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CONFORMATIONAL ANALYSIS OF DIBROMOCYCLOHEXANES BY NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY

EVIDENCE FOR THE PARTICIPATION OF A TWIST FORM TO THE CONFORMATIONAL EQUILIBRIUM OF *r*-1, *t*-2-DIBROMO-*c*-3-t-BUTYLCYCLOHEXANE

P. L. Barili, G. Bellucci, G. Ingrosso, F. Marioni and I. Morelli
Istituto di Chimica Organica dell'Università di Pisa, 56100 Pisa, Italy

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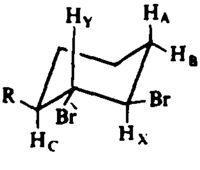
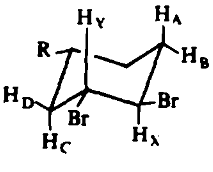
Abstract—The NMR parameters of several substituted *trans*-1,2-dibromocyclohexanes, *trans*-2-bromocyclohexanols and their derivatives have been measured in order to investigate their conformational features. An analysis of these data and the temperature dependence of the coupling constants of *r*-1, *t*-2-dibromo-*c*-3-t-butylcyclohexane demonstrate that an appreciable population of the twist conformer **1t** contributes to the conformational equilibrium of this dibromide. The destabilization of its triequatorial chair conformation **1e** with respect to the twist one **1t** is attributed to a strong *gauche* interaction between equatorial t-butyl and bromine and dipole–dipole repulsion between the two halogen atoms.

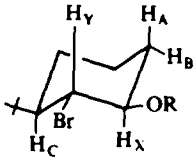
In a previous paper[1] we reported the activation parameters for the thermal equilibration of some *trans*-1,2-dibromocyclohexanes carrying substituents at C-3 or C-4. While very close values for the activation energy, and very low or zero values for the activation entropy have been found for the 4-Me, 4-t-Bu, 4-methoxycarbonyl and 3-Me derivatives, the 3-t-Bu derivative deviates considerably from the general picture, having a lower activation energy and a negative and unexpectedly higher activation entropy. Furthermore, the 3-t-Bu group dramatically influences the equilibrium constant of the diequatorial–diaxial interconversion in favour of the diaxial isomer. From these data it was deduced that the conformational equilibrium of the dibromide **1** probably involves a significant population of a twist conformer in which the halogen atoms have an *anti*-parallel disposition. We report here the results of an NMR study of the *trans*-dibromides **1**–**4**, the *trans*-bromohydrins **5** and **7** and their derivatives **6** and **8**, which support our assumption.



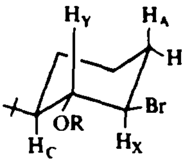
1: R = $C(CH_3)_3$
2: R = CH_3



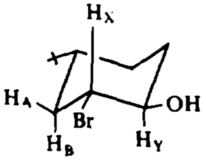
3: R = $C(CH_3)_3$
4: R = CH_3



5: R = H
6: R = $COC_6H_4NO_2(P)$



7: R = H
8: R = $CONHC_6H_5$



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The low-field part of the 100 MHz NMR spectrum of the dibromide 1 shows eleven lines, interpretable as the XY part of an ABXYC system, in which $J_{AY} = J_{BY} = J_{CX} = 0$. The protons α to bromine (X and Y) give rise to an XY type quartet,[2] the X components of which are split into two quartets by protons A and B, and the Y components by proton C into doublets whose inner lines overlap (Fig 1). The spectra

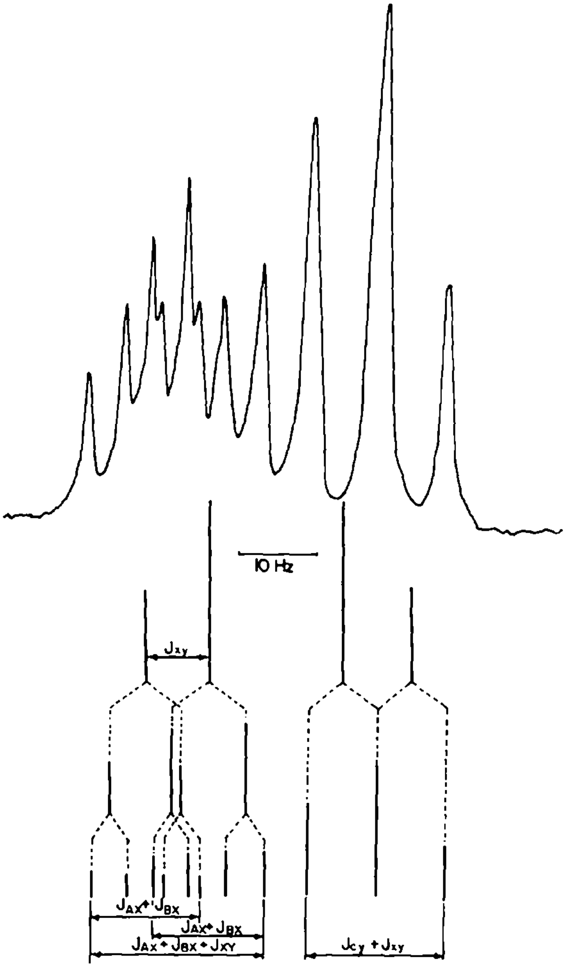


Fig. 1. XY part of the 100 MHz NMR spectrum of 1 in CCl_4 at 30°C.

of compounds **2**, **7** and **8** are similar to that of **1** but the differences in chemical shift between the signals of protons X and Y are larger, and in **8** proton Y resonates at a lower field with respect to X. In the case of compound **6**, the signals for H_X and H_Y are well separated, but the X part is not well resolved. The H_X and H_Y resonances partially overlap in the 60 MHz spectrum of the corresponding bromohydrin **5** in CCl_4; however, the difference of chemical shift *strongly* increases in the presence of $Eu(dpm)_3$,[3] the signal of the proton α to hydroxyl being more shifted to lower field. The spectral parameters of compounds **1–9**, deduced as shown in Fig 1, are reported in Table 1.

TABLE 1. NMR PARAMETERS (Hz) OF COMPOUNDS 1–9

Compound	Solvent	T(°C)	$J_{AX}+J_{BX}$	$J_{AX}+J_{BX}+J_{XY}$	$J_{CY}+J_{XY}$	J_{XY}	$\Delta\nu_{XY}$
1[a]	CCl_4	50	12·4	19·4	14·8	7·0	21·2
	CCl_4	30	12·8	20·0	15·4	7·3	22·2
	CCl_4	− 40	13·5	22·7	18·4	9·2	27·2
	C_6D_6	50	12·8	20·0	15·0	7·2	15·9
	C_6D_6	30	13·0	20·6	15·2	7·5	17·2
2[a]	CCl_4	30	15·9	26·2	20·1	10·3	38·8
	CCl_4	− 40	16·0	26·1	20·2	10·3	38·6
3[b]	CCl_4	25	16·5	26·9	22·5	10·4	16·4
4[b]	CCl_4	25	16·5	26·9	22·5	10·4	15·3
5[c, d]	CCl_4	22	14·9	24·1	19·1	9·2	*e*
6[c]	$CDCl_3$	22	*f*	23·8	19·0	*f*	70·9
7[c]	CCl_4	22	15·9	25·3	18·5	9·4	32·1
8[c]	$CDCl_3$	22	16·0	25·9	19·2	9·9	58·5
9[g]	CCl_4		15·7	25·0		9·3	

[a] 100 MHz spectrum. [b] Calculated from the 220 MHz spectrum. [c] 60 MHz spectrum. [d] In the presence of $Eu(dpm)_3$. [e] Variable with the amount of $Eu(dpm)_3$. [f] Not measurable. [g] Ref. 16.

Computer simulation of the spectra gave values for the coupling constants the sums of which were in good agreement with the parameters obtained by direct measurement of the spectra. For instance the following values were obtained for **1** and **2** in CCl_4 at 30°: **1**, $\Delta\nu_{XY} = 22{\cdot}1$, $J_{AX} = 8{\cdot}7$, $J_{BX} = 4{\cdot}3$, $J_{XY} = 7{\cdot}5$, $J_{CY} = 7{\cdot}9$ Hz; **2**, $\Delta\nu_{XY} = 39{\cdot}1$, $J_{AX} = 11{\cdot}4$, $J_{BX} = 4{\cdot}6$, $J_{XY} = 10{\cdot}2$, $J_{CY} = 10{\cdot}2$ Hz. It was thought however that it would be preferable for obtaining the conformational data we were interested in, to use the parameters measured directly from the spectra rather than the computer calculated ones, because the simplification of treating the system as a five spin one could possibly cause some errors.[4]

It was not possible to measure directly the spectral parameters of dibromides **3** and **4**, since the chemical shift of the X and Y protons are not different enough to give rise to separate multiplets even at 220 MHz: dibromide **3** shows only one symmetrical multiplet (width 45·7 Hz) in which ten lines are present, with splitting of 4·2 Hz between lines 1–2, 3–4, 7–8 and 9–10 and 6·3 Hz between lines 2-3, 4–5, 6–7 and 8–9 (Fig 2). However, the experimental spectrum is in good agreement with the theoretical one, calculated by computer using the following parameters: $\Delta\nu_{XY} = 16{\cdot}4$ Hz, $J_{AX} = J_{CY} = 12{\cdot}1$ Hz, $J_{BX} = J_{DY} = 4{\cdot}4$ Hz, $J_{XY} = 10{\cdot}4$ Hz. The X and Y protons of the 4-Me derivative **4** also give an analogous multiplet (width 44·5 Hz) with splitting similar to that of **3**, although the two central lines tend to coalesce. Also in this case the experimental spectrum is reproduced by the computer with the same values of the coupling constants as for **3** and $\Delta\nu_{XY} = 15{\cdot}3$ Hz. Since the 60 MHz spectra of both **3** and **4** are also fairly well reproduced by using the above coupling constants, misleading virtual couplings[4] seem rather improbable. The value of $J_{AX} + J_{BX}$ (or $J_{CY} + J_{DY}$) thus obtained for **3** and **4** (16·5 Hz) is in good agreement with the value 16·3 Hz reported by Altona *et al.*[5] for conformationally homogeneous diequatorial dibromocyclohexanes.

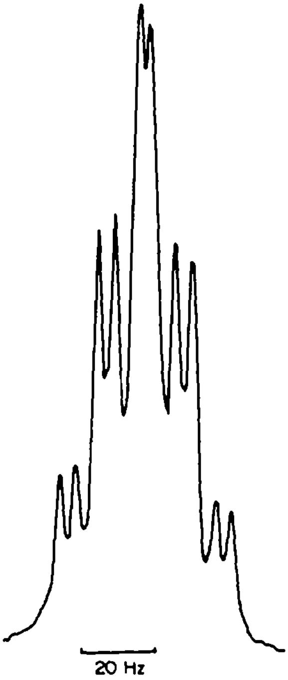


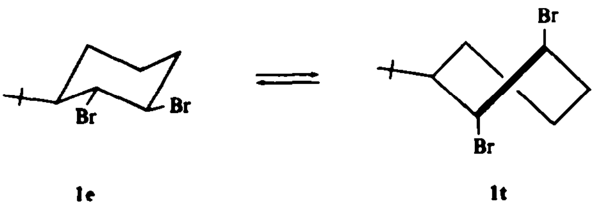
FIG. 2. XY part of the 220 MHz NMR spectrum of 3 in CCl_4.

The results reported above show that dibromide **4** may be considered as conformationally homogeneous; furthermore, the substitution of a methyl by a t-Bu group on C-4 does not introduce appreciable distortion in the ring geometry about the bonds 1–2, 2–3 and 1–6, in agreement with the calculations of Altona and Sundaralingam.[6]

The spectral parameters of the 1,2,3-trisubstituted compounds (except **1**) fall into a rather narrow range, although a general comparison cannot strictly be made because of the dependence of the vicinal coupling constants on substituent electronegativities.[7] However, within the set of the dibromoderivatives, it may be pointed out that the values found for **2** are very close to those deduced for **3** and **4** and this would suggest a very high preference for the triequatorial chair conformer in dibromide **2**. This is in agreement with a rough estimate of the free energy difference between the triequatorial and the triaxial conformer of **2** which should be of about 2 kcal/mol if one uses: (1) ΔG^0 value of *trans*-1,2-dibromocyclohexane, 0·8 kcal/mole in CCl_4,[5] (2) *gauche* interaction energies between equatorial Me and Br in the triequatorial conformation, about 0·25 kcal/mol[8] and (3) *syn*-diaxial interaction energy between Me and Br in the triaxial one, about 3·2 kcal/mol.[9]

On the contrary, the 3-t-Bu substituted dibromide **1** shows band widths of X and Y protons and $J_{AX} + J_{BX}$ and J_{XY} values which are definitely smaller than those of all other examined compounds. A straightforward comparison may be made with the parameters of **2**, as the differences found in these two compounds cannot be affected by substituent electronegativity effects on the coupling constants and should be merely due to different conformational situations.

A shift in the equilibrium constant of conformationally mobile *trans*-1,2-dihalogenocyclohexanes is generally observed by changing the solvent from carbon tetrachloride to benzene.[9] The value of $J_{AX} + J_{BX}$ for *trans*-1,2-dibromocyclohexane, for instance, changes from 7·9 Hz in the first to 9·3 Hz in the latter solvent.[5] This "benzene effect", favouring the diequatorial (or *gauche*) conformers, has also been found in a number of *trans*-1,2-dihalocyclopentanes[10] and in open-chain vicinal dihalides.[11] The band widths and the individual coupling constants of the dibromides **1** and **2** show only very little or no increase when the solvent is changed from carbon tetrachloride to benzene. This could indicate that **1** is not a conformationally mobile system. However, whereas the methyl derivative **2** in carbon tetrachloride shows only a negligible temperature dependence of the X and Y proton band widths and of $J_{AX} + J_{BX}$ and J_{XY}, the t-Bu derivative **1** undergoes a definite decrease in these parameters when the temperature is raised from − 40 to 50°. A similar trend was found in the variable temperature NMR spectra of *t*-2-t-butyl-*t*-5-methyl-*r*-1, *c*-4-cyclohexanediol;[12] this provides evidence for the fact that compound **1** does not really exist as a frozen chair conformation, but rather as a mixture of different conformations, the equilibrium constant being temperature but not solvent dependent. At lower temperatures the parameters of **1** approach those of **2**, showing an increasing contribution of the triequatorial chair conformer **1e**, whose geometry should be similar to that of **2**. With raising temperature an increase takes place in the population of conformers whose coupling constants and dihedral angles between X and Y, A and X, and C and Y protons are smaller and dihedral angle between the two C—Br bonds is higher than in **1e**. Since a chair conformation of **1** with three axial substituents is very unlikely, the decrease observed in the coupling constants of **1** must be due to a twist conformation, in which the two bromine atoms tend to reach an *anti*-coplanar disposition, as in **1t**.



1e **1t**

The steric interaction between the t-Bu group and the vicinal Br atom should be minimized in the conversion **1e** → **1t**. The *gauche* t-Bu/Br interaction energy has been roughly evaluated as 2·4 kcal/mol in 1,2-dibromo-3,3-dimethylbutane[11] and it could be higher in cyclic compounds, such as **1**, **5** and **6**, owing to the more rigid character and to the ring distortion about the t-Bu substituent,[6] which increases the repulsive interaction with the 2-equatorial substituent. The latter effect has been shown[13] in the 2-t-butylcyclohexanols, in which the *cis*-isomer (axial OH) is favoured by about 0·55 kcal/mol over the *trans*-isomer (equatorial OH). Further destabilization of the chair **1e** with respect to the twist conformation **1t** arises also from the dipole–dipole repulsion[1,14] between the two electronegative vicinal atoms. The latter factor is not important in the derivatives **5** and **6**, as is shown, for example, by the strong preference for the diequatorial conformation in *trans*-2-bromocyclohexanol.[15] On the contrary, the decrease of the *gauche* t-Bu/Br interaction involved in the conversion of **5** and **6** from triequatorial chair to twist conformations similar to **1t** should be at least partially counterbalanced by the increased steric interactions of the hydroxyl or *p*-nitrobenzoyl group in a pseudoaxial position. In the case of the bromohydrin **5** the formation of a H-bond between the equatorial OH and Br may cause further stabilization of the chair conformation. Neither **5** nor **6** have actually considerable populations of non-chair conformers, since both have NMR parameters which are fairly close to those of the bromohydrin **7** and its phenylurethane **8**; moreover **5** and **7** have the same J_{XY} values as the isomeric bromohydrin **9**, which can be considered as a model for a frozen undistorted chair conformation.[15]

The following conclusions can be drawn from the results reported above: the presence of a t-Bu group is not always sufficient to freeze a cyclohexane ring in a chair conformation. When a vicinal substituent is present, whose *gauche* interaction with the t-Bu group is large enough, the presence of a third adjacent substituent, its orientation and its interactions with the second one may become very important in determining the conformation of the cyclohexane ring.

EXPERIMENTAL

The syntheses of compounds **1**, **2**, **3**, **4**, **7** and **8** have been previously described;[1,16–18] the preparations of **5** and **6** will be reported in a forthcoming publication.

The NMR spectra of dibromides **1–4** were obtained from their mixtures with the corresponding diaxial isomers, the low field signals appearing well separated for axial and equatorial compounds. The following spectrometers were used: a Varian HR 220 for **3** and **4**; a Jeol PS-100 for **1** and **2**; a Jeol C-60 HL for **5**, **6**, **7** and **8**; concentrations were about 25% w/w; TMS internal standard. In the case of **5**, the compound (180 mg) and Eu(dpm)$_3$ (50 mg) were shaken with CCl_4 (0·4 ml) until most of Eu(dpm)$_3$ had dissolved; the spectrum was recorded on the filtered soln. The values of the spectral parameters should be accurate to ± 0·3 Hz. The theoretical spectra of the dibromides **3** and **4** were calculated by use of a LAOCOON2 iterative program,[19] run on an IBM 7090 computer.

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