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STEREOCHEMICAL STUDIES—XXVI

CONFORMATIONAL EQUILIBRIA OF KETALS OF 2-SUBSTITUTED CYCLOHEXANONES

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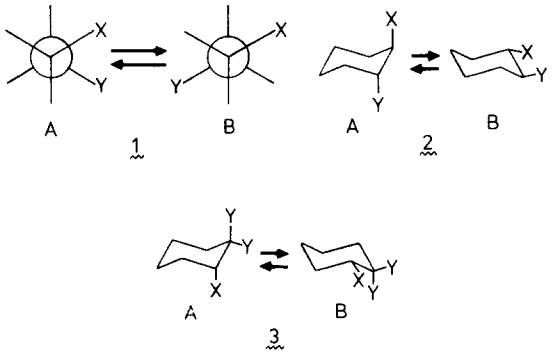
Abstract—The positions of the conformational equilibria in a series of 2-substituted cyclohexanone ketals have been determined by ^{1}H NMR. For the ethylene ketals **6** the equatorial conformer has been found to be enthalpically preferred. The other ketal systems (**5**, **7–9**), in contrast, display predominance of axial conformers. The reasons for this behavior are discussed in terms of rotameric conformations of acetal chains.

Enormous amounts of quantitative data about conformational equilibria of different kinds are now accumulated in the literature due to the progress of the methods for their determination. However the interpretation and theoretical understanding of this vast material is lagging and the predictive power of the concepts of conformational analysis is frequently inadequate. Classical conformational analysis deals, at least qualitatively, with pairwise interactions of nonbonded atoms.[1] In an oversimplified approach, many conformational problems may be viewed in terms of gauche interactions of two types: (a) *gauche* interactions in the 1,2-disubstituted ethane framework, **1** and (b) interrelation of *gauche* conformations in a sequence of two neighboring bonds. Thus, the presence of $g\mp g\pm$ conformations frequently gives rise to severe steric interference (1,3-*syn* repulsive interactions or "pentane type" interferences[2]). Hence, knowledge about *gauche* interactions and about regularities of their changes depending on structure is a very important component part of the theory of conformational analysis.

There is plenty of evidence that *anti* conformations, **1B**, are of lower energy than *gauche* conformations, **1A**, this conformational preference presumably being due to steric and electrostatic repulsions of substituents X and Y. The general idea had been put forward that the difference in energy between *anti* and *gauche* conformations could be used additively to evaluate the relative stabilities of conformers in more complicated cases. For example, the simple addition of *gauche*-butane conformations permits one to predict correctly the relative stability of boat⇄chair or $Me_{axial}\rightleftarrows Me_{equat.}$ equilibria in cyclohexanes.[1]

However the real situation is more complicated due to (i) the existence of structures with predominance of *gauche* over *anti* forms[1,3] and (ii) the dependence of the sign and magnitude of *gauche*-interactions on structure. In fact, the first apparent violation of the "rule" of predominant stability of anti conformations—in the case of 1-chloropropane (**1**, X = Cl, Y = Me)—was found as early as 1949.[4] In his well known papers Wolfe has summarized these facts and suggested the existence of a conformational *gauche*-effect[5,6] (i.e. extra *gauche* attraction, see[7,8]). On the other hand Zefirov *et al.*[7–9] and Eliel *et al.*[10] have substantiated the conformational effect of extra *gauche* repulsion ("hockey-stick" effect,[9a] see also Refs. 7*b*, 11).



Previously, two types of structures, namely (a) 1,2-disubstituted ethanes, **1**[3,6], and (b) *trans*-1,2-disubstituted cyclohexanes, **2**[8,9a,c,12], have been extensively used as models to study the problem of *gauche* interactions. Recently we suggested consideration of the 1,1,2-trisubstituted cyclohexanes, **3**, for this purpose, since the values of *gauche* interactions would appear to be derivable from experimentally observed ΔG_{eq} values (*vide supra*).[13,14] In our work[14], and that of Schneider *et al.*[15], compounds of type **3** with alkyl substituents in 1,1-positions have, however, been shown to demonstrate unexpected conformational behavior inconsistent with the usually accepted values of $\Delta G_{X/Y}$ *gauche* repulsions. An apparent decrease of *gauche* repulsion is found in the framework $CX\text{–}(CH_3)_2C$.

The aim of the present paper is to investigate the conformational equilibria of 1,1,2-trisubstituted cyclohexanes in which the 1,1-substituents are OR groups (for a preliminary communication see Ref. 16). Here, in contrast to the previous work,[14] we use oxygen-containing polar groups to introduce electrostatic interactions. As it will be evident from the discussion below, this study reveals some surprising and intriguing conformational phenomena.

RESULTS

(A) *Synthesis*

All the compounds investigated were obtained from the ketone precursors (**4**) by standard syntheses which are summarized in Chart 1.

(B) *Determination and rationalization of the position of conformational equilibria*

We reasonably assume that all compounds investigated exist in chair conformations (see Ref. 17). The positions of conformational equilibria of these compounds, **3A**⇄**3B**, can be estimated by the Eliel equation (1) using the bandwidth of the H_x signal. Details of this procedure have been presented elsewhere.[12,14]

$$W_{obs} = W_{3A}(1-n) + W_{3B} \cdot n = (1-n)(I_{ee} + I_{ea}) + n(I_{aa} + I_{ea}). \quad (1)$$

The main difficulties are usually connected with the choice of "standard" or "limiting" values of W for the individual conformers A and B[13,14,17,18], and the most precise ones may be obtained from NMR measurements below the coalescence temperature. However, due to technical difficulties (solubility, spectral resolution, etc.), we have been able to obtain only a limited number of such data. They are the following: $W_{3B} = 15.7 \pm 0.3$ Hz(6a), $W^{3B}_{1/2} = 16.7 \pm 0.4$ Hz(6a), $W^{3A}_{1/2} = 5.6 \pm 0.3$ Hz(5a), 5.4 ± 0.3 Hz(9a) and 5.4 ± 0.5 Hz(9d).

Based on these data, we have used for all compounds investigated the following "standard" values: $W_{3B} = 15.7$ Hz, $W^{3B}_{1/2} = 16.7$ Hz, $W_{3A} = W^{3A}_{1/2} = 5.5$ Hz. The oversimplification of our calculations is obvious, since differences in geometry and in electronegativities of substituents X—which affect coupling constants and hence band width—for the compounds under investigation must be appreciable (see data in Refs. 8, 12, 14, 18). Moreover, there is rather poor quantitative agreement between the data obtained from parameters W and $W_{1/2}$, in contrast to the data in Ref. 14. The error due to the inaccuracy using standard parameters is evidently increased for the more one-sided equilibria. For example increasing the standard parameter W_{3B} by 1 Hz leads to a change in the calculated conformer population of 5% (change of $\Delta G = 0.12$ kcal/mol) and of 8.3% (change of $\Delta G = 0.54$ kcal/mol) in the case of experimental values of W equal to 11 Hz and 15 Hz, respectively.

However, the data derived from $W_{1/2}$ are parallel to those from W exhibiting identical regularities with change of solvent, group X, and ketal framework. Usually the data based on $W_{1/2}$ are less positive (% of **3A**) or more negative (ΔG) than ones from W. Thus, though the data obtained have only semiquantitative or qualitative meaning, they appear quite sufficient for the purposes of the present paper. The NMR and equilibria data are presented in Table 1.

For discussion of the data, it is expedient to introduce a new term "conformational (axial or equatorial) shift" which designates the change of the position of some conformational equilibrium as compared to a reference one. For example ketals **5** show an "axial shift" as compared with corresponding monosubstituted cyclohexanes.

For the calculation of the values of *gauche* interactions from the experimental data one needs to compare the observed ΔG_{eq} values with the ones of the reference series. For example, the experimentally observed ΔG_{eq} values for the 1,2-*trans*-disubstituted cyclohexanes had been partitioned into three terms in accordance with eqn (2),[8] where ΔG_X and ΔG_Y are the free energies corresponding to conformational

$$\Delta G_{eq} = \Delta G_X + \Delta G_Y + \Delta G^{gauche}_{X/Y}\,(\mathbf{2}) \quad (2)$$

$$\Delta G_{eq} = \Delta G_X + \Delta G^{gauche}_{X/Y}\,(\mathbf{3}) \quad (3)$$

equilibria in monosubstituted cyclohexanes ($C_6H_{11}X$, $C_6H_{11}Y$), and the term $\Delta G^{gauche}_{X/Y}$(**2**) reflects the interaction of substituents in the diequatorial conformation, **2B**, as compared with the diaxial one, **2A** (*gauche* interaction; the parenthetic **2** indicates that this term relates to disubstituted cyclohexanes). Analogously for compounds **3** eqn (3) has been suggested assuming that *gauche* interactions $X_e \ldots Y_a$ and $X_a \ldots Y_e$ are equal.[14]

It is evident from eqns (2) and (3) that the last terms, reflecting the *gauche* interaction of substituents, are at the same time measures of the values of the conformational shifts of these compounds as compared to monosubstituted cyclohexanes. The values of the conformational shifts, $\Delta G_{eq} - \Delta G_X$ (using the values of ΔG_X of Ref. 19) are summarized in Table 2. The analogous data for reference 1,1-dialkylcyclohexanes (except for X = OH)[14] are shown in Chart 2.

(C) *Empirical regularities in the conformational equilibria*

The previous study[17] of the 1,1,2-trihalocyclohexanes **10a** and **11b** has revealed the normally expected dependence of conformational equilibria on solvent, namely increase of the equatorial conformation **3B**, with increase in solvent polarity (Table 1). Only in the case of 1,1-dichloro-2-alkylthio- (or -arylthio)cyclohexanes the position of conformational equilibria does not noticeably depend on solvent.[13a]

The data of Table 1 reveal a quite complicated picture for the ketal systems **5–9**: the dependence of conformational equilibria on solvents seems unpredictable. The "benzene effect" seems to exist for the majority of the compounds with exclusion of **8b**, **9b**, **d** and **e**. But contrary to **10a** and **11b** one-third of the compounds studied exhibit equal or even diminished stability of

Chart 1.

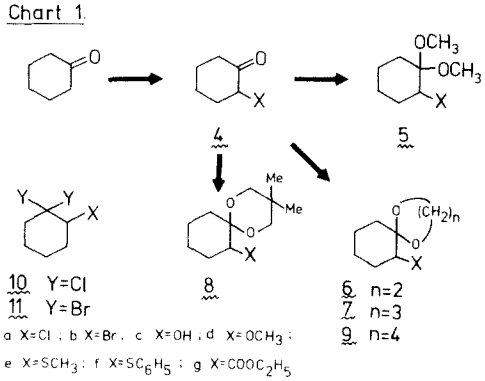


Chart 2.

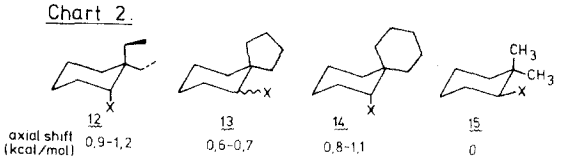


Table 1. ^{1}H NMR[a] and conformational data

Comp.	Solv.	H_X (ppm)	W (Hz)	$W_{1/2}$ (Hz)	% of 3A		ΔG_{e-a} (kcal/mol)	$\Delta G^{gauche}_{X/Y} = \Delta G_{e-a} - \Delta G_X$
5e	CCl_4[b]	3.9_5		(6.6 ± 0.2)		(90.2 ± 1.8)	(1.33)	(1.83)
	CS_2	4.0_3	5.8 ± 0.4	(6.4 ± 0.4)	97.1 ± 3.9	(92.0 ± 3.6)	2.11 (1.47)	2.61 (1.97)
	C_6H_6[b]	3.9_6		(7.2 ± 0.2)		(84.8 ± 1.8)	(1.04)	
	CD_3CN[b]	4.1_7		(6.5 ± 0.2)		(91.1 ± 1.8)	(1.40)	
5b	CCl_4[b]	4.1_2		(6.5 ± 0.3)		(91.1 ± 2.7)	(1.40)	(1.88)
	C_6H_6[b]	4.0_7		(6.5 ± 0.1)		(91.1 ± 0.9)	(1.40)	
	CD_3CN[b]	4.3_3		(6.5 ± 0.2)		(91.1 ± 1.8)	(1.40)	
5c	CCl_4	4.2_0		(7.0 ± 0.5)		(86.6 ± 4.5)	(1.12)	(1.67)
5f	CCl_4	3.4_8		(7.3 ± 0.4)		(83.9 ± 3.6)	(1.00)	(2.1)
	C_6H_6	3.6_0		(8.1 ± 0.8)		(76.8 ± 7.1)	(0.72)	
	CD_3CN	3.5_5		(7.3 ± 0.4)		(83.9 ± 3.6)	(1.00)	
5g	CS_2	2.7_7		(7.85 ± 1.5)		(79.0 ± 13.4)	(0.80)	(2.0)
6a	CCl_4[b]	3.7_5	12.8 ± 0.2	(14.5 ± 0.4)	28.4 ± 2.0	(19.6 ± 3.6)	−0.56 (−0.85)	−0.06 (−0.35)
	CS_2	3.7_6	13.5 ± 0.2	(14.8 ± 0.1)	21.6 ± 2.0	(17.0 ± 0.9)	−0.78 (−0.96)	
	C_6H_6[b]	3.6_8	13.2 ± 0.2	(14.4 ± 0.3)	24.5 ± 2.0	(20.5 ± 2.7)	−0.68 (−0.81)	
	CD_3CN[b]	4.0_0	12.6 ± 0.2	(14.1 ± 0.3)	30.4 ± 2.0	(23.2 ± 2.7)	−0.50 (−0.72)	
	—						−0.5 ~ 0.7[c]	
	CCl_4						−0.75[d]	
	CCl_4						−0.45[e]	
6b	CCl_4[b]	3.9_1	13.2 ± 0.2	(14.6 ± 0.4)	24.5 ± 2.0	(18.8 ± 3.6)	−0.68 (−0.88)	−0.2 (−0.4)
	C_6H_6[b]	3.8_4	13.8 ± 0.2	(14.9 ± 0.3)	18.6 ± 2.0	(16.1 ± 2.7)	−0.89(−1.00)	
	CD_3CN[b]	4.1_4	13.1 ± 0.2	(14.5 ± 0.4)	25.5 ± 2.0	(19.6 ± 3.6)	−0.65 (−0.85)	
	CCl_4						~0[d]	
	CCl_4						−0.3[e]	
6c	CCl_4	3.3_5	10.3 ± 0.4		52.9 ± 3.9		0.07	0.62
	CD_3CN	3.4_2	11.8 ± 0.5		38.2 ± 4.9		−0.29	
6d	CCl_4	2.9_4	11.0 ± 0.3	(13.0 ± 0.7)	46.1 ± 2.9	(33.0 ± 6.3)	−0.09 (−0.43)	0.46 (0.12)
	CS_2	2.9_4	10.75 ± 0.2	(12.6 ± 0.2)	48.5 ± 2.0	(36.6 ± 1.8)	−0.04 (−0.33)	
	C_6H_6	3.0_5	11.0 ± 0.4	(13.2 ± 0.6)	46.1 ± 3.9	(31.3 ± 5.4)	−0.09 (−0.47)	
	CD_3CN	2.9_4	11.4 ± 0.3	(13.0 ± 0.3)	42.2 ± 2.9	(33.0 ± 2.7)	−0.19 (−0.43)	
6e	CCl_4	2.4_7		(16.2 ± 0.4)		(4.5 ± 3.6)	(−1.84)	(−0.84)
	C_6H_6	2.5_0	14.2 ± 0.5	(15.9 ± 0.3)	14.7 ± 4.9	(7.1 ± 2.7)	−1.06 (−1.54)	
	CD_3CN	2.4_6	13.2 ± 0.3	(14.8 ± 0.3)	24.5 ± 2.9	(17.0 ± 2.7)	−0.68 (−0.96)	
6f	CCl_4	3.2_8	15.2 ± 0.6	(17.0 ± 0.7)	4.9 + 5.8[f]	(2.5 + 5.9)[f]	−1.79[f] (−2.2)[f]	−0.69 (−1.1)
	C_6H_6	3.2_4	15.8 ± 0.5	(17.3 ± 0.5)	< 4.9[f]	(< 4.2)[f]	< −1.95[f] (< −1.9)[f]	
	CD_3CN	3.2_5	14.7 ± 0.4	(16.4 ± 0.5)	9.8 ± 3.9[f]	(7.6 ± 4.2)[f]	−1.34[f] (−1.5)[f]	
6g	CCl_4	2.5_0	11.6 ± 0.4	(12.6 ± 0.2)	40.2 ± 3.9	(36.6 ± 1.8)	−0.24 (−0.33)	0.96 (0.87)
	C_6H_6	2.6_2	12.0 ± 0.4	(13.6 ± 0.2)	36.3 ± 3.9	(27.7 ± 1.8)	−0.34 (−0.58)	
	CD_3CN	2.5_5	13.2 ± 0.3	(13.9 ± 0.2)	24.5 ± 2.9	(25.0 ± 1.8)	−0.68 (−0.66)	
7a	CCl_4	4.1_6	8.1 ± 0.4	(10.3 ± 0.4)	74.5 ± 3.9	(57.1 ± 3.6)	0.65 (0.17)	1.15 (0.67)
	CS_2	3.5_8	8.6 ± 0.3	(10.8 ± 0.7)	69.6 ± 2.9	(52.7 ± 6.3)	0.50 (0.06)	
	C_6H_6	4.1_3	8.4 ± 0.3	(10.3 ± 0.1)	71.6 ± 2.9	(57.1 ± 0.9)	0.56 (0.17)	
	CD_3CN	4.3_0	9.9 ± 0.3	(12.5 ± 0.2)	65.7 ± 2.9	(37.5 ± 1.8)	0.39 (−0.31)	
7b	CCl_4	4.4_5	9.3 ± 0.5	(10.9 ± 0.2)	62.8 ± 4.9	(51.8 ± 1.8)	0.3 (0.04)	0.79 (0.52)
	C_6H_6	4.2_2	9.8 ± 0.5	(11.3 ± 0.5)	57.8 ± 4.9	(48.2 ± 4.5)	0.19 (−0.04)	
	CD_3CN	4.4_5	11.0 ± 0.4	(13.3 ± 0.2)	46.1 ± 3.9	(30.4 ± 1.8)	−0.09 (−0.50)	
7c	CCl_4	3.5_2	7.9 ± 0.5	(9.45 ± 0.7)	76.5 ± 4.9	(64.7 ± 6.3)	0.7 (0.37)	1.26 (0.92)
	C_6H_6	3.7_0	7.95 ± 0.5	(9.3 ± 0.2)	76.0 ± 4.9	(66.1 ± 1.8)	0.69 (0.40)	
7e	CCl_4	2.8_0	9.1 ± 0.5	(12.0 ± 0.6)	64.7 ± 4.9	(42.0 ± 5.4)	0.36 (−0.20)	1.36 (0.80)
	CS_2	2.8_2	9.8 ± 0.3	(11.1 ± 0.8)	57.8 ± 2.9	(50.0 ± 7.1)	0.19 (0.00)	
	C_6H_6	2.8_8	9.8 ± 0.4	(12.5 ± 0.4)	57.8 ± 3.9	(37.5 ± 3.6)	0.19 (−0.31)	
	CD_3CN	2.9_8	9.9 ± 0.6	(13.0 ± 0.4)	56.9 ± 5.9	(33.0 ± 3.6)	0.17 (−0.43)	
7f	CCl_4	3.4_2		(12.7 ± 0.5)		(35.7 ± 4.4)	(−0.35)	(0.75)
7g	CCl_4	2.8_5	7.4 ± 0.7	(8.8 ± 0.3)	81.4 ± 6.9	(70.5 ± 2.7)	0.89 (0.53)	2.09 (1.73)
	CS_2	2.9_0	7.5 ± 0.4	(8.4 ± 0.3)	80.4 ± 3.9	(74.1 ± 2.7)	0.85 (0.63)	
	C_6H_6	3.0_6	7.7 ± 0.7	(9.6 ± 0.2)	78.4 ± 6.9	(63.4 ± 1.8)	0.78 (0.33)	
	CD_3CN	2.8_2		(9.8 ± 0.3)		(61.6 ± 2.7)	(0.28)	
8a	CCl_4	4.1_3	9.1 ± 0.5	(11.4 ± 0.2)	64.7 ± 4.9	(47.3 ± 1.8)	0.36 (−0.06)	0.86 (0.44)
	CS_2	4.1_0	9.6 ± 0.3	(11.5 ± 0.4)	59.8 ± 2.9	(46.4 ± 3.6)	0.24 (−0.09)	
	C_6H_6	4.1_2	10.2 ± 0.4	(11.0 ± 0.6)	53.9 ± 3.9	(50.9 ± 5.4)	0.10 (0.02)	
	CD_3CN	4.1_7	11.2 ± 0.5	(13.4 ± 0.6)	44.1 ± 4.9	(29.5 ± 5.4)	−0.14 (−0.53)	
	—				~85[g]			
8b	CCl_4	4.2_5	10.8 ± 0.8	(11.9 ± 0.7)	48.0 ± 7.8	(42.9 ± 6.3)	−0.05 (−0.17)	0.43 (0.31)
	C_6H_6	4.1_7	10.5 ± 0.3		51.0 ± 2.9		0.02	
	CD_3CN	4.3_5	13.3 ± 0.6	(15.1 ± 0.4)	23.5 ± 5.9	(14.3 ± 3.6)	−0.71 (−1.08)	
	—				~85[g]			
8c	C_6H_6	3.6_8	7.9 ± 0.5	(9.5 ± 0.4)	76.5 ± 4.9	(64.3 ± 3.6)	0.71 (0.35)	

Table 1. (*Contd*).

Comp.	Solv.	H_X (ppm)	W (Hz)	$W_{1/2}$ (Hz)	% of **3A**		ΔG_{e-a} (kcal/mol)	$\Delta G^{gauche}_{X/Y} = \Delta G_{e-a} - \Delta G_X$
8d	CCl_4	3.1_5	6.5 ± 0.8		90.2 ± 9		1.34	1.89
8e	CCl_4	2.1_7	10.7 ± 0.4	(13.4 ± 0.2)	(49.0 ± 3.9)	(29.5 ± 1.8)	0.02 (−0.53)	0.98 (0.47)
	C_6H_6	2.7_5	11.7 ± 0.7	(13.9 ± 0.4)	39.2 ± 6.9	(25.0 ± 3.6)	−0.26 (−0.66)	
	CD_3CN	2.8_6	11.8 ± 0.6	(14.4 ± 0.5)	38.2 ± 5.9	$(20.5 \pm 4.5$	−0.29 (−0.81)	
8g	CCl_4	2.8_2		(9.7 ± 0.7)		(62.5 ± 6.3)	(0.31)	(1.51)
	C_6H_6	2.9_6	8.2 ± 0.5	(10.7 ± 0.5)	73.5 ± 4.9	(53.6 ± 4.4)	0.62 (0.09)	
	CD_3CN	2.7_8	10.8 ± 0.5	(13.0 ± 0.4)	48.0 ± 4.9	(33.0 ± 3.6)	−0.05 (−0.43)	
9a	CCl_4	4.0_0		(7.5 ± 0.5)		(82.1 ± 4.5)	(0.92)	(1.42)
	CS_2	4.0_4	6.0 ± 0.7	(7.5 ± 1.0)	95.1 ± 6.9	(82.1 ± 8.9)	1.79 (0.92)	2.29 (1.42)
	C_6H_6	3.9_5		(8.1 ± 0.7)		(76.8 ± 6.3)	(0.72)	
	CD_3CN	3.9_0	6.2 ± 0.5	(7.4 ± 0.4)	93.1 ± 4.9	(83.0 ± 3.6)	1.57 (0.96)	
9b	CCl_4	4.2_0		(6.5 ± 0.2)		(91.1 ± 1.8)	(1.40)	(1.88)
	C_6H_6	4.1_7		(6.4 ± 0.2)		(92.0 ± 1.8)	(1.47)	
	CD_3CN	4.3_8		(7.6 ± 0.6)		(81.3 ± 5.4)	(0.88)	
9c	C_6H_6	3.8_0		(6.8 ± 0.6)		(88.4 ± 5.4)	(1.22)	
9d	CCl_4	3.0_8		(7.8 ± 0.4)		(79.5 ± 3.6)	(0.81)	(1.36)
	CS_2	3.1_1		(7.5 ± 0.3)		(82.1 ± 2.7)	(0.92)	
9e	CCl_4	2.8_2		(8.8 ± 0.5)		(70.5 ± 4.5)	(0.53)	(1.53)
	C_6H_6	2.8_8		(8.4 ± 0.4)		(74.1 ± 3.6)	(0.63)	
	CD_3CN	2.9_7		(8.0 ± 0.6)		(77.7 ± 5.4)	(0.75)	
9g	CCl_4	2.7_2		(6.9 ± 0.3)		(87.5 ± 2.7)	(1.17)	(2.37)
	C_6H_6	2.9_0		(7.2 ± 0.4)		(84.8 ± 3.6)	(1.04)	
	CD_3CN	2.5_1		(8.5 ± 0.3)		(73.2 ± 2.7)	(0.61)	
10a	CCl_4[h]				36[i]		−0.34[i]	0.16
	C_6H_6[h]				27[i]		−0.59[i]	
10f	CCl_4	3.2_8	14.6 ± 0.3		14.4 ± 3[i]		−1.07[i]	0.03
	C_6H_6	3.3_0	14.3 ± 0.4		17.5 ± 4.1[i]		−0.93[i]	
	$CHCl_3$	3.3_0	14.8 ± 0.3		12.4 ± 3.1[i]		−1.18[i]	
	CD_3CN	3.4_4	14.6 ± 0.3		14.4 ± 3[i]		−1.07[i]	
11b	CCl_4[h]				40[i]		−0.24[i]	0.24
	C_6H_6[h]				31[i]		−0.48[i]	

[a]90 MHz in CS_2 and 80 MHz in other solvents; [b]60 MHz; [c]Ref. 20a(IR); [d]Ref 20b(DM); [e]Ref. 20b(IR); [f]calculated using $W_{3B} = 15.8$ Hz and $W^{3B}_{1/2} = 17.3$ Hz; [g]Ref. 22; [h]100 MHz; [i]calculated using $W_{3B} = 16.0$ Hz and $W_{3A} = 6.3$ Hz (Ref. 17).

Table 2. Conformational shifts of the ketals of 2-substituted cyclohexanones relatively to the monosubstituted cyclohexanes ($\Delta G^{gauche(3)}_{X/Y} = \Delta G_{eq} - \Delta G_X$)[a] (kcal/mol)

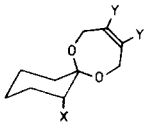
	X <Y	 5	 6	 7	 8	 9	 10	 11	$\Delta G^{gauche(2)}_{X/OCH_3}$
a	Cl	2.6 (1.8)	−0.1 (−0.4)	1.15 (0.7)	0.9 (0.4)	2.3 (1.4)	0.2[b,c]		0.85[d]
b	Br	(1.9)	−0.2 (−0.4)	0.8 (0.5)	0.4 (0.3)	(1.9)		0.2[b,c]	0.7[d]
c	OH	(1.7)[e]	0.6[e]	1.3 (0.9)[e]					−0.36[f]
d	OCH_3		0.5 (0.1)[e]	[e]	1.9[e]	(1.4)			0.8[g]
e	SCH_3		(−0.8)	1.4 (0.8)	1.0 (0.5)	(1.5)			1.1[d]
f	SPh	(2.1)	−0.7 (< −0.9)	(0.75)			0.0[b,h]		1.06[d,i]
g	COOEt	(2.0)	1.0 (0.9)	2.1 (1.7)	(1.5)	(2.4)			

[a]Positive sign means axial shift and *vice versa*; in brackets the data of $W_{1/2}$. [b]$\Delta G^{gauche(2)}_{Cl/Cl} = 1.2$; Br/Br = 1.9[12a]; PhS/Cl = 1.69 kcal/mol.[8] [c]Ref. 17. [d]Ref. 8. [e]Conformational shifts for the corresponding *gem*-dialkylcyclohexanes[14] (kcal/mol) are 0.5(**12c**), 0.1(**13c**), 0.6(**13d**), 0.7(**14c**), 0.8(**14d**); in accordance with[22] this value > 1.04 for **18a, b** (Y=CH_3). [f]Ref. 9c. [g]Ref. 12c. [h] Ref. 13a. [i]for PhS/OAc.

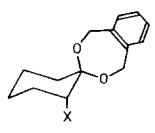
equatorial conformers **3B** in CD_3CN as compared with CCl_4. Thus, the presence in **5–9** of three adjacent groups with different polarity, rotameric conformations, and interrelationships among them leads to a complicated dependence on solvent characteristics. Some other empirical regularities are: (1) the carboethoxy derivatives, **g**, the hydroxy- and alkoxy-derivatives, **c** and **d**, as well as the spiro-13-dioxaryl compounds, **7** and **8**, have the normal type of dependence on solvent polarity and (2) Hal and RS-derivatives of series **5** and **6** have increased content of the equatorial conformer, **3B**, in C_6H_6 as compared to both CCl_4 and CD_3CN. For the following discussion we shall use the data obtained in CCl_4 and, occasionally, in CS_2 because these solvents are commonly used as "non-polar" media.

The most important result of the present study is the demonstration of the crucial influence of the type of the ketal group on the conformational equilibria. Indeed, the ketals of type **5** and **7–9** are characterized by an appreciable predominance of the axial conformations, **3A**, most notably so in the case of **5** and **9**. In contrast, the ethylene ketals, **6**, exist predominantly in the equatorial conformations **3B**. These regularities are clearly shown for Hal and even RS derivatives and less pronouncedly for RO containing compounds.

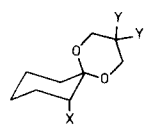
Miscellaneous data from the literature seem to support this conclusion. The preference of equatorial conformation **3B** for halogenated ethylene ketals, **6**, has been confirmed by IR[20] and dipole-moment[20b] methods. The equatorial conformation **3B** is also predominant in the case of 1,1,2-trihalogenocyclohexanes **10a** and **11b**[17] and 1,1-dichloro-2-phenylthiocyclohexanes, **10f**.[13a] This conformational phenomenon will be discussed later. On the other hand, the predominance of axial conformation **3A** has been supported by IR and dipole moment measurements in the case of a series of ketals **16** and **17** containing 7-membered rings,[21] and of halogenosubstituted ketals **7** and **18**.[22]



16
X=Cl, Br
Y=H, Cl



17
X=Cl, Br



18
X=Cl, Br
Y=Cl, CH_3

Those conformers which are preferred at room temperature are also more stable at low temperatures and hence are the enthalpy preferred ones. Indeed, the low temperature ^1H NMR spectra (at −90° and −105°C) of **5a**, **g** and **9a**, **d** and **e** in CS_2 and in $(CD_3)_2CO$ display only the signal of equatorial H_x (badly resolved multiplet with $W_{1/2} \sim 5.5$ Hz; axial conformer **3A**). In contrast, the corresponding spectrum of **6a** displays only the signal of axial H_x (quadruplet, W = 15.7 Hz, equatorial conformer **3B**). This observation is in agreement with our previous data for 2-substituted 1,1-diethylcyclohexanes, **12**, and spiro[4,5]decanes, **13**:[14] at low temperature exclusive predominance of the axial conformer for **12** but the equatorial one for **13** have been observed.

DISCUSSION

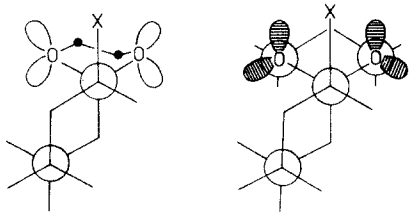
Let us first consider the problem of constancy and transferability of the values of the *gauche*-interaction, $\Delta G^{gauche}_{X/Y}$. These values may be extracted either from eqn (2) for compounds **2** (Table 2) or from eqn (3) for compounds **3** (Tables 1, 2). The comparison of the $\Delta G^{gauche}_{X/Y}$ (**2**) and $\Delta G^{gauche}_{X/Y}$ (**3**) values is disapointing: there are large and non-systematic variations of this conformational parameter even for closely related compounds. For example, the *gauche* interaction is systematically larger by ~1 kcal/mol for **5** (with exclusion of **5c**, X = OH) than for *trans*-2-X-methoxycyclohexanes. For the other series, **6–11**, the values of $\Delta G^{gauche}_{X/Y}$ (**2**) and $\Delta G^{gauche}_{X/Y}$ (**3**) are also completely different, and moreover their relative difference is not even approximately constant, as was observed for **5**. Roughly speaking, the *gauche* (**3**) interaction is increased over appropriate *gauche* (**2**) for **9** by 0.5–1.5 kcal/mol and for **7** by 0–0.3 kcal/mol but is approximately the same for series **8** (except **8d**). For series **6** the situation is the opposite: the *gauche* interaction is decreased for **6a**, **b**, **e** and **f** by ~0.8–1.7 kcal/mol. Here the conformational shifts for the series **2** and **3** tend to go in opposite directions: there is generally an equatorial shift for **6** as compared with the axial shift for the model compounds of series **2**. These facts clearly evidence that *gauche* interactions are drastically influenced by structural differences (probably including slight changes in ring geometry, differences in rotameric conformations, non-additive changes of electrostatic interactions, etc).

Thus the parameters of *gauche* interaction, $\Delta G^{gauche}_{X/Y}$, are not transferable even within groups of structurally related compounds and, in general, one needs a separate determination of these values for each particular type of compound. Unfortunately, the non-additivity and non-transferability of conformational parameters (see for example the ΔG values for mono-[19] and 1,4-disubstituted cyclohexanes[3,12a,23]) is quite common for polar groups, and sharply limits the predictive ability of a simple classical approach to conformational problems involving such substituents (*vide supra*, see also Ref. 7*a*).

We have already alluded to crucial influence of the structure of the ketal group on the equilibria; we shall now discuss this problem in detail. If one tries to predict the possible shift of equilibria in going from 1,1-dialkyl systems (**3**, Y = alk) to the corresponding ketals e.g. **12**→**5**, **13**→**6** and **14**→**7**, one would want to take into account the increase of *gauche* electrostatic repulsions upon substitution of CH_2 by oxygen, which must result in an axial shift. The above mentioned results clearly demonstrate the failure of such oversimplified considerations. In fact, the data evidence predominance of the equatorial conformation for ketals **6** containing a 5-membered 1,3-dioxolane ring. Moreover this conformation is the enthalpy preferred one as proven by low temperature ^1H NMR. In general, the conformational behavior of ketals **6** is opposite to that of the series **5** and **7**.

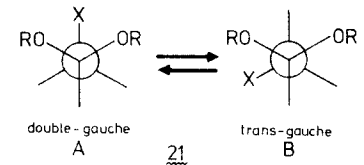
Comparison of the relative conformational shifts in the model systems **13**→**12** and **13**→**14** indicates a slight increase of the axial shift (by ~0.2 to 0.6 kcal/mol).[14] Thus, spiro-compounds containing 5-membered rings (type **6** and **13**) show increased content of the equatorial conformers as compared with "diethyl" (**12** and oxa analog **5**) and spiro-"undecane" (**13** and oxa analog **8**) series. The authors of Ref. 22 even concluded that "it is expedient to accept the different nature of acetal bonds C–O in 1,3-dioxolanes as compared with 1,3-dioxanes". Previously we had explained this difference for **13** as compared to **14** by the flattening of the 5-membered ring as compared with a 6-membered one.[14b] This flattening leads to an outward tilting of axial C–H bonds of CH_2

groups leading in turn to a decrease in 1,3-*syn*-axial repulsions H...X. Pictorially, the replacement of CH_2 by oxygen and of C–H bonds by lobes of electron pairs represents the analogous "geometrical" explanation of the conformational peculiarity of **6** (formula **19**) as compared with **7** (formula **20**). As a matter of fact this approach has been used for the explanation of the difference in rotational barriers of t-Bu groups in 1,3-dioxanes as compared with 1,3-dioxolanes.[24]

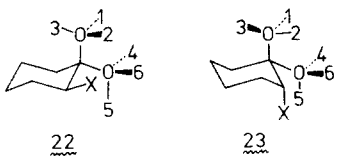


19 20

The observed equatorial shifts in series **6** are especially pronounced for the halogeno (**a** and **b** series) and RS-derivatives (**f** series). It is of interest to compare these data with literature ones. There are many observations in the literature which reveal the increased content of *gauche*-conformation **1A** for the Hal–C–C–OR moiety and of double-*gauche*-conformation **21A** for the Hal–C–C(OR)$_2$ moiety. Thus the investigation of conformational equilibria for methyl ethers of 1,2-halohydrins (**1**, X = Hal, Y = OCH_3) by NMR,[25a] IR[25b] and by a combination of dipole moment and Kerr-constant[26a] methods led to an evaluation of the preference for *gauche*-conformations about the C–C bond (**1A**). The content of rotameric conformation **1A** (Y = OMe) has been evaluated to be approximately 60% (X = Cl) and 50% (X = Br).[26a,27] X-Ray data are in agreement with these observations. For example, the bromoethyl ether side chain in a derivative of dothistromin has been found to adopt the *gauche*-conformation about the BrC–CO bond, (**1A**).[28]



21



22 23

As for doubly *gauche* interactions, the dimethyl acetal of 2-bromoacetaldehyde was found to exist preferentially in conformation **21A** (X = Br, R = Me) with the C–Br bond bisecting the O–C–O angle.[26b] Probably the most closely related model compounds are the 2-chloromethyl- and 2-bromomethyl-1,3-dioxolanes.[20b] The dipole moment data for these compounds show that the equilibria are shifted to the double-*gauche*-conformation **21A** (X = Cl, Br, R,R = $-CH_2CH_2-$) with $\Delta G \sim 0.4$ kcal/mol.[20b] One may summarize these empirical conformational regularities as follows: for some structural series there seem to exist a tendency of the Hal–C–C–OR and Hal–C–C(OR)$_2$ moieties to adopt the conformation with a maximum of *gauche* Hal...OR interactions. The conformational behavior of ketals **6a** and **b** fits this regularity perfectly. The origin of this phenomenon is still not fully understood and may be connected either with electrostatic attraction[26b] or with the special orbital interactions ("*gauche*-effect", see discussion in Refs. 5, 6, 12*c*).[29] It is worth adding that the conformational behavior of Hal–C–CHal$_2$ framework seems to be quite different in that double-*gauche* conformations (analogous to **21A**) are relatively destabilized, as observed for 1,1,2-trihalogenoethanes[3] and 1,1,2-trihalogenocyclohexanes (**3**, X = Y = Cl, Br).[17]

However the conformational behavior of the series **5**, **7–9** appears to be in apparent contradiction to the above stated tendency, because all compounds in these series exhibit a remarkable axial shift. Let us consider this problem in detail. Consideration of rotameric possibilities for the equatorial form, **22**, and the axial form, **23**, reveals that both of them possess those rotameric conformations which are free from unfavorable 1,3-*syn*-repulsive interations, i.e. those with Me in positions 1 and 5 for **22** and 1 and 6 or 2 and 4 for **23**.[32] In respect to the pentane-like moiety these are *gauche–trans* conformations for **22** and *gauche–gauche* conformations for **23**. Now we are ready to explain the appreciable axial shift in ketal **5**: this phenomenon is connected with destabilization of the **gt**-conformation of the CH_3O–C–OCH_3 framework relative to the **gg**-conformations. Indeed, there is much evidence that for a dialkoxymethane framework the **gg**-conformation is appreciably more stable than the **gt**-one.[10a,30] For example the **gg**-conformation of dimethoxymethane itself has been found to be more stable by 3.4 kcal/mol than the **tt**-form and by 1.7 kcal/mol than gt-form.[30a] This phenomenological conformational effect has been called "rabbit ears" effect.[31] The extra destabilization of the rotameric conformation with Me in 1 and 5 in **22** (**gt**-form of MeO-COMe fragment) leads to the disappearance of any rotameric conformation for equatorial form **22** which would be free from strong destabilizing interactions. The result is a relative stabilization of the axial conformation, **23**, which has two such conformations with Me in 2 and 4 (**23**) or 1 and 6 (**23**), which are free from 1,3-syn interactions and represent favorable **gg**-conformations for the dimethoxymethane chain. In other words, the axial shift of the ketals **5** is the unusual result of the operation of the "rabbit ears" effect in ketal groups.[16]

Now it is instructive to discuss the conformational behavior of the open (**5**) vs cyclic (**6–9**) ketals. The difference between series **5** and **6** is clearly understandable from formulas **22–23**. The cyclic structure of the ketal framework in **6** forces the dialkoxymethane fragment to accept the g^+g^--conformation (methylenes in 1–4 or 2–6) for both **22** and **23**. Conformation 1–4 in **22** is free from 1,3-*syn* repulsion with the substituent which, in turn, leads to the relative stabilization of the equatorial conformation in **6**. In other words, the difference between **5** and **6** is conditioned by the necessary existence in equatorial **5** (but not axial **5**) of some unfavorable steric or polar conformational interactions among the three substituents. In contrast, in **6** these interactions are equalized as between equatorial and axial conformations by the ketal ring formation.

The 7-membered ketals, **9**, also show an appreciable

axial shift (see also Ref. 21). Can this fact be explained analogously as in **5**? Indeed, it is known that 1,3-dioxepan and its derivatives contain appreciable content of the twist conformation where the $-CH_2-O-CH_2-O-CH_2$ framework adopts the g^+g^+-conformation.[21,30c] The analogous twist of the 7-membered ring in ketals **9** requires the existence of the 1–6 or 2–4 rotameric conformations (probably distorted to some extent) which again leads to the presence of unfavorable 1,3-repulsions in the equatorial conformation **22**. The drawback of this explanation is connected with the small population of twist-conformations and predominance of chair-like forms for 1,3-dioxepane rings.[21,30c]

The most difficult problem is the explanation of the conformational behavior of 6-membered ketals **7** and **8**. They still show the axial shift although it is less than in the case of **5** or **9**. (See also Ref. 22.) The previously suggested explanation using the consideration of rotameric forms **22** and **23** is obviously not helpful here. Indeed, the chair⇄twist equilibrium for 1,3-dioxanes is almost completely shifted to the chair conformation with the difference in free energy as much as 8.5 kcal/mol.[33] Hence, ketals **7** and **8** must adopt the rotameric forms 1–4 and 2–4 for both conformations **22** and **23**.

The same general dependence of conformational behavior on the size of acetal ring has been observed for the acetals of 2-haloacetaldehyde where the double-*gauche* conformation, **21A**, is preferred for the ethylene acetals[20b] and the *trans-gauche* conformation, **21B**, is preferred for the trimethylene acetals.[22,34] Probably more precise data will help shed light on this problem. In conclusion, we should like to say that the data presented here demonstrate the complexity of finding an unambiguous interpretation of the conformational behavior of 1,1,2-trisubstituted cyclohexanes. Clearly more work is required to solve the problem of *gauche*-interactions and explain the relative stability of cyclohexane derivatives. However, some generalities can be extracted even at this stage from the data here presented.

EXPERIMENTAL

^{1}H NMR spectra were obtained using Varian T-60 (60 MHz) and BS-487B Tesla (80 MHz) instruments. Concentrations of 10 mol% were used (HMDS-hexamethyldisiloxane—as internal standard). The values of W and $W_{1/2}$ were obtained as averages from 5–7 measurements. Satisfactory analytical data were obtained for all compounds investigated (±0.3% for C and H).

Syntheses of **4a**,[35] **4b**,[36] **4c**,[37] **4e**,[38] **4f**,[38] **4g**[39] were accomplished as described in literature.

The dimethyl ketals, **5**, were prepared via reflux of the appropriate ketones, **4**, in abs MeOH with Me_2SO_3 in the presence of gaseous HCl as catalyst:[40] **5a**, b.p. 72–73° (7 mm); n_D^{20} 1.4662; **5b**, b.p. 62–65° (2 mm), n_D^{20} 1.4856; **5c**, b.p. 80–81° (15 mm), n_D^{20} 1.4530; **5f**, b.p. 110–112 (1 mm), n_D^{20} 1.5778; **5g**, b.p. 84–85° (1 mm), n_D^{20} 1.4550.

The ketals **6–9** were obtained from appropriate ketones and glycols by standard methods. The mixture of 13.2 g of **4a**, 6.8 g of ethylene glycol and 2–3 crystals of *p*-TsOH was refluxed in 100 ml of dry benzene with Dean–Stark trap until the theoretical amount of water had been collected (usually 2–3 hr), cooled, thoroughly washed with water, dried over Na_2SO_4, evaporated and the residue was distilled at reduced pressure: **6a**, b.p. 81–82° (7 mm), n_D^{20} 1.4872; D_4-**6a** [from $(CD_2OH)_2$]—same properties; D_4-**6b**, b.p. 82–84° (3 mm), n_D^{20} 1.5100; **6c**, b.p. 85–87° (5 mm), n_D^{20} 1.4786; **6e**, b.p. 63–65° (1 mm), n_D^{20} 1.5083; **6f**, b.p. 138–140° (0.8 mm), n_D^{20} 1.5498; **6g**, b.p. 85–86° (1 mm), n_D^{20} 1.4658; **7a**, b.p. 86–88° (1 mm), n_D^{20} 1.4958; **7b**, b.p. 92–93° (1 mm), n_D^{20} 1.5149; **7c**, b.p. 62–64° (3 mm), n_D^{20} 1.4871; **7e**, b.p. 78–80° (1 mm), n_D^{20} 1.5171; **7f**, b.p. 144–146° (0.8 mm), m.p. 28–29°; **7g**, b.p. 90–91° (1 mm), n_D^{20} 1.4716; **8a**, b.p. 62–64° (90.5 mm), n_D^{20} 1.4921; **8b**, b.p. 93–94° (1 mm), n_D^{20} 1.5045; **8c**, m.p. 84–85°; **8e**, b.p. 87–89° (1 mm), n_D^{20} 1.5032; **8f**, b.p. 138–140° (0.8 mm), n_D^{20} 1.5634; **8g**, b.p. 95–96° (1 mm), n_D^{20} 1.4670; **9a**, b.p. 62–64° (0.5 mm), n_D^{20} 1.4921; **9b**, b.p. 86–87° (1 mm), n_D^{20} 1.5116; **9c**, b.p. 64–66° (0.5 mm), m.p. 38–40°; **9e**, b.p. 86–88° (1 mm), n_D^{20} 1.5137; **9f**, b.p. 136–138° (0.5 mm), n_D^{20} 1.5873; **9g**, b.p. 94–95° (1 mm), n_D^{20} 1.4719.

The ketals of 2-methoxycyclohexanone, **5d–9d**, were obtained by methylation of alcohols **5c–9c** with MeI in HMPA as described elsewhere:[14b] **5d**, b.p. 83–84° (15 mm), n_D^{20} 1.4471; **6d**, b.p. 81–83° (10 mm), n_D^{20} 1.4736; **7d**, b.p. 80–82° (7 mm), n_D^{20} 1.4744; **8d**, b.p. 85–86° (5 mm); n_D^{20} 1.4646; **9d**, b.p. 79–80° (4 mm), n_D^{20} 1.4725.

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