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CONFORMATIONAL EQUILIBRIA OF 2-SUBSTITUTED 1,1-DIALKYLCYCLOHEXANES

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Abstract—The positions of the conformational equilibria in a series of 1,1,2-trisubstituted cyclohexanes have been determined by ^{1}H NMR. The *gauche*-interaction of substituents in the 1,1-dimethyl series are, in general, very close to those of monosubstituted cyclohexanes. However, in the *spiro*-compounds **5** and **6** the equatorial conformers are somewhat destabilized by *gauche*-interactions though still enthalpy preferred. In contrast, the enthalpy preferred conformer in the 1,1-diethyl series is the axial one.

Classical conformational analysis deals, *inter alia*, with contributions to molecular enthalpy from bond length and bond angle deformation, torsional strain and non-bonded interactions. In an oversimplified view, many conformational problems may be viewed, at least qualitatively, in terms of pairwise interactions of non-bonded atoms, usually repulsive. Thus the well known equatorial preference in monosubstituted cyclohexanes is usually discussed in terms of 1:3 X:H repulsive interactions which occur in the axial conformation. The magnitude of such repulsions can often be connected with well-defined structural factors (C–X bond length, effective volume of X, etc).[2] Thus one tries to ascribe to these pairwise interactions a physical meaning in terms of supposedly well understood effects (steric, electrostatic, stereoelectronic, etc). Comparison of a particular example with an appropriately chosen comparison model may reveal some unanticipated and therefore novel type of specific interaction of substituents ("conformational effect").[3] Thus study of *trans*-1,2-disubstituted cyclohexanes[3,4] as well as 5-substituted 1,3-dioxanes[5] with appropriate large polar substituents (such as S, Br) has revealed the "*gauche*-repulsive effect" (formerly called "hockey-stick effect"). 1,3-Dioxanes have been found particularly useful models for the investigation of special conformational effects.[5,6] Clearly the choice and adequacy of the comparison model (e.g. methoxycyclohexane as a model for 2-methoxyoxane in the study of the anomeric effect) is a matter of crucial importance.

Earlier we have shown, that 1,1,2-trisubstituted cyclohexanes may be used as good models for conformational studies.[7] For such compounds with identical substituents in the 1-position the conformational equilibrium may be represented by **1A**⇌**B**. If one assumes that *gauche*-interactions $X_e \ldots R_a$ and $X_a \ldots R_e$ are equal, the experimentally observed free energy value can be partitioned in accordance with eqn (1). In other words, **B** has one more X/R *gauche* interaction than **A**.

$$\Delta G_{exp} = \Delta G_x + \Delta G_{X \ldots R}^{gauche}. \qquad (1)$$
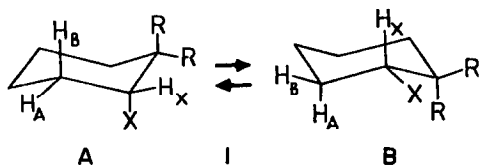
Hence, the study of conformational equilibria of type **1** should shed light on the problem of *gauche*-interactions.
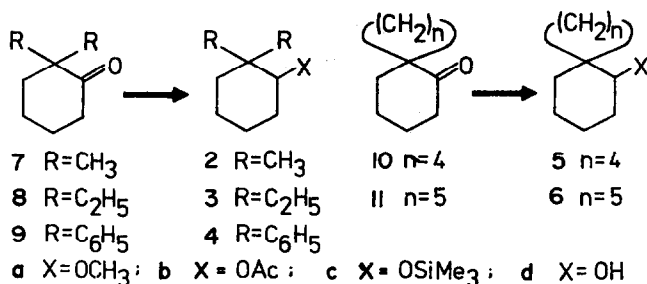
The present work involves study of the conformational equilibria of a number of trisubstituted cyclohexanes of type **1** in which R is alkyl or phenyl. It is reasonable to assume that electrostatic *gauche*-interactions for such uncharged substituents do not come into play and that the conformational preference is controlled exclusively by steric *gauche*-interactions. Hence, the conformational equilibria studied may be regarded as "standard" or "reference" ones for compounds of type **1** in which the R groups are polar.

RESULTS

All compounds investigated were obtained from alcohols **2d–6d** by well known transformations of the OH group. Alcohols **2d–6d** in turn were prepared by reduction of the corresponding ketones **7–11** (Scheme 1).

It was reasonably assumed that all compounds investigated, **2–6**, exist in the chair conformation.[8] The position of conformational equilibrium **1A**⇌**1B** can be estimated in terms of the mole fraction *n* of conformation **B** by the widely used eqn (2) using the bandwidth of the H_x signal. This signal may be treated as the X part of the ABX system and its width is equal to

A   1   B

7 R=CH₃   2 R=CH₃   IO n=4   5 n=4
8 R=C₂H₅   3 R=C₂H₅   II n=5   6 n=5
9 R=C₆H₅   4 R=C₆H₅

a X=OCH₃ ;   b X = OAc ;   c X = OSiMe₃ ;   d X= OH

$|J_{AX} + J_{BX}|^{7b,c-9}$. Appropriate NMR spectral data are listed in Table 1.

$$W_{obs} = W_{1A} \cdot (1-n) + W_{1B} \cdot n$$
$$= (1-n)(J_{ee} + J_{ea}) + n(J_{aa} + J_{ae}). \quad (2)$$

Difficulties are often connected with the choice of the "standard" or "limiting" coupling constants of the individual conformers W_{1A} and W_{1B}. Their values are frequently taken from the NMR spectra of rigid model compounds. However, more precise values may be obtained from low temperature NMR data.[10] We have performed appropriate measurements at −105° where conformational interconversion is sufficiently slow to permit the observation of the signals of individual conformers.

For badly resolved multiplets of H_x the bandwidths at half-height, $W_{1/2}$, were measured; for well resolved signals of H_X (usually quadruplets) their widths, W_1, from one outermost peak to the other were determined. The data obtained at −105° are as follows: $W_{1B} = 14.2$ Hz (2a), 13.7 Hz (5a) and 14.7 Hz (6a); $W_{1/2}^{1B} = 17.0$ Hz (2b), 20.3 Hz (6b); $W_{1/2}^{1A} = 5.9$ Hz (3a), 5.4 Hz (3b) and 5.0 Hz (6b). Based on these data, we have used the following "standard" values: $W_{1B} = 14.2$ Hz for 2–4, 13.7 Hz for 5 and 14.7 Hz for 6; $W_{1/2}^{1B} = 17$ Hz for 2–5 and 20.3 Hz for 6; $W_{1A} \equiv W_{1/2}^{1A} = 5.9$ Hz for 2–5, except b, and 5.5 Hz for 6, except for 6b. Because of the larger electronegativity of the acetoxy group, the value W_{1A} for the acetoxy series, b, has been assumed to be by 0.5 Hz less than the value $W_{1/2}^{1A}$ for the other compounds of analogous structure.

The percentages of equatorial conformer n_{1B}, and the values of the conformational free energy ΔG_{e-a}, for the compounds investigated are summarized in Table 1. It should be noted that there is good agreement between

Table 1. Data of ¹H-NMR spectra of conformational equilibria (90 MHz in CS₂ and 80 MHz for other solvents)

Comp.	Solvent	δH_x ppm (HMDS)	W in Hz ($W_{1/2}$ in Hz)	n_{1B}, %	ΔG_{e-a} kcal/mol	ΔG_m kcal/mol	$\Delta G_m - \Delta G_x$ kcal/mol
2a	CCl₄	2.6₃	12.0±0.2	73.5±2.4	−0.61±0.08	−0.54	0.0
	CS₂ᵃ	2.6₅	11.6±0.3	68.7±3.6	−0.47±0.11		
	C₆H₆ᵃ	2.5₀	11.7±0.3	69.9±3.6	−0.51±0.11		
	CD₃CNᵃ	2.7₀	12.2±0.3	75.9±3.6	−0.69±0.13		
2b	CCl₄ᶜ	4.5₀	11.8±0.4	72.7±4.6	−0.59±0.15	−0.56	0.1
	CS₂	4.4₁	(13.6±0.5)	(70.7±4.3)	(−0.53±0.13)		
	C₆H₆ᵇ	4.6₂	12.4±0.4	79.5±4.6	−0.82±0.18		
	CH₃CNᵃ	4.5₆	11.3±0.4	67.0±4.6	−0.43±0.13		
2c	CCl₄ᶜ	3.1₈	12.7±0.4	81.9±4.8	−0.91±0.22	−0.91	0.0
D-2d	CCl₄ᵇ	3.1₂	(13.8±0.4)	(71.2±3.6)	(−0.54±0.11)	−0.54	0.0
	C₆H₆ᵇ	3.0₇	(14.8±0.3)	(80.2±2.7)	(−0.84±0.11)		
3a	CCl₄	2.8₂	8.8±0.4	34.9±4.8	0.37±0.12	0.30	0.9
	CS₂	2.7₉	9.3±0.2	41.0±2.4	0.22±0.06		
	C₆H₆	2.7₄	9.0±0.5	37.3±6.0	0.31±0.15		
	CD₃CN	2.8₀	(11.2±0.5)	(47.7±4.5)	(0.05±0.11)		
3b	CCl₄	4.5₇	8.8±0.8	38.6±9.1	0.28±0.22	0.17	0.9
	CS₂	4.5₉	9.6±0.3	47.7±3.4	0.05±0.08		
	C₆H₆	4.8₀	9.9±0.5	51.1±5.7	−0.03±0.14		
	CD₃CN	4.5₈	9.3±0.6	44.3±6.8	0.14±0.16		
3c	CCl₄	3.4₄	8.9±0.4	36.1±4.8	0.34±0.12	0.34	1.2
	C₆H₆	3.4₈	9.7±0.3	45.8±3.6	0.10±0.09		
	CD₃CN	3.5₀	8.9±0.5	36.1±6.0	0.34±0.15		

Table 1. (*Contd*)

$3d$	CCl_4	3.6_1	10.2 ± 0.7	51.8 ± 8.4	-0.04 ± 0.21	-0.04	0.5
	C_6H_6	3.2_5	10.7 ± 0.5	57.8 ± 6.0	-0.19 ± 0.15		
	CD_3CN	3.6_0	(12.1 ± 0.5)	(55.9 ± 4.5)	(-0.14 ± 0.11)		
$4a$	CCl_4	3.8_0	8.2 ± 0.5	27.7 ± 6.0	0.58 ± 0.18	0.53	1.1
	CS_2	3.8_2	8.5 ± 0.2	31.3 ± 2.4	0.47 ± 0.07		
	C_6H_6	3.7_2	8.0 ± 0.3	25.3 ± 3.6	0.65 ± 0.11		
	CD_3CN	4.1_5	(8.9 ± 0.3)	(27.0 ± 2.7)	(0.60 ± 0.08)		
$4b$	CCl_4	5.8_0	7.8 ± 0.4	27.3 ± 4.6	0.59 ± 0.13	0.56	1.3
	CS_2	5.7_5	8.0 ± 0.2	29.5 ± 2.3	0.52 ± 0.06		
	C_6H_6	6.0	8.0 ± 0.4	29.5 ± 4.6	0.52 ± 0.13		
	CD_3CN	5.9_0	(9.1 ± 0.5)	(31.9 ± 4.3)	(0.46 ± 0.12)		
$4c$	CCl_4	4.6_0	8.2 ± 0.4	27.7 ± 4.8	0.58 ± 0.14	0.58	1.5
	C_6H_6	4.5_5	8.9 ± 0.4	36.1 ± 4.8	0.34 ± 0.12		
$4d$	CCl_4	4.3_0	7.9 ± 0.3	24.1 ± 3.6	0.69 ± 0.11	0.69	1.2
	C_6H_6	4.2_6	8.1 ± 0.3	26.5 ± 3.6	0.61 ± 0.11		
	CD_3CN	4.6_2	(9.8 ± 0.5)	(35.1 ± 4.5)	(0.37 ± 0.12)		
$5a$	CCl_4	2.7_1	9.7 ± 0.5	48.7 ± 6.4	0.03 ± 0.15	0.02	0.6
	CS_2	2.7_0	9.8 ± 0.3	50.0 ± 3.8	0.00 ± 0.09		
	C_6H_6	2.6_3	9.4 ± 0.4	44.9 ± 5.1	0.12 ± 0.12		
	CD_3CN	2.7_7	9.7 ± 0.5	48.7 ± 6.4	0.03 ± 0.15		
$5b$	$CCl_4{}^a$	4.5_1	10.1 ± 0.2	56.6 ± 2.4	-0.16 ± 0.06	-0.10	0.6
	CS_2	4.5_0	9.7 ± 0.3	51.8 ± 3.6	-0.04 ± 0.09		
	C_6H_6	4.8_5	10.6 ± 0.4	62.7 ± 4.8	-0.31 ± 0.13		
	CD_3CN	4.5_5	9.6 ± 0.7	50.6 ± 8.4	-0.01 ± 0.20		
$5c$	CCl_4	3.3_0	(12.4 ± 0.5)	(58.6 ± 4.5)	(-0.21 ± 0.11)	-0.21	0.7
	C_6H_6	3.2_8	10.1 ± 0.3	53.8 ± 3.8	-0.09 ± 0.09		
	CD_3CN	3.3_2	(13.1 ± 0.5)	(64.9 ± 4.5)	(-0.37 ± 0.12)		
$5d$	CCl_4	3.3_3	(13.4 ± 0.4)	(67.6 ± 3.6)	(-0.44 ± 0.10)	-0.44	0.1
	C_6H_6	3.3_0	(13.3 ± 0.3)	(66.7 ± 2.7)	(-0.42 ± 0.07)		
$6a$	CCl_4	2.7_0	8.9 ± 0.3	37.0 ± 3.3	0.32 ± 0.08	0.24	0.8
	CS_2	2.6_9	9.5 ± 0.2	43.5 ± 2.2	0.16 ± 0.05		
	C_6H_6	2.6_0	9.6 ± 0.4	44.6 ± 4.3	0.13 ± 0.11		
	CD_3CN	2.7_4	10.0 ± 0.9	48.9 ± 9.8	0.03 ± 0.24		
$6b$	CCl_4	4.5_7	(10.4 ± 0.5)	(35.3 ± 3.3)	(0.36 ± 0.08)	0.40	1.1
	CS_2	4.5_0	8.2 ± 0.4	33.0 ± 4.1	0.43 ± 0.11		
	C_6H_6	4.7_0	9.8 ± 0.5	49.5 ± 5.2	0.01 ± 0.12		
	CD_3CN	4.5_2	8.3 ± 0.5	34.0 ± 5.2	0.40 ± 0.13		
$6c$	CCl_4	3.1_4	9.4 ± 0.4	42.4 ± 4.3	0.18 ± 0.11	0.18	1.1
	C_6H_6	3.2_0	10.1 ± 0.5	50.0 ± 5.4	0.00 ± 0.13		
$6d$	CCl_4	3.2_0	(12.1 ± 0.6)	(44.6 ± 4.1)	(0.13 ± 0.1)	0.13	0.7
	C_6H_6	3.1_0	(13.3 ± 1.3)	(52.7 ± 8.8)	(-0.07 ± 0.22)		
	CD_3CN	3.1_6	(12.4 ± 0.4)	(46.6 ± 2.7)	(0.08 ± 0.07)		

[a] 100 MHz; [b] 60 MHz; [c] 300 MHz

the values obtained by the W and $W_{1/2}$ versions of eqn (2). For example, for **2a** in CS_2 these values are -0.47 ± 0.11 kcal/mol and -0.42 ± 0.07 kcal/mol respectively.

DISCUSSION

Perusal of Table 1 does not reveal any clear systematic influence of solvent upon the conformational equilibria of **2–6**. To a first approximation, taking into account the experimental error limits, one may regard the free energies of the equilibria to be independent of solvent polarity. In this respect the compounds **2–6** resemble monosubstituted cyclohexanes.[2,11] However, it appears that there is some slight if perhaps not systematic solvent dependence. For example, the equatorial conformations are slightly more preferred for all alcohols, **d**, in C_6H_6 and in CD_3CN as compared to CCl_4 and CS_2, for acetoxy derivatives, **b**, (except **4b**) in C_6H_6 as compared to the other solvents, and for methoxy derivatives, **a**, (except **2a**) in CS_2 as compared to CCl_4. For further discussion we shall use the mean values, ΔG_m, as between the CCl_4 and CS_2 data, because these solvents are the most widely employed in conformational investigations as "nonpolar" media.

In accordance with eqn (1) one should expect the content of the axial conformer, **1A**, to be increased over that of the corresponding monosubstituted cyclohexanes (ΔG_x), this increase being caused by the term $\Delta G^{gauche}_{X...R}$. However, note a surprising finding:[23] the experimental values $-\Delta G$ for the dimethyl series **2** are essentially equal to the $-\Delta G_x$ values of the substituents[2] X (especially taking into account the variance in even the best A-values). Thus, the formal interpretation of Eqn (1) leads to an apparently mysterious result: $\Delta G^{gauche}_{X...R} \sim 0$. However similar results have already been observed in the literature.[7b,c,8,12] For example, the equilibrations of 3-t-butylcyclohexanol and 2,2-dimethyl-5-t-butyl cyclohexanol in isopropyl alcohol with aluminum isopropoxide have ΔG_{e-a} values of -1.07 and -1.15 kcal/mol.[12] Corresponding values for the equilibration of 4-butylcyclohexanol and 2,2-dimethyl-4-t-butyl cyclohexanol are -0.84 and -0.87 kcal/mol. respectively.[12] The second set of these data is remarkably close to our data (*cf* **2d** in C_6H_6, Table 1). Analogous observations of apparently vanishing *gauche*-interactions have also been made in aliphatic structures. For example, the two possible rotamers of 2,3-dimethylbutane possessing different numbers of *gauche*-Me...Me interactions have equal energy.[13] Thus our data and those in the literature lead us to the recognition of a new phenomenological conformational effect (for terminology see Ref. 3) concerned with the apparent decrease of *gauche*-repulsion in the framework $-CX-C(CH_3)_2-$.

The nature of this obviously intriguing conformational phenomenon cannot be clearly understood in the absence of experimental data concerning the geometry of these compounds (X-ray or molecular mechanics data). Lacking such data we may hypothesize that the origin of this phenomenon is destabilization of the axial conformer **1A** by increased repulsion of X...e-Me resulting from a buttressing effect.[14] Indeed, the axial Me group should be slightly tilted from the ideal axial position, which causes tilting of the e-Me (reflex effect[14]), leading in turn to decrease of the torsion angle e-Me-C-C-X (for a discussion of flattening of the ring in 1,1-disubstituted cyclohexanes see Ref. 12).

This conclusion may be compared with the data of Sicher and Tichy.[12] They found the following values (in

isopropanol) for the magnitude of *gauche*-interactions: 0.38 kcal/mol for e-Me...e-OH, 0.66 kcal/mol for e-Me...a-OH and 0.8 kcal/mol for a-Me...e-OH interactions (repulsion). Application of these values, additively, to the 1,1-dimethyl-2-OH-cyclohexane fragment gives an extra *gauche*-repulsion $0.38 + 0.8 - 0.66 = 0.52$ kcal/mol for conformation **1B**. Because the experimental data show that this extra *gauche*-repulsion somehow disappears, it is reasonable to assume, without more detailed evidence, that the geometric distortion leads to an increase of the e-Me...a-OH and decrease of the e-Me...e-OH interactions.

The other series of compounds, **3–6**, show the expected "axial shift" $\Delta G - \Delta G_x$, increasing in the order $5 < 3 \sim 6 < 4$, as compared to the reference 1,1-dimethyl series, **2**. Undoubtedly, this shift is caused by an increase of steric repulsion of the type R...X with increasing steric bulk of the gem-substituents. Empirically, an R...X repulsion, where X = OR', may be divided into two terms: R...O and R...R' repulsions. It is reasonable to accept the axial shift for the alcohols, **d**, as being equal to the R...O parameter, in which case the values of pertinent R...R' interactions may be estimated as the differences between axial shifts of alcohol derivatives **a–c** and free alcohols **d**. The data of Table 1 show that the R...O repulsion also increases in the order $2 < 5 < 3 \sim 6 < 4$. The R...R' repulsions increase in the order Me < Ac < Si(Me)$_3$ for sufficiently bulky R, as in **3–6** (*vide infra*) and in the order $2(\sim 0) < 4(-0.1-+0.3) < 6(0.1-0.4) < 5(0.5-0.6) \sim 3(0.4-0.6$ kcal/mol) which does not correlate with the order of R...O interactions.

The conformational behavior of **4** (which implies substantial stabilization of the axial conformer A, eqn (1)) may be understood through consideration of the rotameric conformations of phenylcyclohexane[15a] and of the conformations of diarylmethyl systems.[15b] It was shown by Allinger and Tribble[15a] that equatorial phenylcyclohexane exists in the so-called "parallel" conformation (phenyl ring in bisector plane of cyclohexane) whereas the axial one is in the "perpendicular" conformation (phenyl ring at right angles to the bisector plane of cyclohexane). The 1,1-diarylmethyl systems have been shown to assume one of two conformations: helical or perpendicular.[15b] In any case the (perpendicular) axial phenyl group subjects the equatorial OR gauche to it to strong steric repulsion which is relieved when OR becomes axial. (The equatorial phenyl being parallel does not interact strongly with the axial OR gauche to it.) As a result, there is a substantial preference for axial OR (conformation **1A**, eqn (1)) in **4**.

The increase of *gauche*-interactions in going from **2** to **6** may be explained in terms of ring distortion and geometrical changes. First, a decrease in the R-C$_1$-R bond angle in **6** as compared to **2** causes a concomitant increase in the C$_2$-C$_1$-C$_6$ bond angle of the ring[16] leading, in turn, to a bending of R toward X giving rise to unfavorable van der Waals interactions (*cf* the discussion about "buttressing" effects[13]). Secondly, the decrease of the R-C$_1$-R valence angle implies a decrease in the XC$_2$C$_1$R dihedral angles leading to the same result.

The 5-membered ring in **5** is considerably flattened compared to the 6-membered one in **6**. This change results in a splaying of the C-H bonds of the CH$_2$ groups next to the 6-membered ring away from the 1,3-*syn*-axial H...X interactions in **5** as compared to **6**. This change is visualized in formulations **12** and **13**.

The substituents investigated are non-centrosymmetric

12 13
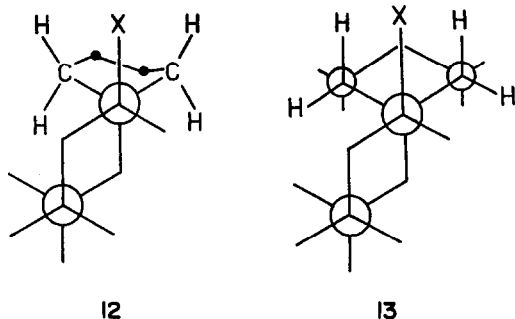
groups and their "effective steric bulk" is thus expected to depend sensitively on their detailed steric environment. Hence, it is expedient to consider the rotameric conformations of the compounds investigated as shown in **14** and **15**. A count of unfavorable 1,3-*syn*-axial C...C or C...O interactions reveals the possible rotameric conformations. For the compounds **6** the ring closure forces the ring methylenes to occupy sites 1–4 or 2–6 for both equatorial (**14**) and axial (**15**) conformations. Hence the rotameric conformations 1–4–7 for equatorial and 1–4–7 and 2–6–7 for axial conformations do not suffer from 1,3-repulsive (*syn*-axial) interactions. For the diethyl compounds **3** the conformations of type 1–4 to 2–6 (**14** and **15**) are disfavored by *syn*-axial Me/Me interactions. In contrast, conformations 1–5–7 for equatorial and 1–6–7 and 2–4–7 for axial conformations, respectively, are free from such 1,3-repulsive interactions. Thus one may expect **3B** to exist in conformation **14** with Me's in positions 1 and 5 in R in position 7. In addition to two O/CH$_2$ *gauche* interactions, this conformation has *four* butane-*gauche* interactions. Compound **3A** with R at position 7 and methyls at positions 1 and 6 or 2 and 4, in contrast, besides also having four butane *gauche*-interactions, has only one CH$_2$O *gauche* interaction and, in addition, is favored, entropywise, by Rln2. The resulting stabilization of **3A** by one CH$_2$/O-*gauche*-interaction plus RTln2 accounts for about 0.8 kcal/mol at room temperature, which appears close to the experimentally found difference between series **2** and series **3** (*cf* Table 1).

14

15
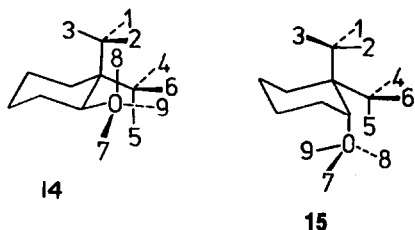
These considerations clarify the observed order of R...O interactions. The problem of the order of R...R' interactions is more complex. As a matter of fact, one may pose the question as to why R...R' interactions exist at all. To take an example, the R...R' contact in the stable rotameric conformation of the equatorial conformer **3B** (**14**, Me groups in 1 and 5, R group in 7) is non-existent, and the data obtained for **2** illustrate the absence of such interaction. While a number of *ad-hoc* explanations could be adduced we prefer to leave this problem open.

For a deeper insight into the above conformational problems, one would want to analyze the free-energy differences in terms of enthalpy and entropy differences. According to the well-known relationship $\Delta G = \Delta H - T\Delta S$, the sign of ΔG (and hence the position of the equilibrium **1**) at very low temperature is determined by the sign of ΔH; as a result the amount of the conformer of lower enthalpy increases as the temperature is lowered. As the temperature is raised, the amount of the higher-enthalpy isomer increases—the more rapidly the larger ΔS.

The position of the equilibria at low temperature has been observed by temperature-variable NMR study. In the case of **2a**, **2b** and **5a**, on lowering the temperature the equilibria are shifted so far to one side that only the signals of axial H$_x$ (equatorial conformer **1B**) are observed. Thus, **1B** is the enthalpy preferred conformer. In the cases of **2a** and **5a** the signals of H$_x$ (quadruplets) were well resolved, but compound **2b** exhibited only a badly resolved multiplet for axial H$_x$ at $-105°$ with a bandwidth at half-height of 17 Hz. We were not able to obtain low-temperature ^{1}H NMR spectra for **4a** and **4b** due to their low solubility. Fortunately, the low temperature spectra of **6a** and **6b** in CS$_2$ contain the signals of *both* conformers, **1A** and **1B**. The axial H$_x$ (equatorial conformer **1B**) was observed at higher field and the difference in chemical shifts, $\delta_e - \delta_a$, was 0.84 ppm and 0.79 ppm for **6a** and **6b**, respectively. The integration of the appropriate signals permitted determination of the population of each conformation at $-105°$, and the content of equatorial conformer **1B**, was then found to be $82 \pm 2\%$ and $82 \pm 1.5\%$ for **6a** and **6b**, respectively. The comparison of these percentages with the data of Table 1 permits one to evaluate the values of $\Delta H \sim -1.4$ kcal/mol and $\Delta S \sim -5$ e.u. for **6a** and $\Delta H \sim -1.7$ kcal/mol and $\Delta S \sim -7$ e.u. for **6b**. These figures show a large enthalpy preference of the equatorial conformers, **1B**, for **6**. At the same time, the axial conformers, **1A**, for **6** are entropy preferred and, as explained above, thus become predominant at room temperature.

In striking contrast, in the cases of **3a** and **3b**, on lowering the temperature the equilibria are also shifted completely to one side, but the singlets of only *equatorial* H$_x$ (axial conformer **1A**) can be observed. The width of half height of these singlets has been found to be 5.9 Hz and 5.4 Hz, correspondingly. Since, at room temperature, ΔG is only 0.2–0.3 kcal/mol, it follows that, whereas *the enthalpy preferred conformer is the axial one*, **1A**, *the entropy preferred conformer* (see Table 1) must be the equatorial one, **1B**. The conformational behavior of the geminal diethyl compounds **3** is thus in complete disagreement, in respect to the value of ΔS and to the sign of ΔH, with expectations based on conformational arguments (see above). There is also a complete lack of analogy between the thermodynamic parameters of **3** and those of the ring-closed analogs, **6**.

Both the absence of the ΔG_{gauche} term (eqn (1)) in series **2** and the unpredicted trend of the termodynamic parameters in **3** suggest that the conformational behavior of 1,1,2-trisubstituted cyclohexanes is as yet far from being understood. Hopefully additional experimental (including X-ray structural data combined with force-field calculations) will throw light on the puzzles revealed (or confirmed) in the present investigation.

used (HMDS–hexamethyldisiloxane- as the internal standard). The values of W and $W_{1/2}$ were obtained as averages from 3–7 measurements. Satisfactory analytical data were obtained for all compounds investigated ($\pm 0.3\%$ for C and H). Syntheses of 7[17], 9[18] and 10[19] were accomplished by rearrangement of the corresponding pinacols. Ketone 8 was obtained via alkylation of cyclohexanone with EtI in the presence of $NaNH_2$[20] with subsequent separation of isomers[21]: b.p. 82–84° (8 mm), n_D^{20} 1.4618. Ketone 11 was obtained by alkylation of cyclohexanone with 1,5-dibromopentane in the presence of t-BuOK.[22] Alcohols 2d–6d were obtained from the ketones by reduction with LAH in ether: 2d, b.p. 72–73° (13 mm), n_D^{20} 1.4648 3d, b.p. 87–88° (5 mm), n_D^{20} 1.4770; 4d, m.p. 80–82° (from hexane); 5d, b.p. 75–76° (2 mm), n_D^{20} 1.4974; 6d, b.p. 112° (1 mm), n_D^{20} 1.5012.

Procedure for methylation of 2d–6d. To a stirred soln of 2d–6d (0.034 mol) in 20 ml of HMPA (N_2 atmosphere) K (1.17 g, 0.03 mol) was added in portions. The mixture was stirred until the blue color of K had disappeared, cooled (ice water) and MeI (0.05 mol) was added dropwise. The mixture was stirred for 1 hr at 20°, for 3–3.5 hr at 40–50° and then 100 ml of water was added. The mixture was extracted with ether, the extracts washed with $Na_2S_2O_3$ followed by water, dried over Na_2SO_4, evaporated and residue was distilled at reduced pressure over Na: 2a, b.p. 68–69° (45 mm), n_D^{20} 1.4413; 3a, b.p. 77–78° (10 mm), n_D^{20} 1.4571; 4a, m.p. 64–65°; 5a, b.p. 71–72° (2 mm), n_D^{20} 1.4737; 6a, b.p. 97–98° (3 mm), n_D^{20} 1.4808.

The *acetates* 2b–6b were obtained by acetylation of 2d–6d with $Ac_2O–H_2SO_4$: 2b, b.p. 42–43° (2 mm), n_D^{20} 1.4451; 3b, b.p. 64–65° (1 mm), n_D^{20} 1.4557; 4b, m.p. 92–93°; 5b, b.p. 94–96° (2 mm), n_D^{20} 1.4812; 6b, b.p. 117–120° (2 mm), n_D^{20} 1.4783.

Procedure for silylation of alcohols 2d–6d. In each case 0.03 mol of Me_3SiCl was added dropwise at 8–10° to a stirred soln of 0.024 mol of 2d–6d and Et_3N (3.03 g) in 50 ml benzene. The mixture was stirred 1 hr at 10°, 3 hr at 75–80°, filtered, washed with water and dried over $MgSO_4$. The evaporation of the solvent and purification gave 2c–6c: 2c, chromatography on alumina, n_D^{20} 1.4390; 3c, b.p. 87–88° (5 mm), n_D^{20} 1.4502; 4c, chromatography on alumina, n_D^{20} 1.5458; 5c, b.p. 76–78° (1 mm), n_D^{20} 1.4624; 6c, b.p. 115–116° (2 mm), n_D^{20} 1.4682.

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