Nuclear Magnetic Resonance Experiments on Acetals. Part XXXIII.† Conformational Equilibria in Some 4,4-*gem*-Substituted Cyclohexanone Dimethyl Acetals

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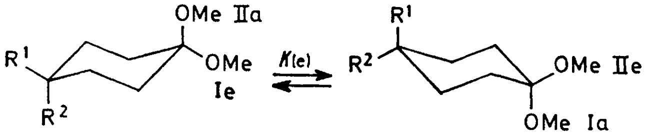
Thermodynamic parameters for the conformational equilibria of seven 4-methyl-4-R-1,1-dimethoxycyclohexanones (R = Et, $\mathrm{Pr^n}$, $\mathrm{Pr^i}$, $\mathrm{Bu^n}$, and $\mathrm{Bu^t}$) were obtained from temperature-adapted shift values. It was assumed that bulkier alkyl groups will take the equatorial position rather than the methyl group. $\Delta\Delta G°$ values are found to be larger than expected from the additivity principle, except for $\mathrm{Bu^t}$ where the contrary is found. For all derivatives $\Delta\Delta H°$ = *ca.* 485 cal $\mathrm{mol^{-1}}$. Unfavourable entropic contributions are found for axial α-branched substituents.

Shifts for methoxy-groups are different when in either the axial or equatorial position,[1] allowing this group to be used as a possible probe for conformational studies. A systematic study of some cyclohexanone dimethyl acetals, substituted in the 3- and/or 4-position, and of some bicyclic derivatives, has shown,[2] however, that the interpolation of absolute shift values, as observed in conformational heterogeneous systems between those found in ' model ' compounds, gives unreliable results. Shift values of the methoxy-signals are influenced by substituents on C(3) and C(4), and attempts to predict this influence by comparison with suitable model compounds were unsuccessful. Thus, we attempted to predict the influence of the Me-4*eq* or Me-4*ax* group on the shift of the methoxy-group by comparison of Δν in 1,1-dimethoxy-3-methylcyclohexane with Δν in *cis*-1,1-dimethoxy-3,5-dimethylcyclohexane. From this, a correction (0·92 in CS_2 and 0·82 Hz in $CDCl_3$) might be introduced for the Δν values observed in *cis*- and *trans*-1,1-dimethoxy-3,4-dimethylcyclohexane leading to Δν(Me-4*ax*) (2·44 in CS_2 and 3·73 Hz in $CDCl_3$) and to Δν(Me-4*eq*) (3·53 and 4·80 Hz). Finally from the value observed in 1,1-dimethoxy-4-methylcyclohexane (3·36 in CS_2 and 4·50 Hz in $CDCl_3$) one would predict $K_e(CS_2) = (2{\cdot}44 + 3{\cdot}36)/(3{\cdot}53 - 3{\cdot}36) = 33$ [$\Delta G°_{301}(\mathrm{Me}) = 2{\cdot}08 \pm 0{\cdot}2$ kcal $\mathrm{mol^{-1}}$] and $K_e(CDCl_3) = (3{\cdot}73 + 4{\cdot}50)/(4{\cdot}80 - 4{\cdot}50) = 27$ [$\Delta G°_{301}(\mathrm{Me}) = 1{\cdot}96 \pm 0{\cdot}13$ kcal $\mathrm{mol^{-1}}$] and these values are certainly too high, the expected value being 1·69 kcal $\mathrm{mol^{-1}}$.[3,4]



The absolute shift method definitely fails when trying to evaluate the position of equilibrium as a function of temperature. Thus it was found that even for anancomeric models $\Delta\nu_m$ changes with temperature, the variation being of the same magnitude as that caused by the equilibrium changes in conformational heterogeneous systems. Together with the fact that the observed shift differences are relatively small (*e.g.*, 0—0·065 p.p.m.) it follows that direct shift interpolation is useless. In the light of recent data one may wonder if this is not generally true, and that the method based on the use of model compounds should be interpreted only with extreme care.[5]

Methoxy-signals (δ 3·2—3·3) however remain attractive probes for conformational studies if the appropriate procedure, *e.g.*, exclusion of reference to model compounds as such, is followed. The signals are sharp and intense, allowing accurate measurements by the wiggle-beat method, or occasionally directly by peak areas (*e.g.*, at $T < T_c$).

In the present study a method taking into account the intrinsic changes of relative shifts with temperature[6,7] was applied to 4-alkyl-1,1-dimethoxy-4-methylcyclohexanes. The methyl group was introduced as a *gem*-substituent in order to counterbalance possibly biased equilibria. Above T_c (the coalescence temperature) shift differences Δν for two ‡ methoxy-signals are measured as a function of temperature. Variations in Δν occurs for two reasons: (*a*) a continuous change of the equilibrium state and (*b*) an intrinsic dependence of shift values on temperature. The latter phenomenon can clearly be followed by studying the behaviour of $\Delta\nu_m$ of anancomeric systems over a wide temperature range (−120—+60 °C), for which it is found that an exponential relationship (1) holds good. Suitable anancomeric systems were 1,1-dimethoxy-4-methyl-4-t-butyl- § and 1,1,4-trimethoxy-4-phenyl-cyclohexane.

$$\Delta\nu_m = \Delta\nu_0 e^{-BT} \qquad (1)$$

$$\Delta\nu = I_0 e^{-CT} \qquad (2)$$

$$K_e = (\Delta\nu_m - \Delta\nu)/(\Delta\nu_m + \Delta\nu) \qquad (3)$$

When conformational heterogeneous systems are investigated, the observed shift difference Δν changes

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† Part XXXII, M. Anteunis, G. Swaelans, and J. Gelan, *Tetrahedron*, 1971, **27**, 1917.

‡ $\Delta\nu = 0$ if the equilibrium reaches unity, *e.g.*, in equienergetic conformational systems.

§ This system in fact turned out to be not entirely anancomeric; see Table 1.

[1] M. Anteunis, *Bull. Soc. chim. belges*, 1964, **73**, 731; M. Anteunis and D. Tavernier, *Tetrahedron Letters*, 1964, 3949.

[2] D. Tavernier and M. Anteunis, *Bull. Soc. chim. belges*, 1967, **76**, 575.

[3] E. L. Eliel, S. I. Angyal, N. L. Allinger, and G. A. Morrison, ' Conformational Analysis,' Interscience, New York, 1965; J. A. Hirsch, in ' Topics in Stereochemistry,' ed. N. L. Allinger and E. L. Eliel, Wiley, New York, 1967, vol. I, 199.

[4] M. Hanack, ' Conformational Theory,' Academic Press, New York, 1965.

[5] M. Anteunis, in ' Conformational Analysis,' ed. G. Chiurodoglu, Academic Press, New York, 1971, pp. 31—50.

[6] J. Gelan, Ph.D. Thesis, Gent, 1971.

[7] J. Gelan and M. Anteunis, *Bull. Soc. chim. belges*, 1969, **78**, 590.

distinctly at a certain temperature (−60 to −80 °C). With (nearly) isoenergetic systems, this temperature (T_c) is more or less accurately measureable, because the two signals collapse giving a broad absorption band with a horizontal plateau. The shifts observed below T_c are those of $\Delta\nu_m$ of the 'frozen' conformers (Figure 1).

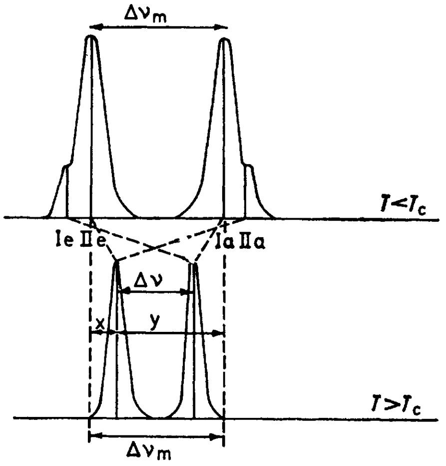

FIGURE 1 Methoxy-signals below and above coalescence temperature, defining $\Delta\nu$ and $\Delta\nu_m$. Lines of low intensity coincide with the intense couple

Possibly two doublets, one for each conformer, may be observed, although this was not the case in the compounds under study, and in fact both maximal shift values seemed to coincide within the possibilities of instrumental resolution. From the behaviour of $\Delta\nu_m(T < T_c)$ with temperature one can extract the values $\Delta\nu_0$ and B [equation (1)]. Above T_c it was found experimentally that in all cases we have a relationship as expressed in (2), a new constant I_0 being introduced. Because at $T = 0$ $\ln K_e = \infty$, $K_e(T = 0) = 0$ as follows from $-RT \ln K_e = \Delta H° - T\Delta S°$. From equation (3) it follows that $\Delta\nu_m(T = 0) = \Delta\nu(T = 0)$ hence $\Delta\nu_0 = I_0$. This allows the determination of C from an additional study of $\Delta\nu$ in the region of $T > T_c$ by use of equation (2). The equilibrium constant at any given temperature can now be calculated according to relation (3) or equation (4) where it is determined by the experimentally available quantities B and C.

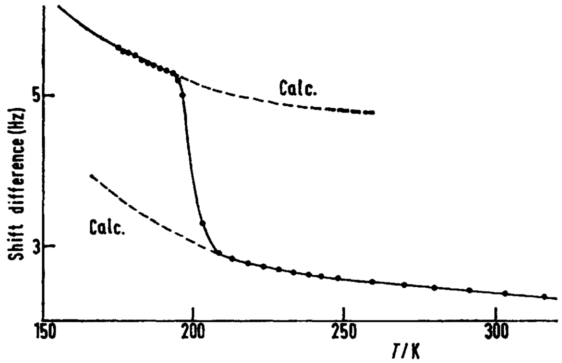

FIGURE 2 Experimental shift difference for methoxy-signals as a function of temperature in 4-isopropyl-1,1-dimethoxy-4-methylcyclohexane showing the discontinuity at $T \simeq T_c$ ($\Delta\nu \longrightarrow \Delta\nu_m$)

$$K_e = (e^{-BT} - e^{-CT})/(e^{-BT} + e^{-CT}) \qquad (4)$$

If $B = C$ we have anancomeric models ($K_e = 0$); if $B \neq C$ we have not, and there will be a net discontinuity at $T \simeq T_c$ in the graphical representation of $\Delta\nu$ and $\Delta\nu_0$ against T, as illustrated in Figure 2, which shows the case for 4-isopropyl-1,1-dimethoxycyclohexane. Figure 3 illustrates the mode of calculation for $K_e = f(T)$, how $\Delta\nu$ at $T < T_c$ can be obtained, and how the correct equilibrium constant at any given temperature can be computed. This method was followed in a series of 4,4-dialkyl-1,1-dimethoxycyclohexanes. Spectra were taken with 50 Hz sweep-width at 5 K temperature intervals ($T > T_c$), or at 2·5 K intervals ($T < T_c$) from −100 °C up to +40 °C, and broad bands were recorded by the accumulation method in order to avoid saturation effects. Data were

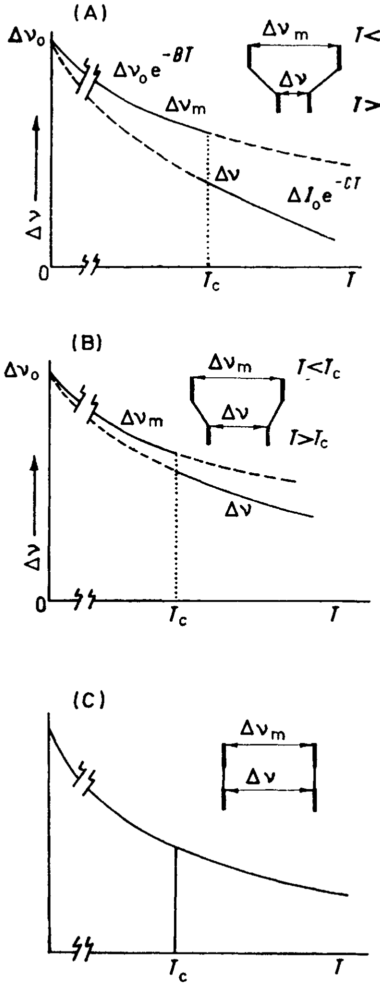

FIGURE 3 Variation of $\Delta\nu$ as a function of temperature. A, Conformationally heterogeneous system; B, almost anancomeric system; C, anancomeric system

computed with the aid of a programme[8] suited for an Olivetti 101 desk calculator. The correlation coefficient[9] r for the regression line relating $\Delta\Delta G^\circ$ with T was calculated, together with values of $\Delta\Delta H^\circ$ and $\Delta\Delta S^\circ$ and their associated errors.*[9] It was assumed that the bulkiest group prefers the equatorial position.

RESULTS AND DISCUSSION

Data for $\Delta\Delta G^\circ$ and $\Delta\Delta S^\circ$ were obtained for the cyclohexanone dimethyl acetals shown in Table 1. Owing to the large overlap of peaks it was not possible † to make accurate measurements of peak area (*e.g.*, of OMe and Me signals) at $T < T_c$ in order to check by this direct method the values obtained by the shift method in Table 1.

Groups without α-branching have comparable conformational energies, resulting from almost identical $\Delta\Delta H^\circ$ values and negligible entropy differences. α-Branching causes an increase in $\Delta\Delta G^\circ$ (in favour of the bulkiest group in an equatorial position), which is mainly the result of variation of the $\Delta\Delta S^\circ$ values, the $\Delta\Delta H^\circ$ values being comparable with those of the unbranched series. This might be expected because the main contribution to the energy difference between straight and branched substituents comes from the more favoured equatorial position for entropy of the branched groups.[3]

TABLE 1

Spectral parameters and computed thermodynamic data for the conformational equilibria in 4,4-R^1,R^2-1,1-dimethoxycyclohexanes [10% CS_2 (v/v), 100 MHz]

R^1	R^2	$\Delta\nu$ (317 K) Hz	$\Delta\nu_m$ (175 K) Hz	$\Delta\nu_0$ Hz	$\Delta\Delta G^\circ_{200}$ cal mol^{-1} (95% error)	$\Delta\Delta G^\circ_{300}$ cal mol^{-1} (95% error)	$\Delta\Delta H^\circ$/cal mol^{-1} (95% error)	$\Delta\Delta S^\circ$/cal mol^{-1} K^{-1} (95% error)	K_e (300 K)	K_e (200 K)
Me	Et	1·46	5·20	10·80	584·5 (4·9)	634 (3·3)	486 (12)	−0·49 (0·03)	0·345 (74·3% Me*ax*)	0·247 (80·2% Me*ax*)
Me	Pr^n	1·23	5·55	12·44	491 (4·2)	504 (2·8)	466 (15)	−0·125 ($0·02_5$)	0·429 (75·6% Me*ax*)	0·323 (69·9% Me*ax*)
Me	Pr^i	2·31	5·41	9·09	839·7 (5·6)	1004·7 (3·7)	509 (21)	−1·65 (0·08)	0·185 (84·4% Me*ax*)	0·124 (89% Me*ax*)
Me	Bu^s	2·20	5·62	10·52	825·5 (5·6)	983·7 (3·8)	509 (20)	−1·58 (0·08)	0·192 (83·9% Me*ax*)	0·129 (88·6% Me*ax*)
Me	Bu^t	3·40	4·50	7·36	1336 (6)	1745 (4)	518 (22)	−4·1 (0·08)	0·066 (93·8%)	0·044 (95·8%)
Me	Bu^n	1·22	5·22	10·48	442 (3·8)	436 (2·5)	453 (14)	+0·05 (0·05)	0·480 (67·6%)	0·412 (70·8%)
Me	Bu^i	1·15	5·05	9·23	439 (4)	431 (2·5)	456 (14)	+0·08 (0·03)	0·480 (67·6%)	0·460 (68·5%)

In the case of 1,1-dimethoxy-4-methyl-4-t-butylcyclohexane a much higher value of $\Delta\Delta H^\circ$ (and $\Delta\Delta G^\circ$) than actually found was expected. The low value may indicate that the additivity principle cannot be applied, *i.e.*, geminal substitution causes deformations and interactions not met in monosubstituted derivatives. The $\Delta\Delta G^\circ$ values in the other derivatives are higher than expected from the additivity principle. For extreme equilibrium states such as met in the *gem*-methyl-t-butyl derivative, large errors may be involved in the evaluation of the necessary coefficients B and C. Thus at low temperature, less than 5% of the axial t-butyl derivative is present, and appreciable error certainly occurs. We have tried to obtain more accurate results by a low-temperature study of the line-shape but those obtained were less reliable than those from the shift study. The fact however that with the latter method $\Delta\Delta H^\circ$ is comparable with that found in the other derivatives seems to be more than fortuitous.

EXPERIMENTAL

Except for 4,4-dimethyl- and 3,3-dimethyl-cyclohexanone dimethyl acetals, the compounds are new. The purity of the parent cyclohexanones was checked by g.l.c., and also additionally purified (prep. g.l.c.). Elemental analyses were in excellent agreement with predicted values. Mass spectra of the corresponding methyl acetals give systematically as highest mass peak $M^+ - 32$ as the result of the extreme ease of loss of methanol, in accordance with the low stability of these acetals during g.l.c. analyses.

The 4,4-disubstituted cyclohexanones were obtained by reduction of the corresponding cyclohexenones prepared by condensation of disubstituted acetaldehydes with methyl vinyl ketone with sodium methoxide or Triton-B in t-butyl alcohol (method A [11-15]); the procedure is well suited for 4-aryl substitution. Alternatively (method B), the enamine of the disubstituted acetaldehyde is first prepared (in piperidine–benzene or neat with sodium carbonate) and is subsequently made to react with methyl vinyl ketone at room temperature for 60 h. The initial adduct is further

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* This is equal to the product of the standard deviation, σ, and the experimental error T.[9]

† Except for dimethoxy-4-methyl-4-phenylcyclohexane[10] where such data were consistent with those obtained from the shift method.

[8] J. Gelan, unpublished work.

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[15] F. G. Bordwell and K. M. Wellman, *J. Org. Chem.*, 1963, **28**, 2544.

treated with strong acid when the keto-aldehyde cyclizes.[16-18] The 4,4-disubstituted cyclohexenones are then reduced with palladium on carbon in methanol, and subsequently acetalized in excellent yield with trimethyl orthoformate in a slightly acid medium. The acetals cannot be purified by g.l.c., the corresponding methyl enol ether being formed quantitatively. Purification was by distillation over sodium.

TABLE 2

Yields and b.p. of dimethyl acetals of 4,4-disubstituted cyclohexanones from the acetaldehydes $R^1R^2CH{\cdot}CHO$

R^1 and R^2	Enamine procedure (yield/%)	B.p. (°/mmHg)	Cyclohexenone B.p. (°/mmHg) (yield/%)	Cyclohexanone B.p. (°/mmHg) (yield/%)	Methyl acetal of cyclohexanone B.p. (°/mmHg) (yield/%)
Me, Me	B/K_2CO_3 (80)	80/13	76/18 (66)	*c* (90)	*c* (100)
Me, Bu^s	B/K_2CO_3 (88)	94/14	72/0·15 (30)	126/15 (90)	128°/17 (100)
Me, Bu^i	B/C_6H_6 (72)	95/18	120/20 (73)	*c* (90)	*c* (100)
Me, Bu^n	B/K_2CO_3 (98)	98/17	120/16 (48)	66/0·05 (88)	*c* (100)
Me, Ph	A/Triton-B		107/0·04 (65)	120/0·1 (90) [a]	*c* (100)
	B/K_2CO_3		(35)		
Me, Pr^i	B/K_2CO_3 (75)	75/12	103/13 (33)	*c* (90)	*c* (100)
Me, Et	B/K_2CO_3 (70)	72/14	91/14 (65)	*c* (90)	*c* (100)
Et, Bu^n	B/C_6H_6 (98)	103/20	78/0·05 (52)	130/15 (88)	*c* (100)
Et, Et	B/C_6H_6 (82)	82/14	85/0·05 (60)	105/13 (97)	108/13 (100)
Me, Pr^n	B/K_2CO_3 (70)	85/13	113/15 (53)	63/0·1 (92)	*c* (100)
Pr^i, Pr^i	(80)		(0) [b]		
CF_3, Ph	A or B (0)				
Me, Bu^t	B/C_6H_6 (77)	85/13	120/15 (13)	*c* (90)	*c* (100)

[a] Slow reaction. [b] No reaction owing to steric hindrance. [c] Separation and purification by g.l.c.

TABLE 3

Preparation and properties of some disubstituted acetaldehydes

Starting ketone R^1COR^2	Procedure	B.p. (°/mmHg) and yield (%) of glycidic ester	B.p. (°/mmHg) and yield (%) of glycol monomethyl ether	B.p. (°/mmHg) and yield (%) of $R^1R^2CH{\cdot}CHO$
Me, Pr^n	D	92/12 (85)	—	116° (58)
Me, Pr^i	D and E	40/0·02 (90)	51/14 (74)	G.l.c. (70)
Me, Bu^n	D	57/0·05 (92)		132 (60)
Me, Bu^i	D	109/18 (84)		122 (95)
Me, Bu^s	C or D [a]	65/0·15 (80)		131 (35)
Me, Bu^t	C or D	(0)		
	E		68/18 (73)	50/18 (62)
Pr^i, Pr^i	E		75/15 (70)	66/28 (80)
Bu^i, Bu^i	E		60/0·07 (65)	80/19 (72)
CF_3, Ph [b]	E		80/9 (70) M.p. 58°	(0) [c]

[a] B.p. of ethyl 2-chloro-3-hydroxy-3,4-dimethylhexanoate (64%) (procedure C) is 48°/13 mmHg. [b] See ref. 22 for preparation of the ketone. [c] The corresponding glycol monomethyl ether could not be hydrolysed even in concentrated polyphosphoric acid at 100 °C.

For the preparation of 1,1-dimethoxy-3,3-dimethylcyclohexanone, dimedone was converted into the monoethyl enol ether (ethanol–toluene-*p*-sulphonic acid azeotropic water removal; yield 87%), reduced with lithium aluminium hydride in ether (95%), treated with hydrogen chloride (70%), and finally reduced. Table 2 summarizes the results.

The disubstituted acetaldehydes were prepared either from the corresponding ketones by a Darzens condensation (for unhindered ketones) or a Grignard condensation (for branched ketones).

Darzens Procedure with Ethyl Dichloroacetate [19] (*Procedure C*).—An equimolecular mixture of ethyl chloroacetate and a suitable ketone in ether was added to magnesium amalgam. After addition (exothermic), stirring was continued for 6 h and the usual work-up afforded the 2-chloro-3-hydroxy-ester. The corresponding glycidic ester was obtained after treatment with sodium methoxide and was

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[17] J. Fleming and M. H. Karger, *J. Chem. Soc.* (*C*), 1967, 226.

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subsequently hydrolysed with sodium hydroxide. Acidification followed by heating under nitrogen of the residue of an extract gave, by pyrolytic decarboxylation, the desired with aldehyde.

Darzens Condensation with Ethyl Chloroacetate[20] (*Procedure D*).—The glycidic ester is obtained by condensation of a suitable non-hindered ketone and ethyl chloroacetate with potassium t-butoxide.

Grignard Method with Chloromethyl Methyl Ether[21] (*Procedure E*).—This method is suitable for sterically hindered ketones. The chloromethyl ether was added to 1 g. atom of etched magnesium in tetrahydrofuran together with 0·5 equiv. of the ketone. The mixture is cooled at −10 °C and left overnight. After the usual work-up with ammonium chloride, the hydroxy-ether is treated with 98% formic acid to give the desired aldehyde. Table 3 contains the results.

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