} = 7.0 c/s.

predict that severe repulsive interactions between the methyl groups of an equatorial *t*-butyl group at C_4 and the ring hydrogen atoms at C_3 and C_5 exist, causing a significant twist of the *t*-butyl group from the perfectly staggered conformation. Nevertheless, *no* deformation in the remote part of the ring (C_6-C_1-C_2) appears, as the torsional angles ψ_{61} and ψ_{12} were calculated (19) to be $56._3^{\circ}$ in 4-*t*-butylcyclohexane as well as in 4-methylcyclohexane, whereas $56._1^{\circ}$ was calculated for the torsional angles in unsubstituted cyclohexane. In the 1,3-dioxane ring no hydrogen atoms are present on the ring atoms α to the atom carrying the equatorial 2-*t*-butyl group so that the unfavorable interactions are expected to be lower than in the corresponding cyclohexanes (the steric requirement of a lone pair was found to be much lower than that of a hydrogen atom (4)), *i.e.* ring deformation in the C_4-C_5-C_6 moiety caused by an equatorial 2-*t*-butyl group in the 1,3-dioxane system is not expected and, as seen above, is not, in fact, experimentally found.

Note: For some 2-substituted 1,3-dioxanes, vicinal coupling constants from first-order analysis of 60 Mc/s NMR spectra have been published (4,20). Computer calculations (13) show that this procedure, applied to compound V, yields 11.3 c/s for J_{14} (11.9 c/s from first-order analysis at 100 Mc/s) and 5.5 c/s for J_{24} (5.0 c/s at 100 Mc/s) and thus leads to false conclusions regarding R and ψ , even though correct values for J_{13} and J_{23} are obtained from first-order analysis, even at 60 Mc/s. A further disadvantage in the interpretation of low-field NMR spectra (i.e.60 Mc/s) for I and II is serious overlap of the alkyl signals and those of H_3 or H_4.

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References

1) C.Romers, C.Altona, H.R.Buys and E.Havinga, *Topics in Stereochemistry* **4**, 39 (1969); E.L.Eliel and N.L.Allinger, eds., Interscience.
2) A.J.de Kok and C.Romers, *Rec.Trav.Chim.*, in press.
3) H.T.Kalff and C.Romers, *Acta Cryst.* **20**, 490 (1966).
4) E.L.Eliel and M.C.Knoeber, *J.Am.Chem.Soc.* **90**, 3444 (1968).
5) E.L.Eliel, *Accounts of Chemical Research* **3**, 1 (1970).
6) E.L.Eliel and M.K.Kaloustian, *Chem.Comm.* **1970**, 290.
7) E.L.Eliel and D.I.C.Raileanu, *Chem.Comm.* **1970**, 291.
8) H.R.Buys, *Rec.Trav.Chim.* **88**, 1003 (1969).
9) N.de Wolf and H.R.Buys, *Tetrahedron Letters* **1970**, 551.
10) H.R.Buys, *Rec.Trav.Chim.*, in press.
11) H.R.Buys, *Rec.Trav.Chim.*, in press.
12) C.Barbier, J.Delmau and J.Ranft, *Tetrahedron Letters* **1964**, 3339.
13) The spectra have been analyzed with the aid of the iterative computer program LAME (Laocoon (14) with Magnetic Equivalence). A copy of this program was kindly provided by Drs. J.A.den Hollander who had obtained the listing of the program from Dr.C.W. Haigh. The calculations were carried out on the IBM 360/50 computer of the "Centraal Reken Instituut" of the University of Leiden.
14) See e.g. J.D.Swalen, *Progress in NMR Spectroscopy* **1**, 205 (1966); J.W.Emsley, J.Feeney and L.H.Sutcliffe, eds., Pergamon Press.
15) J.B.Lambert, *J.Am.Chem.Soc.* **89**, 1836 (1967).
16) See e.g. E.L.Eliel, N.L.Allinger, S.J.Angyal and G.A.Morrison, *Conformational Analysis*, Interscience (1965); E.L.Eliel, *J.Chem.Educ.* **37**, 126 (1960).
17) Objections to the use of *t*-butyl as a "holding group" have been raised a) with respect to the kinetic method: H.Kwart and T.Takeshita, *J.Am.Chem.Soc.* **86**, 1161 (1964); E.L.Eliel and F.J.Biros, *ibid.* **88**, 3334 (1966); b) with respect to the NMR method: E.L.Eliel et al., *Tetrahedron Letters* **1962**, 741; S.Wolfe and J.R.Campbell, *Chem.Comm.* **1967**, 872; E.L.Eliel and R.J.L.Martin, *J.Am.Chem.Soc.* **90**, 682 (1968); F.R.Jensen, C.H.Bushweller and B.H.Beck, *ibid.* **91**, 344 (1969); c) See also E.L.Eliel et al., *ibid.* **88**, 3327 (1966); F.Shah-Malak and J.H.P.Utley, *Chem.Comm.* **1967**, 69.
18) C.Altona, H.R.Buys, H.J.Hageman and E.Havinga, *Tetrahedron* **23**, 2265 (1967).
19) C.Altona and M.Sundaralingam, *Tetrahedron* **26**, 925 (1970).
20) M.Anteunis, D.Tavernier and F.Borremans, *Bull.Soc.Chim.Belges* **75**, 396 (1966).