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NMR-EXPERIMENTS ON ACETALS—IVL

THE CONFORMATIONAL EQUILIBRIUM IN SOME 4,4-DISUBSTITUTED-1,1-DIMETHOXYCYCLOHEXANES. A CHALLENGE FOR THE "ADDITIVITY" PRINCIPLE[a]

H. DE BEULE, D. TAVERNIER and M. ANTEUNIS*

Laboratory for NMR Spectroscopy, Department for Organic Chemistry, State University of Gent, Krijgslaan, 271 (S4), B-9000 Gent, Belgium

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Abstract—Nine 4,4-disubstituted-1,1-dimethoxycyclohexanes have been synthesized. The 4-geminal substituents are: methyl-neopentyl, methyl-cyclohexyl, methyl-benzyl, methyl-vinyl, methyl-phenyl, methyl-chloromethyl, methyl-dichloromethyl, methyl-trichloromethyl, and isopropyl-phenyl.

The conformational chair–chair equilibrium for the title compounds was established using variable temperature ^{1}H-NMR spectroscopy. Apart from the integration of appropriate signals (methyl, methylene, methoxyl) of the slow exchange spectra, the shift of one group (benzyl) and the shift difference of the methoxy groups for all compounds also have been employed.

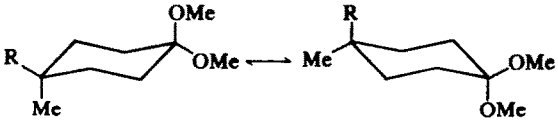
The use of chemical shift differences is discussed with respect to possible ambiguities.

The free energy difference of the two chair forms at 200°K is reported and compared to literature data. The conformer with equatorial methyl is favoured by 200 and 340 cal/mole for methyl-vinyl and methyl-phenyl *gem*-substitution. Axial methyl is favoured for methyl-benzyl, methyl-chloromethyl, methyl-dichloromethyl, methyl-cyclohexyl by 250, 320, 400 and 300 cal/mole. The free energy difference for methyl-neopentyl is 300 cal/mole but it could not rigorously be proven what conformer was the more stable. Finally the conformational equilibrium is extreme (a lower limit of 1200 cal/mole is estimated) for methyl-trichloromethyl and isopropyl-phenyl. The trichloromethyl- and isopropyl groups occupy equatorial positions.

Conformational free energies for monosubstituted cyclohexanes are by now well established.[1] As pointed by Eliel[2] little is known however about conformational free energies in *gem*-disubstituted cyclohexanes. In general, additivity is not observed. We wish to report upon some results in this field, obtained from ^{1}H-NMR spectroscopic data of 4,4-disubstituted-1,1-dimethoxycyclohexanes.

GENERAL CONSIDERATIONS

The free activation energy for "ring-topomerization"[3] in 4,4-dimethyl-1,1-dimethoxycyclohexane is 11·3 kcal/mole.[4] Similarly, for the investigated compounds a slow exchange spectrum could easily be obtained in carbon disulphide as the solvent. A spectrum results in simply the superposition of two spectra, e.g. one for each chair conformer, the intensity being proportional to their molar fraction. Integration of two signals, each originating from one of the forms gives directly the conformer ratio. If each line can be unambiguously assigned to one conformer, it is also known what form is the more stable one. In this respect, the signals from the geminated Me group are particularly useful, because of (i) their high intensity (three H atoms); (ii) the fact that the signal of only the axial Me group is broadened due to long-range couplings with the anti axial H atoms,[5] and (iii) the Me resonances are often well isolated from the other lines (Me axial being at lower field from Me equatorial). This fortunate situation was met in the following compounds: 4-Methyl-4-cyclohexyl-, 4-methyl-4-benzyl-, 4-methyl-4-chloromethyl-, 4-methyl-4-vinyl-, and 4-methyl-4-phenyl-1,1-dimethoxycyclohexane.



For the 4-methyl-4-benzyl-, and 4 - methyl - 4 - chloromethyl-derivatives the signals of the methylene H atoms could be used for the same purpose (the signal of the axial group being at lower field and broadened compared to the signal of the equatorial group).

We can also rely on the signals originating from the OMe groups. Under slow exchange conditions, a maximum of four signals can be expected (equatorial and axial OMe for each conformer). These signals frequently overlap, but integrations

[a] From the Ph.D. thesis of H.D.B.—Gent 1973.

could be done with the aid of the Du Pont 310 curve resolver (except for the methyl-neopentyl derivative). This peak simulator was also used for the determination of the relative intensities of all signals discussed here (4-Me, 1-MeO, 4-PhC$\underline{H}_2$, 4-ClC$\underline{H}_2$).

For the OMe signals however, it is a drawback that they cannot be assigned to one of the conformers, nor can we distinguish between an axial and an equatorial OMe: thus we are able to determine the ratio of the conformers but we can not identify them. Alternatively, the conformational equilibrium constant can be computed using the formula[6]

$$K = [b]/[a] = (P_a - P_m)/(P_m - P_b) \qquad (1)$$

where P_m, P_a and P_b stand for the numerical values of some property P of respectively the conformational mixture and the conformers a and b. We will call $P_a - P_b$ the "interpolation interval". P_m and the pair P_a and P_b for the same compound are obtained respectively under fast and slow exchange conditions. Hence P_m and P_a, P_b are obtained at different temperatures. This raises the question of the temperature dependence of P_m, P_a and P_b.[8a]

Rather than extrapolating two numbers P_a and P_b from a restricted number of data points, we preferred to adopt the original procedure of Berlin and Jensen[7] and we extrapolated P_m (one number) to lower temperatures (at which P_a and P_b can directly be measured, $T < T_c$.

The change of P_m with temperature reflects also the change of the conformational equilibrium in function of that variable. Garbisch[8b] has shown how, under some limiting conditions such as precisely the temperature independence of P_a and P_b, the equilibrium constant can be obtained from the temperature dependence of P_m alone. To have some indication about what function should be used for extrapolations, we adopted the following approximation.

Eq (1) can be solved for P_m, resulting in the expression:

$$P_m = (P_a + P_b \,.\, K)/(K + 1). \qquad (2)$$

With the requirement that $P_b = -P_a = P'$ (a condition that can always be met by a suitable coordinate transformation, Eq (2) can be written as:

$$P_m = P'(K - 1)/(K + 1). \qquad (3)$$

P_m can be explicited for temperature by putting:

$$K = \exp(-\Delta G/RT) = \exp 2x. \qquad (4)$$

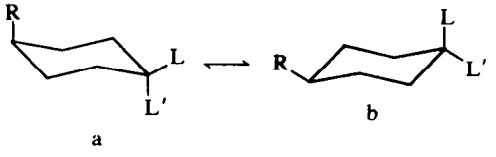
By imposing the constraint that P' and ΔG be temperature independent, Eq (3) is transformed into:

$$P_m = P'(\exp 2x - 1)/(\exp 2x + 1) = P' \tanh x. \qquad (5)$$

As the hyperbolic tangent is a tabellated function, it is a convenient one to employ in simulations. Model calculations show that for small ΔG values (up to 500 cal/mole) an exponential function fitted to the points in the 250–300°K temperature range, satisfactorily predicts the values of P_m in the 170–250°K temperature interval. For higher free energy differences, a linear fitting is more successful in the same temperature ranges. In the present investigation we used the chemical shift *difference* of the methoxy H atoms as the property P_m. Only for the benzyl, methyl-derivative we used the shift of the methylene H atoms too. Because of the small values of these shift differences (0·50 to 6·70 Hz at 100 MHz) only little distinction could be made between an exponential and a linear fitting for the experimental points (within a 220–320°K temperature range). On the other hand extrapolations were made only to the 180–200°K interval, so that the extrapolated shift differences obtained by either method of extrapolation coincided within experimental error. In this way reasonable Ke and $\Delta\Delta G°$ values could be calculated between 180 and 200°K. For the determination of the thermodynamic quantities $\Delta\Delta H°$ and $\Delta\Delta S°$ a more sophisticated approach is called for.[9]

As the chemical shift *difference* parameter is used extensively in our laboratory for the evaluation of conformational equilibria, we wish to discuss in some detail the advantages and possible drawbacks associated with the use of it. A chemical shift difference of two like groups would be expected to be less temperature dependent than the chemical shift of either of the groups. Also, shift differences are likely to result in a larger "interpolation interval" than when using the chemical shift of either group as a property. However, this is not necessarily so and must be checked for every compound.

Let us consider two *gem* ligands L and L', bonded to a cyclohexanoid system undergoing ring inversion between two nonidentical chair forms a and b



a b

We have $P_a = \Delta\nu_a = \delta L(eq)_a - \delta L'(ax)_a$

$P_b = \Delta\nu_b = \delta L(ax)_b - \delta L'(eq)_b$.

For clarity, the conformational nature (axial or equatorial) of the ligands has been specified in these expressions.

It will be advantageous to use the interpolation interval $\Delta\nu_a$, $\Delta\nu_b$ whenever $\Delta\nu_a - \Delta\nu_b$ is larger than either $\delta L_a - \delta L_b$ or $\delta L'_a - \delta L'_b$. Often, the chemical shift (and chemical shift difference) of the ligands is primarily determined by their equatorial and axial nature, and only to a lesser extent by the group R that is setting up the conformational equilibrium. P_a

and P_b have then opposite signs. Occasionally they have like signs. This may happen e.g. when the group R is close to the ligands, or when R has a large magnetic anisotropy (aromatic rings), and of course the easier the chemical shift-difference of the ligands L and L' in the absence of the group R is rather small.

As an example the shift difference of the 4-equatorial and 4-axial H atoms in the anancomeric[10] isomers *cis*- and *trans*-2,5-dimethyl-1,3-dioxanes is $-0{\cdot}15\ \delta$ and $+0{\cdot}74\ \delta$ respectively.[11] The influence of the conformation blocking 2-Me group on the shifts of the 4-H atoms is negligible,[11] and the same situation will also hold for both conformers of 5-methyl-1,3-dioxane.

The situations of like and opposite signs for P_a and P_b can conveniently be illustrated by "mixing diagrams" (Fig 1). When P_a and P_b have the same

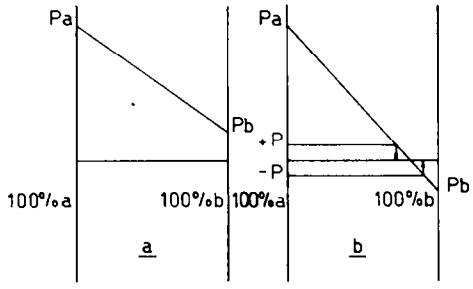


Fig 1.

sign, also the sign of P_m is determined. Even when P_a and P_b have opposite sign, and the absolute value $[P_m]$ is larger than either $|P_a|$ or $|P_b|$, the relative sign of P_m is determined.

If $|P_m|$ is smaller than both $|P_a|$ and $|P_b|$, the sign of P_m is indetermined, and two values of P_m (same magnitude but opposite sign) can be inserted into Eq (1), from which two Ke values may be obtained, one of which is erroneous. It will be noted that the sign of P_m is not necessarily equal to the sign of the value for the property in the more populated conformer, except for the case where $P_a = -P_b$. Fortunately the two above mentioned solutions mostly correspond to rather different percentwise compositions of the conformational mixture, so different in fact that by comparison with the values obtained by direct integration, one of them can be rejected.

Summarizing, in order to compute a meaningful equilibrium constant we must know the signs of P_a, P_b and P_m, and be able to associate P_a and P_b with one or other conformer. Unfortunately, for the compounds presently investigated we could not distinguish between an axial and an equatorial OMe group.

Only one thing can be helpful: if P_m (measured under fast exchange conditions) is smaller than both P_a and P_b, then P_a and P_b have opposite sign.

The problem of finding out what conformer predominates is different from the determination of the relative signs of P_a, P_b, P_m, often though the solutions of these problems entwine. It is not uncommon that one obtains by some technique the numerical values (and relative signs) of P_a, P_b and P_m, without knowing what conformer actually predominates. Stated somewhat differently: the sign of the free energy difference remains uncertain. This situation is especially apt to arise when dealing with small free energy differences.

RESULTS AND DISCUSSION

The data obtained for all products appear in Table 1. We may note that the conformational free energies obtained by the different methods (integration and shift difference) are concordant within experimental error.

The conformer with axial Me is somewhat more stable for *methyl-cyclohexyl* and *methyl-benzyl* substitution. This is, at least for methyl-cyclohexyl, what would be expected assuming additivity[12] or on the basis of a naïve calculation according to Allinger.[13] An independent conformational free energy value for benzylcyclohexane has up to now not been determined. Note added in proof: For the *methyl-neopentyl* compound, neither the Me nor the OMe signals did split up in the slow exchange spectra. Therefore we could not find out what conformer was the more stable one. The coalescence temperature could be obtained as the temperature at which the ($\Delta\nu_{OMe}$, T) curve showed a jump.

Additivity is apparently the case for 4 - *methyl* - 4 - *vinyl* - 1,1 - dimethoxycyclohexane, for the conformer with equatorial methyl is the more stable one. However this is a somewhat circular argument as the reported[14] conformational free energy of the vinyl group was obtained assuming additivity. Interestingly, the conformer with equatorial Me group is the more stable by 340 cal/mole in the *methyl-phenyl* compound. Yet the conformational free energy of phenyl is reported[1] to be much larger than that of the Me group (between 2 and 3 kcal/mole). The present result is in agreement with data given by Shapiro[15] and also with calculations due to Allinger.[16]

Using his new forcefield, Allinger calculated that for 1-methyl-1-phenyl cyclohexane the conformer with equatorial Me would be 900 cal/mole more stable than the inverted chair form. The explanation is that the most stable, i.e. parallel orientation (Fig 2; **18a**) of a monophenyl group becomes energetically unattractive by the introduction of a *gem*-Me group to the point that the phenyl assumes now the "flatsided" orientation (*cf* **18b**)*. On the other hand the more stable "flatsided" rotamer of the axial

*We wish to avoid terms like perpendicular or orthogonal[6] (to the geminal bond) and prefer terms like "flatsided" or "gonal".

Table 1. Conformational data in 4,4-disubstituted-1,1-dimethoxycyclohexanes (NMR-values, when quoted, in Hz at 100 MHz)

R_1	R_2	Solvent	T_c(°K)	$\Delta\Delta G°200$[a] J/mole.	Method	$\Delta\Delta G°$[b] J/mole calculated	Remarks: Δ values at 200° (extrapolated for Δν) ΔI: Δ for the more abundant conformer
Me	*neo* Pe	CS_2	211·5 (OMe)	1460 ± 40[f]	Shift OMe	1300	Only two OMe-signals at $T < T_c$ Hence ΔI = ΔII = 4·37; Δν = 2·05
Me	*c*.Hex	CH_2Cl	201·2 (Me) 204·0 (OMe)	1170 ± 40 1340 ± 40 1340 ± 40	curve res. Me shift OMe[c] shift OMe[d]	1900	ΔI = 5·35; ΔII = 3·90; Δν = 1·24
Me	$CH_2\phi$	CS_2	211·1 (CH_2) 210·1 (OMe) 207·3 (Me)	960 ± 40 1130 ± 40 1000 ± 40 840 ± 40	curve. res. $CH_2\phi$ curve res. OMe curve res. Me shift $\underline{CH_2}\phi$	~ 1300	ΔI = 2·17; ΔII = 7·22; Δν = 1·24
		CS_2 + 3·5 vol% CH_2Cl_2		920 ± 40 960 ± 40	shift $\overline{OMe}$ shift OMe		ΔI = 2·23; ΔII = 8·24; Δν = 1·27
Me	CH_2Cl	CS_2	194·5 (Me) 203·3 (CH_2)	1380 ± 40 1300 ± 40 1050 ± 40	curve res. CH_2Cl shift OMe curve res. OMe		ΔI = 5·08; ΔII = 4·40; Δν = 2·11 No sufficient differentiation for Me signals
Me	$CHCl_2$	COPYC[e]	195·2 (OMe)	920 ± 40 1710 ± 40	curve res. OMe shift OMe		No sufficient differentiation for OMe signals ΔI = 8·30; ΔII = 5·75; Δν = 4·78
		CS_2	195·5 (OMe)	2050 ± 60	shift OMe		ΔI = 6·50; ΔII = 4·45; Δν = 3·87
Me	CCl_3	CS_2	—	> 5000		—	Only one form visible at $T < T_c$
Me	$CH{=}CH_2$	CS_2 + 3·5 vol% CH_2Cl_2	213·9 (Me) 211·3 (OMe)	− 790 ± 40 − 750 ± 40 − 810 ± 30	curve res. Me curve res. OMe shift OMe	− 1500	ΔI = 2·06; ΔII = 4·93; Δν = 0·45
Me	ϕ	CS_2 + 3·5 vol% CH_2Cl_2	220·5 (Me) 212·6 (OMe)	− 1380 ± 40 − 1420 ± 40 − 1460 ± 80	curve res. Me curve res. OMe shift OMe	+ 5·400	ΔI = 7·05; ΔII = 5·54; Δν = 6·52 (at 223°K)
i-Pr	ϕ	CS_2	—	< − 5000		+ 3500	Only one form visible at $T < T_c$

[a] 95% probable error obtained from least squares treatment (ΔG° as f(T)) Positive value if R_1 axial is prefered.

[b] Calculated from additivity principle with following ΔG° values[1] (kJ/mol): Me = 7·1; *i*.Pr = 9; c.Hex = 9; CH_2 = CH = 5·6; *neo* Pe = 8·4 (see however Ref 33); ϕ = 12·5; assumed for $CH_2\phi$: 8·4. See note added in proof.

[c] With Δν extrapolated according to a linear relationship. See text.

[d] With Δν extrapolated according to an exponential relationship. See text.

[e] Ternary mixture: deuterochloroform: pyridine: carbon disulphide, 1:1:4 by volume.

[f] Sign may be reversed if *neo*-Pe would be the smaller group. No individual peaks for CH_3 and CH_2 *t*-Bu were observed at $T < T_c$, thus not allowing conformer assignments from band widths.

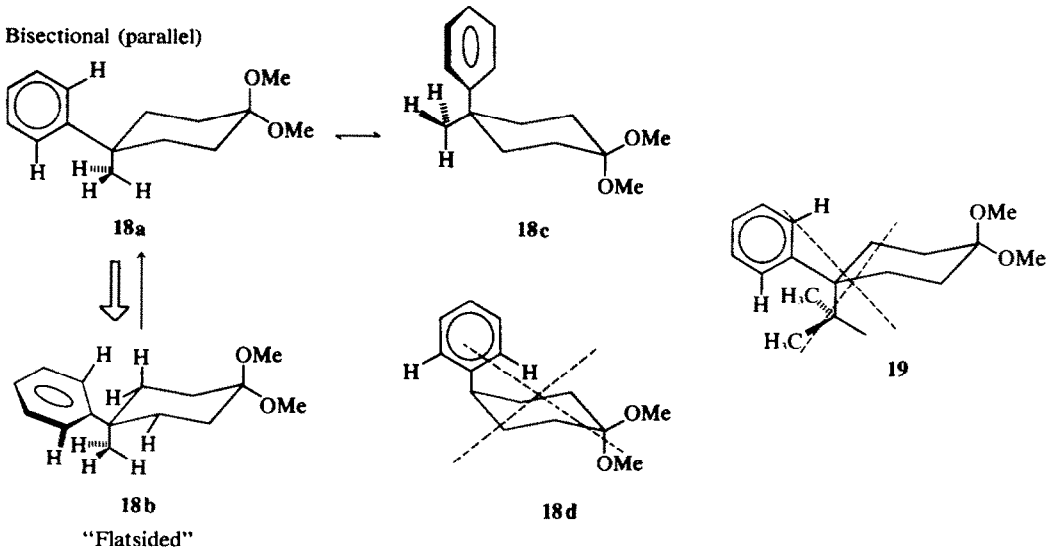


Fig 2.

phenyl group (*cf* **18c**) is not so much affected by the introduction of a *gem*-Me substituent. Our experimental value is smaller than Allinger's calculated value. Whether this discrepancy is due to the presence of the *gem*-dimethoxy group or to some computational insufficiency remains a moot point. In the literature, some other examples are to be found of seemingly anomalous effects arising from geminal substitution of a phenyl and some other group.[17,18]

For 4 - *methyl* - 4 - *chloromethyl* - 1,1 - dimethoxycyclohexane there was little differentiation for the signals of the Me group in the slow exchange spectrum, but the signals originating from the chloromethyl group were completely separated. The less intense peak was broader than the more intense one and was at lower field (from TMS). As axial groups are generally involved in larger long-range couplings than equatorial ones,[5] we ascribe the smaller peak to the axial chloromethyl group. Consequently the conformer with axial Me is the more stable one.

The spectra of 4 - *methyl* - 4 - *dichloromethyl* - 1,1 - dimethoxycyclohexane were run in the usual solvent (CS_2) and also in COPYC (a ternary mixture of CS_2, $CDCl_3$ and pyridine 4 : 1 : 1 in volume). In the latter solvent a more differentiated OMe pattern at $T < T_c$ was found. However the determination of the relative intensities for the OMe signals remained difficult (Me signals are not at all separated at low temperatures). From the obtained free energy differences we conclude that the dichloromethyl group is about 100 cal/mole "heavier" than the chloromethyl group, if the conformer with axial Me is predominating for both compounds. This is reasonably so if we consider the data for the trichloromethyl derivative (see below).

For 4-*methyl*-4-*trichloromethyl*-, and 4-*isopropyl*-4-*phenyl*-1,1-dimethoxycyclohexane the NMR-spectra changed only little with temperature down to −100°. No line broadening due to slacking down exchange phenomena could be detected. This points to one of the chair forms being much more stable than the other one (we discount the hypothesis that the free energy for ring inversion would be 3 to 4 kcal/mole lower than for the other compounds reported in the present study). For the trichloromethyl compound a long range coupling of 0·8 Hz (300 MHz) could be detected for the Me signal, which shows[5] that the conformer with axial Me is favoured. It is clear that in the conformers with equatorial Me in the chloro- and dichloromethyl compounds, the voluminous Cl atoms can avoid the 1,3-diaxial interactions by turning away and pointing a H atom above the ring. This explains why the free energy values for these two groups do not differ so much. With a trichloromethyl group this is no longer possible. One Cl atom of the axial trichloromethyl group is forced above the plane of the ring which causes the extreme equilibrium.

For the *phenyl-isopropyl* derivative we *propose* the conformer with axial phenyl as the most stable. Inspection of Dreiding models show (Fig 2; **19**) that for equatorial phenyl the ortho H atoms and the Me hydrogens are at close distance for any orientation of the phenyl ring, as long as the isopropyl-methyl groups do not stick above the plane of the cyclohexane ring (which is improbable, *cf.* axial *t*-Bu). On the other hand, in the inverted chair form the now equatorial isopropyl group has a greater rotational freedom and the interaction between the isopropyl and the phenyl group can be relieved more effectively.

In order to asign a lower limit to the conformational free energies in these anancomeric compounds, we estimate, perhaps conservatively, that we would not fail to detect 5% of a minor conformer. This gives 1200 cal/mole as a lower limit to the conformational free energy differences.

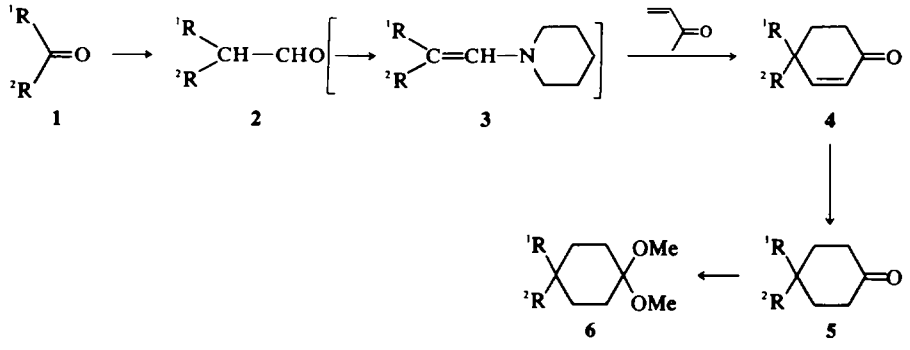
EXPERIMENTAL

The NMR spectra were recorded on a VARIAN HA 100 apparatus in a 10% (vol/vol) soln. The temp was measured with the VARIAN MeOH calibration graph. All pertinent synthetic data are gathered in Table 2.

In scheme 1 the general synthetic route to the 1,1-dimethoxy-4,4-disubstituted cyclohexanes **6** is depicted. It implicates the condensation of α,α-disubstituted acetaldehydes **2** either with methyl vinyl ketone via its piperidine-enamine 3,[19] or by direct base catalyzed condensation in the case of aromatic substituents.[20]

The aldehydes were obtained from the corresponding ketones **1** either by reaction with the Grignard reagent from methylchloromethyl ether followed by formic acid treatment of the resulting carbinol[21,22] or by a Wittig reaction using methyl chloromethyl ether and perchloric acid treatment of the vinyl ether.[23] The cyclohexenones **4** so obtained were easily hydrogenated to the corresponding cyclohexanones **5**. Final acetalisation was performed with trimethylorthoformate in slightly acidic methanol. The 4-methyl-4-neopentyl-, 4-methyl-4-phenyl-, and 4-isopropyl-4-phenyl compounds were prepared in this way.

4-Benzyl-4-methyl-cyclohexanone (*Scheme* 2). To the Grignard reagent **7** prepared from 0·63 mole Mg and benzylchloride in ether, was added at −10°, 0·63 mole



SCHEME 1

Table 2. Elemental analysis and mass spectral data of new compounds.

A. 4,4-Disubstituted cyclohexanones:

R_1	R_2	formula	C calcd.	C found.	H calcd.	H found.	O calcd.	O found
Me	*neo* Pe	$C_{12}H_{22}O$	79·12	79·00	12·09	12·19	8·79	8·81
Me	*c*-Hex	$C_{13}H_{22}O$	80·41	80·30	11·34	11·40	8·25	8·30
Me	CH_2Cl	$C_8H_{13}OCl$	59·83	59·72	8·10	8·20	9·97	10·00
i-Pr	Ph	$C_{15}H_{18}O$	84·11	84·19	8·41	8·0	7·48	7·40

B. 4,4-Disubstituted-1,1-dimethoxycyclohexanes:

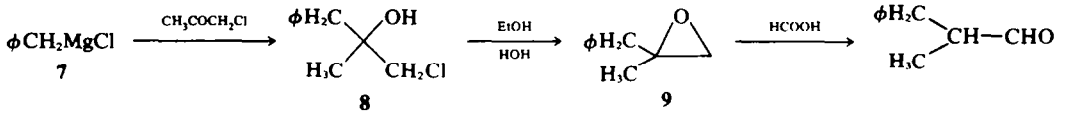
R_1	R_2	formula	C calcd.	C found	H calcd.	H found	O calcd.	O found	Mass spectral data *m/e* (% intensity)
Me	*neo* Pe	$C_{14}H_{28}O_2$	73·68	73·50	12·28	12·35	14·04	14·15	197(M-31)$^+$ (11); 125(22), *101* (100), 88(13), 84(20), 55(16), 57(*t*-Bu)$^+$ (22).
Me	*c*-Hex	$C_{15}H_{28}O_2$	75·00	75·00	11·67	11·60	13·33	13·40	209(M-31)$^+$ (5), *101* (100), 88(18), 84(15), 55(82), 83(*c*-Hex)$^+$ (39), 82 (cyclohexene)$^{+\cdot}$ (35).
Me	CH_2Cl	$C_{10}H_{19}O_2Cl$	58·13	58·00	9·20	9·32	15·50	15·43	175(M-31)$^+$ (15), 125(11), *101* (100), 88(10), 55(17).
Me	$CHCl_2$	$C_{10}H_{18}O_2Cl_2$	49·81	49·70	7·47	7·55	13·28	13·10	209(M-31)$^+$ (21), 125(31), *101* (100), 55(16).
Me	CCl_3	$C_{10}H_{17}O_2Cl_3$	43·58	43·50	6·17	6·22	11·62	11·70	—
Me	$PhCH_2$	$C_{16}H_{24}O_2$	77·42	77·30	9·68	9·58	12·90	13·12	217(M-31)$^+$ (7), 125(40), *101* (100), 88(13), 84(14), 55(15), 91($PhCH_2$)$^+$ (26).
Me	vinyl	$C_{11}H_{20}O_2$	71·74	71·65	10·87	10·80	17·40	17·55	
i-Pr	Ph	$C_{17}H_{26}O_2$	77·80	77·73	10·00	10·13	12·20	12·14	

monochloro acetone. After standing overnight, the mixture was worked up in the usual way. The crude carbinol **8** was then treated with one equiv KOH in EtOH at − 10°. The oxirane **9** was isolated in 36% yield (calculated on benzylchloride) and had a b.p. of 92°/16 mm. Treating the epoxide with 98% formic acid (exothermic reaction), neutralizing the acid and distilling the residue of the ether extract afforded the aldehyde **2** (^{1}R=Me, ^{2}R=PhCH$_2$), yield: 60%, b.p. 100°/16 mm.

4-Trichloromethyl-4-methyl-cyclohexanone (*Scheme* 3). Starting from *p*-cresol the cyclohexadienone **10** was prepared by Friedel–Crafts reaction in CS_2 according to the Zincke and Suhl[24] procedure, yield: 36%, m.p. 104° (from hexane).

Hydrogenation with Pd/C in MeOH gave the cyclohexanone **5** (^{1}R=Me, ^{2}R=CCl$_3$) in 83% yield (m.p. 125°).

4-Dichloromethyl-4-methyl-cyclohexanone (*Scheme* 3). A Reimer–Tiemann reaction with chloroform on *p*-



7 8 9

SCHEME 2

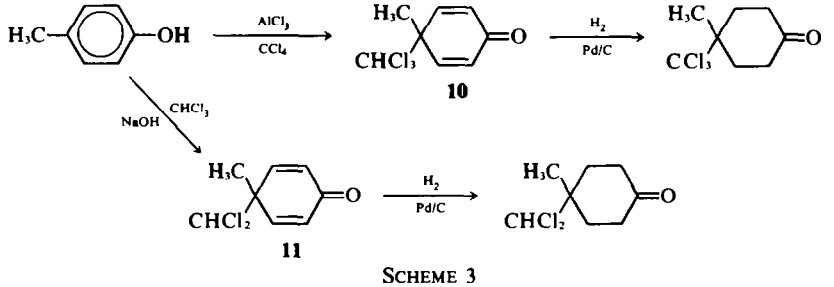
The enamine was prepared by refluxing the aldehyde with 1·5 equiv piperidine in benzene, and removing the water with the aid of a water-separator (yield of crude product: 55%).

At 0° one equiv of freshly distilled methyl vinyl ketone was added to the crude enamine (under N_2). The mixture was left at room temp during 4 days. After acidifying with 20% HCl and stirring another 24 h at room temp the cyclohexenone **4** (^{1}R=Me, ^{2}R=PhCH$_2$) was obtained. Catalytic hydrogenation in MeOH with Pd/C yielded the cyclohexanone **5** (^{1}R=Me, ^{2}R=PhCH$_2$).

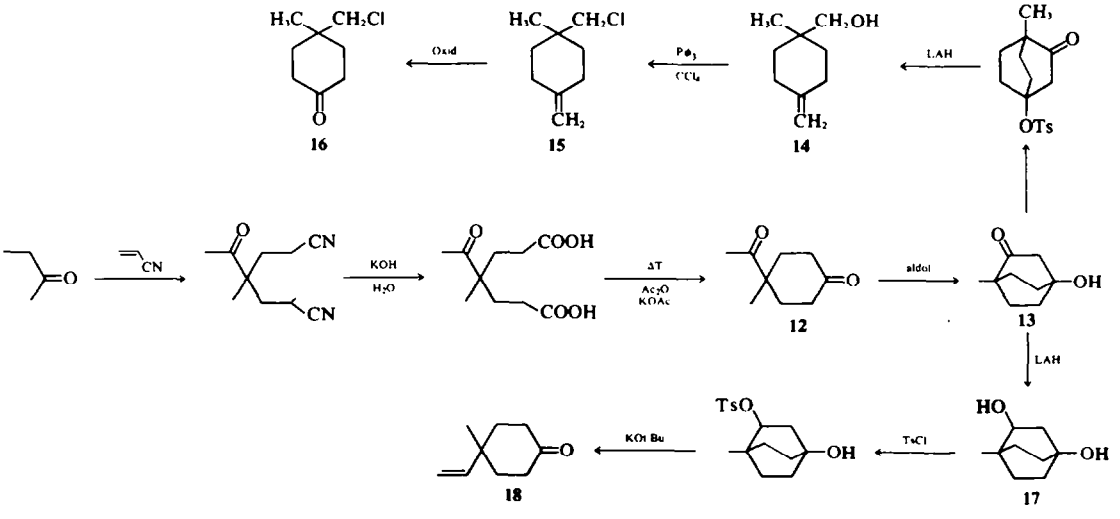
cresol[25] afforded 16% of the cyclohexadienone **11**, which was reduced with Pd/C in MeOH to the desired cyclohexanone, yield: 80%, m.p. 50°.

4 - Monochloromethyl - 4 - methyl - cyclohexanone (*Scheme* 4). The synthesis of 1-Me-4-hydroxy[2.2.2]bicyclooctanone-2 **13** started from a Michael addition between methyl ethyl ketone and acrylonitrile,[26] yield of the dinitrile: 75%, m.p. 65°.

Hydrolysis with KOH, acidification with HCl and continuous ether extraction afforded the dicarboxylic acid in 80% yield (m.p. 123°). The 4-acetyl-4-methyl-



SCHEME 3



SCHEME 4

cyclohexanone **12** was obtained through pyrolysis[27] of the di-acid with varying success (37–62%). From a reaction flask containing a soln of the di-acid in Ac_2O, and provided with an efficient fractionating column the HOAc was slowly distilled off during 10 h (the bath temp should not exceed 170°).

Subsequently the column was removed and the flask thoroughly heated until the formation of CO_2 ceases. The remaining ketone was distilled at 20–30 mm pressure. The entire distillate was poured into water, the acetic acid was neutralized. The evaporated ether-extract consisted of two compounds which could be identified by GC-separation and NMR-analysis as **12** and the corresponding enolacetate. The pyrolysis was tried with KF and Ba $(OH)_2$, avoiding Ac_2O, but without success. The intramolecular aldol condensation,[27] transforming **12** into **13**, was done in water with KOH (48 gr for 0·4 mole or 60 gr **12**). Usual work-up gave **13** in 70% yield. During this reaction the enolacetate contaminating **12** was hydrolysed and gave the same product. The tertiary hydroxyl group of **13** was tosylated in pyridine: yield 68%, m.p. 94°. Reductive elimination[27c] performed with LAH afforded **14** in 80% yield (b.p. 101°/14 mm).

The primary alcohol was transformed into the chloride **15** in 87% yield (b.p. 100°/15 mm) by the P $(Ph)_3/CCl_4$ reagent.[28] Potassium permanganate-periodate oxidation[29] of the methylidene function gave only a mediocre yield of the disired ketone **16**, but ozonisation[30] gave a satisfactory yield (50%, mol. dist. at 16 mm, bath temp 120°).

4 - *Vinyl* - 4 - *methyl* - *cyclohexanone* (*Scheme* 4). Compound **13** was reduced with LAH to **17**, tosylated at the secondary OH group, and reductively fragmentated with *t*-BuOK.[27b,31] It was necessary to purify **18** through the semicarbazone (decomposition by steam distillation in the presence of oxalic acid),[31] yield: 17% based on **13**, b.p. 120°/40 mm.

Acetalisation. The cyclohexanone was dissolved in MeOH in the presence of a small amount of TosOH (0·02 equiv) and a slight excess of trimethylorthoformate was added under cooling. After 24 h at room temp the acid was neutralized with solid K_2CO_3. Dry ether was added, the sulfonate salt filtered off and the mixture evaporated.

Yields, b. or m.p.'s of the methylacetals are given in Table 2. The acetals are unstable, and by heating (GC, partially also by distillation) MeOH is easily eliminated. The presence of the so formed enol ethers is very disturbing for the NMR investigations. They could be removed by shaking the reaction product overnight with a soln of 8 mmole KIO_4, 0·134 mmole $KMnO_4$ and 3 mmole K_2CO_3 in 300 ml water (room temp).[29a] Careful distillation *in vacuo* afforded almost pure dimethylacetals (>98%).

4 - *Cyclohexyl* - 4 - *methyl* - 1,1 - *dimethoxycyclohexane.* Hydrogenation of 2 gr (0·0085 mole) of 4 - methyl - 4 - phenyl - 1,1 - dimethoxycyclohexane in 20 ml MeOH with 0·5 gr of a 5% Rh/Al_2O_3 catalyst at 600 psi affords after 2 h 1·4 gr (70%) of the cyclohexyl compound (mol. dist. at 16 mm, bath temp 130°).

Characterisation of new compounds. All details of characterisation are given in Table 2. Common fissions to all examined acetals are shown in Scheme 5. For *m/e* 101, 88 and $(M-31)^+$ see Ref 32.

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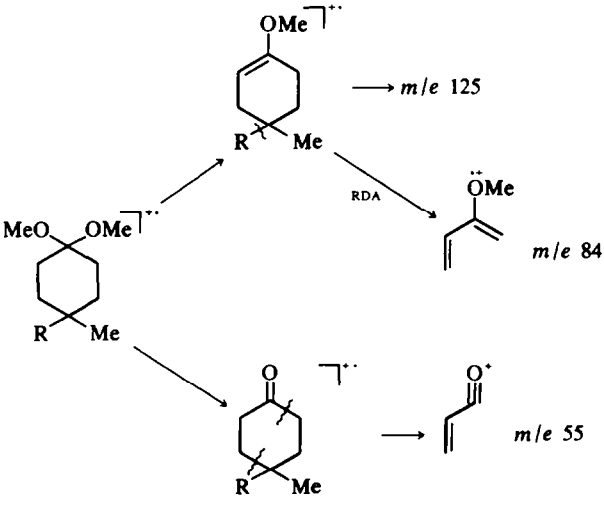

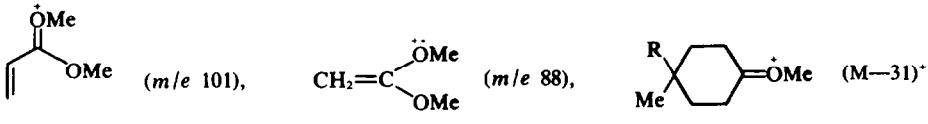

SCHEME 5

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