Reactions between Aldehydes and Polyhydric Alcohols. VI.*

Conformational Analysis of Methyl Substituted

cis-2,4,7,9-Tetraoxabicyclo[4.4.0]decanes

L. NØRSKOV, R. B. JENSEN and G. SCHROLL

Department of General and Organic Chemistry, The H. C. Ørsted Institute, University of Copenhagen, Universitetsparken 5, DK-2100 Copenhagen, Denmark

Methyl substituted 2,4,7,9-tetraoxabicyclo-[4.4.0]decanes (cis-tetraoxadecalins) have been examined with respect to the so-called 'O-inside – H-inside' equilibrium. Axial 5,10-dimethyl substitution in the O-inside form is shown to produce an otherwise unobservable equilibrium. ΔH and ΔS for the conformational reaction are determined by temperature dependent NMR and a set of diastereomers have been equilibrated by means of acid catalysis and studied by GLC providing a ΔG for the isomerization. Observed solvent effects in the latter case produce a favouring of the O-inside form in polar solvents and correlate very well with results on similar systems. Molecular mechanics calculations have been applied to the system and are found to provide useful information in cases where the experimental data are scarce.

In 1955 Mills[2] realized the possible existence of an O-inside and an H-inside form of cis-2,4,7,9-

tetraoxabicyclo[4.4.0]decane. He furthermore suggested a relative instability of the H-inside form due to H-H repulsion, a view also sustained by Lemieux and Howard.[3] In 2,4,7,9-tetraoxabicyclo[4.4.0]decane the conformational equilibrium between the two forms (corresponding to the enantiomers of cis-decalin) is shifted to the O-inside conformation by an unknown ΔG.[3] Attempts to force the equilibrium towards the H-inside by 1,6-dimethyl substitution (2–O, 2–H) failed as no 2–H was observed[4] ($\Delta G > 1.3$ kcal mol^{-1}). This indicates the parent system to be, in fact, very biased towards the O-inside. Appropriate methyl substitution at the 5 and 10 positions (compounds 3–O and 3–H) would expectedly destabilize the O-inside and has indeed been shown to give a mixture of the conformers.[5] Further evidence of the possible existence of the H-inside conformation has appeared recently.[6,7] We now wish to report on the isolation of the isomeric compounds, 4–O and 5–H, which adopt
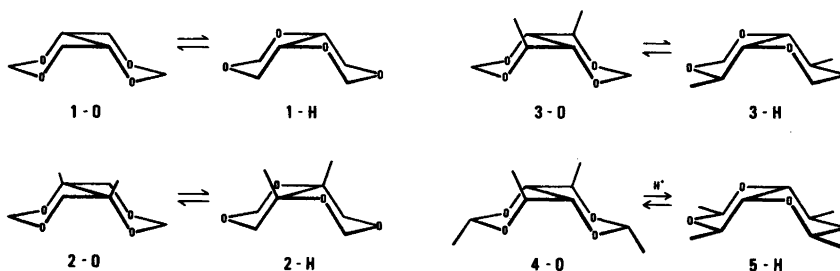
* For part V, see Ref. 1.

Fig. 1.

the O-inside and H-inside conformations, respectively. Also a more detailed study of the conformational equilibrium $3-O \rightleftharpoons 3-H$ has been undertaken.

The compounds 3, 4 and 5 were synthesized from D-mannitol in order to get the correct stereochemistry of the carbon frame, such that the methyl groups adopt axial positions in the O-inside conformation. By condensation with acetaldehyde it is possible to obtain the two forms as stable diastereomers (4–O, 5–H). The interconversion of the two is, however still feasible via acid-catalyzed equilibration. From similar systems other isomers than the tetraoxadecalins have been found, either from the synthesis or during equilibration experiments.[8] In the present study no effort was made at isolating or identifying such isomers. During equilibration of the isomers 4–O and 5–H, only these two were observed.
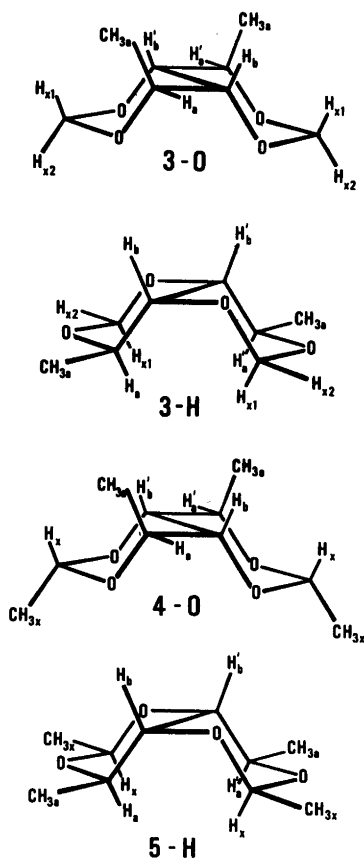
NMR ANALYSIS

The spectral data for the compounds 3, 4–O and 5–H are summarized in Tables 1a, 1b and 1c. They provide fairly strong evidence that the 4–O and 5–H compounds are in fact O- and H-inside isomers. E.g., the coupling constant J_{ab} (Fig. 2) is consistent with a gauche arrangement in 4–O and anti in 5–H. Furthermore the chemical shifts of H_a and H_b imply these protons to have the axial/equatorial positions shown. As far as compound 3 is concerned, most of the NMR parameters show values intermediate to those of the conformationally stable homologues 4–O and 5–H, indicating the presence of the H-inside isomer in the equilibrium $3-O \rightleftharpoons 3-H$.

The structure of the H-inside isomer 5–H was further affirmed by a nuclear Overhauser experiment on the 'inside' protons. Being close to each other one would expect an intensity increase in

Fig. 2. Proton labelling for compounds 3–5.

Table 1a. NMR data for compound 4–O.

	ppm		Hz
$\delta(H_{3a})$	1.35	$J(H_a,H_{3a})$	7.2
$\delta(H_{3x})$	1.37	$J(H_x,H_{3x})$	5.0
$\delta(H_b)^a$	3.47^b	$J(H_a,H_b)$	1.23^c
$\delta(H_a)$	4.16^d	$J(H_b,H_b)$	1.56^e
$\delta(H_x)$	5.04	$J(H_a,H_b')$	–0.48

^{a} The chemical shifts and coupling constants for H_a and H_b are obtained from a LAOCOON simulation. ^{b} Compare with 3.62 ppm in the parent compound, cis-tetraoxabicyclo[4.4.0]decane 1–O. ^{c} Ca. 0.3 Hz in cis-2,4,7,9-tetraoxabicyclo[4.4.0]decane. ^{d} 4.15 ppm in cis-2,4,7,9-tetraoxabicyclo[4.4.0]decane. ^{e} Ca. 0.0 Hz in cis-2,4,7,9-tetraoxabicyclo[4.4.0]decane.

Table 1b. NMR data of compound 5–H.

	ppm		Hz
$\delta(H_{3a})$	1.33	$J(H_a,H_{3a})$	5.8
$\delta(H_{3x})$	1.27	$J(H_x,H_{3x})$	4.9
$\delta(H_b)^a$	3.78	$J(H_a,H_b)$	10.61
$\delta(H_a)$	4.31	$J(H_b,H_b)$	6.23
$\delta(H_x)$	4.94	$J(H_a,H_b')$	–0.54

^{a} Chemical shifts and coupling constants of H_a and H_b were obtained from a LAOCOON spectrum simulation.

Table 1c. NMR data of compound *3* at room temperature.[a]

	ppm		Hz
$\delta(H_{3a})$	1.33	$J(H_a,H_{3a})$	6.6
$\delta(H_b)$[b]	3.65	$J(H_a,H_b)$	6.49
$\delta(H_a)$	4.22	$J(H_b,H_b')$	4.04
$\delta(H_{x1})$	4.79	$J(H_a,H'_b)$	–0.56
$\delta(H_{x2})$	4.81	$J(H_{x1},H_{x2})$	–6.6[c]

[a] Values reported in Ref. 5 are: $\delta(H_{3a})$=1.34, $\delta(H_b)$=3.65, $\delta(H_a)$=4.22, $\delta(H_{x1})$=$\delta(H_{x2})$=4.83 ppm and $J(H_a,H_b)$=5.9 Hz. [b] Chemical shifts and coupling constants of H_a and H_b were obtained from a LAOCOON spectrum simulation. [c] Sign of coupling constant assumed.

Table 1d. Chemical shifts (ppm) of *3–O* and *3–H* at –100 °C. Errors are estimated at 0.05 ppm.

	3–O	3–H
$\delta(H_{3a})$		1.33[a]
$\delta(H_b)$	3.55	3.81
$\delta(H_a)$	4.12	4.30
$\delta(H_{x1})$	5.04	4.72
$\delta(H_{x2})$	4.88	4.85

[a] Overlapping of peaks.

Table 1e. Temperature dependence of coupling constants (Hz) in *3*. Estimated error in coupling constants 0.01 Hz.

	$J(H_a,H_b)$	$J(H_b,H'_b)$	$JH_a,H'_b)$
3 (293 K)	6.49$_3$	4.03$_7$	–0.55$_5$
3 (303 K)	6.75$_7$	4.28$_3$	–0.55$_9$
3 (313 K)	6.91$_4$	4.33$_4$	–0.54$_7$
3 (323 K)	7.09$_7$	4.44$_4$	–0.52$_0$
3 (333 K)	7.20$_0$	4.63$_5$	–0.54$_7$
4–O	1.22$_7$	1.56$_0$	–0.47$_7$
5–H	10.61$_3$	6.22$_7$	–0.54$_1$

one signal (*e.g.* H_a) upon irradiation of the other (H_x).[9] Increases of 18.8 (±1.0) % (H_a) and 19.4 (±1.0) % (H_x) relative to internal $CHCl_3$ standard were observed. The proof of the structure seems convincing.[10] However, we do not feel that any quantitative determinations of the H–H distances should be carried out, as extensive

coupling is involved in the system. Finally, it may be mentioned that the O-inside does not show any nuclear Overhauser effect.

The conformational equilibrium *3–O*⇌*3–H* is, as expected, fast on the NMR time scale at room temperature, showing only 5 chemical shifts. Profound changes in the spectrum occur on cooling, however. At –20 °C the AB quartet of the $O–CH_2–O$ groups narrows to a singlet, but spreads out again upon further cooling. Below –80 °C all lines broaden and finally at –100 °C split into two broad signals of relative intensities *ca.* 3.7 (±0.5):1. Assigned to the O-inside and H-inside, respectively (see discussion), this corresponds to a ΔG_{173} for the above reaction (*O* to *H*) of *ca.* +0.5 kcal mol^{-1}. The NMR data given in Table 1d agree well with the assignment of the conformers when compared to Tables 1a and 1b.

To obtain a more accurate ΔG value (at room temperature) the coupling between H_a and H_b was used as a measure of the equilibrium. The dihedral angle between the two protons being *gauche* in the O-inside and *anti* in the H-inside would expectedly give rise to a marked difference in $^3J_{ab}$. Due to excessive line widths the respective couplings could not be determined from the spectrum of the two conformers at –100 °C. Therefore, *4–O* and *5–H* were used as model systems, the influence of the (equatorial) 3- and 8-methyl groups on ring geometry and J_{ab} being ignored. Thus the O-inside was assigned a J_{ab} of 1.23 (±0.05) Hz and the H-inside 10.61 (±0.05) Hz. Measuring J_{ab} at temperatures ranging from 20 to 60 °C (Table 1e) then gave the equilibrium constants from which the following data were derived:

$$\Delta G_{298} = -0.18 \ (\pm 0.02) \ \text{kcal mol}^{-1}$$
$$\Delta H = +1.5 \ (\pm 0.3) \ \text{kcal mol}^{-1}$$
$$\Delta S = +5.6 \ (\pm 1.0) \ \text{cal mol}^{-1} \ \text{K}^{-1}$$

At –100 °C this gives a ΔG_{173}= +0.52 (±0.13) kcal mol^{-1}, in good agreement with the values found above. The large positive ΔS values for the reaction *3–O*→*3–H* could indicate that the H-form is in fact a chair/twist-boat conformation. However, as the $^2J(OCH_2O)$ of –6.6 Hz is quite normal[11] and the compound further shows characteristics similar to the symmetrical and non-twisted *5–H*, we conclude that the twist-boat conformation is not present to any appreciable extent.

Table 2. Equilibrium constants and derived ΔG values for the equilibrium $4\text{-}O \rightleftharpoons 5\text{-}H$ in 4 different solvents.

Solvent	$[5\text{-}H]/[4\text{-}O]$	ΔG_{298} (kcal mol^{-1})
CCl$_4$	14.3±0.7	−1.57±0.03
C$_6$H$_6$	7.9±0.4	−1.22±0.02
CHCl$_3$	3.0±0.2	−0.65±0.02
CH$_3$CN	1.8±0.1	−0.35±0.02

ACID-CATALYZED EQUILIBRATION

The tetramethyl compounds *4-O* and *5-H* are conformationally stable but can be interconverted by means of an acidic catalyst. The 3- and 8-methyl groups are equatorial and would hardly influence the equilibrium much compared to the compound *3* derived from formaldehyde. The equilibration has been carried out in 4 different solvents at 25.0 °C and the equilibrium constants were determined by GLC. The results are shown in Table 2.

The sizable solvent dependence reflects the more polar character of the O-inside (dipole moment of 3.7 D as calculated by molecular mechanics; the H-inside has one of 2.0 D). Quantitatively, it was somewhat surprising to find that the difference in "effective polarity" between CCl$_4$ and benzene is larger than that between CHCl$_3$ and acetonitrile. In a study of solvent effects on acetal conformations Eliel *et al.*[12] obtained similar results, however. Fig. 3 illustrates this fact as a plot of ΔG (O-inside→H-inside) of this study *versus* ΔG (OMe$_{ax}$→OMe$_{eq}$)
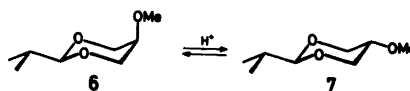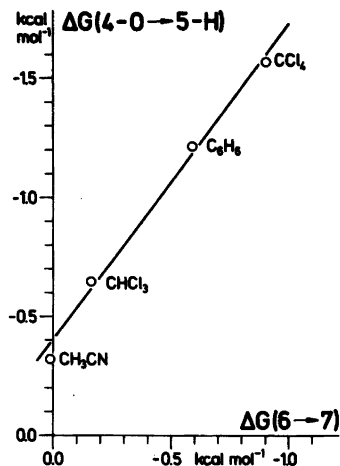

Fig. 3. Plot of observed ΔG for (*4→5*) in different solvents *versus* ΔG for the similar equilibrium in 5-methoxy-1,3-dioxane (*6→7*).[12]

for the acid catalyzed equilibration of 2-isopropyl-5-methoxy-1,3-dioxane.[12] The correlation coefficient is 0.997, slope=1.33 and intercept = 0.40. A slope greater than unity is not surprising since the bicyclic system contains a larger number of polar bonds.

Neither from the syntheses nor from the equilibration reactions have any other isomers been isolated. Formation of isomeric compounds
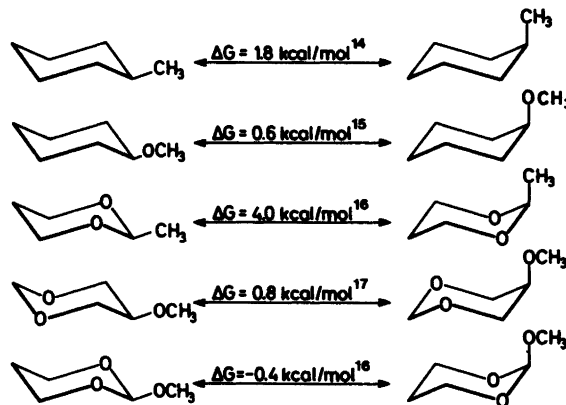

Fig. 4. Model compounds for *gauche* butane interaction terms.

	C-C-C-C	C-C-C-O	C-O-C-C	O-C-C-O	C-O-C-O	Energy (kcal mol⁻¹)	ΔG(O→H) (kcal mol⁻¹)
	0	4	4	3	4	9.6	3.7
	1	4	6	0	4	13.3	
	3	4	6	3	4	16.3	-0.9
	2	8	6	0	4	15.4	
	2	4	6	3	4	15.4	-1.5
	1	6	6	0	4	13.9	

Fig. 5. Schematic enumeration of *gauche* butane interaction terms in compounds *1–O* to *3–H*.

might have been anticipated[4,8] and may well be present in the by-products of the aldehyde condensations. Whether the isomeric bisdioxolanes are energetically unfavourable compared to the bicyclo[4.4.0]decane systems cannot be judged, since the reaction leading to interconversion of *4–O* and *5–H* may not provide a route to 5-membered rings.

FORCE FIELD CALCULATIONS

An estimate of the energy difference between O-inside and H-inside in the parent 2,4,7,9-tetraoxabicyclo[4.4.0]decane system has been made by applying the method of counting *gauche* butane interactions[13] as outlined in Figs. 4 and 5. The increments for CCCC, CCCO, CCOC, COCO and OCCO have been taken from A-values of methylcyclohexane,[14] methoxycyclohexane,[15] 2-methyl-1,3-dioxane,[16] 5-methoxy-1,3-dioxane[17] and 2-methoxy-1,3-dioxane.[16] As shown in Fig. 5 the trend *1* to *2* to *3* is reproduced but the calculated energies are rather poor, *e.g.* $\Delta G = -0.9$ kcal mol⁻¹ for *2–O→2–H* for which no *2–H* has been observed experimentally.[4] Whether this is due to lack of transferability from cyclohexane/1,3-dioxane model compounds or it is due to non-additivity of these contributions we cannot conclude, but the

method seems to be of limited value especially when force field calculations are available.

In order to gain further insight into the O-inside/H-inside problem, we have performed force field calculations on the compounds *1–O–5–H* (Fig. 1) using Allinger's molecular mechanics programs MM1 and MM2.[18,19] Of particular interest in this case is the geometry of the minimum energy conformations, the dipole moments and the relative enthalpy contents. The MM2 program is a somewhat modified version of MM1, but with respect to the geometries of *1–O – 5–H* very little difference is observed.

When assuming tetrahedral angles around all carbon and oxygen atoms one would expect the *trans*-annular H–H repulsions in the H-inside forms to be quite severe.[2] According to the force field calculations, however, the decalin skeleton is sufficiently flexible to allow inter-annular H–H distances of 2.3–2.5 Å in the H-inside forms. The calculated dipole moments (O-inside; 3.7–3.8 D, H-inside: 1.9–2.1 D) agree with the measured values[3,4] for *1* and *2* if these are assumed to exist predominantly as O-inside. Dipole moments are, however, rather insensitive to minor changes in geometry. One geometrical parameter of importance in connection with the NMR studies is the H_a–C–C–H_b torsion angle (Fig. 2). According to the force field calculations this angle varies less

Table 3. Enthalpies of the reaction O-inside⇌H-inside as calculated by the MM1/MM2 force field method. A dielectric constant of 2.2 was employed. Values in parentheses are the experimentally determined ones.

1–O⇌1–H	ΔH=1.97/5.45 kcal mol^{-1} (ΔG≫0)[a]
2–O⇌2–H	ΔH=1.39/2.76 kcal mol^{-1} (ΔG≫0)[b]
3–O⇌3–H ·	ΔH= –0.84/+0.84 kcal mol^{-1} (ΔH= +1.5)[c] (ΔG= –0.18)[c]
4–O⇌5–H	ΔH= –0.75/+0.86 kcal mol^{-1} (ΔG= –0.65)[d]

[a] Estimated from dipole moment in benzene at 25 °C (Ref. 3). [b] Estimated from dipole moment in benzene at 25 °C (Ref. 4). [c] From NMR data in CDCl$_3$ solution (this work). [d] From GLC determination in CHCl$_3$ solution (this work).

than 0.4° when going from *3–O* to *4–O* and from *3–H* to *5–H*, thus justifying the use of *4–O* and *5–H* as model compounds for *3–O* and *3–H* in the NMR experiment.

When turning to the energies (strictly speaking: enthalpies) of these compounds, substantial differences between MM1 and MM2 are found (Table 3). Quantitatively, they show the same trend regarding the ΔH (O-inside→H-inside), that is, 1,6-dimethyl substitution (bridgehead positions) lowers the energy difference and 5,10 (axial in O-inside) even more so. We conclude that MM2 results are superior to those of MM1 and in fairly good agreement with the limited experimental data available. Finally, the difficulty for the force field in calculating energies of polar molecules well should be mentioned as a probable source of error.[20] The above–mentioned results were obtained with the original parameters of the program and a dielectric constant of 2.2 was employed in the dipole–dipole interaction term. Higher dielectric constants favour the O-inside forms and, in fact, at ε=10.0, ΔH=1.37 kcal mol^{-1} for *3–O/3–H* matches the experimental value of 1.5 kcal mol^{-1}.

DISCUSSION

Having shown that the H-inside form can be produced by appropriate methyl substitution,

that is, by destabilization of the O-inside form, it could be tempting to make an estimate of the energy difference between the unsubstituted O-inside and H-inside forms. To this end one could apply purely numerical methods as above, which gives 3.7:1.97:5.45 kcal mol^{-1} from *gauche* butane counting, MM1 and MM2, respectively. These numbers could possibly be refined by assuming constant errors, *i.e.* the calculated value for *3–O→3–H* is set equal to the experimental one (in CDCl$_3$). With these corrections (+3.0:+2.34:+0.66) one obtains ΔH (*1–O→1–H*)=6.7:4.3:6.1 kcal mol^{-1} from the same three methods. Regardless of which of these numbers is the most correct, it does mean that the H-inside form of *cis*-2,4,7,9-tetraoxabicyclo[4.4.0]decane is inherently very unstable, and even trapping of thermally excited molecules (as that of twist-cyclohexane)[21] would hardly enable the observation of this conformation.

There remain a few points to be considered. The substantial solvent effect indicates part of the O-inside/H-inside energy difference to be of electrostatic character and, furthermore, confirms the value of Eliel's scale of solvent polarity [12] as applied to polyoxa compounds. When considering the free energy difference between the dimethyl system (*3–O/3–H*) and the tetramethyl (*4–O/5–H*) of *ca.* 0.5 kcal mol^{-1} this difference could be attributed to buttressing effects. However, the force field calculations do not reproduce this effect.

It has been questioned[22] whether the O-inside isomer *3–O* really is the most stable conformation at low temperature. We find the proton spectrum at –100 °C quite convincing, but one might argue that the presence of the O-inside could be caused by the freon solvent which is known to influence conformations of crown ethers.[23] However, since the equilibrium constants derived from the coupling constants in CDCl$_3$ at ambient temperature and above yield ΔH and ΔS in agreement with the low temperature experiment, any special effect of the freon solvent must be minor, and the low temperature conformation can be stated as being O-inside.

EXPERIMENTAL

The NMR spectra were recorded on a Bruker HX 270 MHz instrument, mass spectra on an

AEI MS-902 and the gas chromatograph was a Hewlett Packard 5840A.

Preparations. 1,6-Dichloro-2S,3S,4S,5S-hexantetraol (*8*) was prepared from D-mannitol.[24]

5,10-Dichloromethyl-2,4,7,9-tetraoxabicyclo-[4.4.0]decane (*9*). 2.19 g of *8* (10 mmol) were mixed with 0.60 g trioxane (6.7 mmol) and 20 mg *p*TsOH (0.12 mmol) in 25 ml CHCl₃ and heated to 50 °C for 25 h, cooled and stirred for 4 h with 1 g NaHCO₃. Filtration and evaporation of solvent yielded 2.5 g of grayish material. Two recrystallizations from absolute ethanol gave 1.49 g (61 %) with m.p. 158 °C (lit. 156 °C).[24]

cis- and *trans*-5,10-dichloromethyl-3,8-dimethyl-2,4,7,9-tetraoxabicyclo[4.4.0]decane (*10, 11*). 5.48 g of *8* (25 mmol) were mixed with 39.6 g of CH₃CHO (0.90 mol, freshly distilled), 30 ml of benzene and 50 mg of *p*TsOH (0.3 mmol) and stirred for 24 h at 25 °C. Then 1 g of NaHCO₃ was added and stirred for 2 h. Filtration and evaporation of solvent gave a sirupy white mass, which upon suction filtration and washing with 2×5 ml ether yielded 1.7 g of a white solid (m.p. 140–150 °C). Preparative TLC (silica, 2×CH₂Cl₂) yielded two fractions (rf. 0.4 and 0.2). Recrystallization from absolute ethanol gave 690 mg (10.2 %) of *10* (*cis*) m.p. 156 °C (lit. 160 °C) and 315 mg (4.6 %) of *11* (*trans*.) m.p. 196 °C (lit. 195 °C).[25]

5,10-Dimethyl-2,4,7,9-tetraoxabicyclo[4.4.0]-decane (*3*) and 3,5,8,10-tetramethyl-2,4,7,9-tetraoxabicyclo[4.4.0]decane (*cis* and *trans*) (*4* and *5*). The compounds were prepared from the corresponding dichloro compounds (*9, 10* and *11*) by adding these (2 mmol) to a suspension of LiAlH₄ (10 mmol) in 75 ml THF and refluxing for 24 h. After successive addition of 1.76 g EtOAc (20 mmol), 380 mg H₂O (21 mmol), 380 mg 4 N NaOH (1.5 mmol) and 1140 mg H₂O (63 mmol),[26] the suspension was filtered on celite and the residue extracted in a Soxhlet extractor for 48 h with ether. Subsequently the combined ether and THF solutions were evaporated to yield a yellow waxy solid. Recrystallization from isopentane yielded 188 mg (54 %) of *3*, m.p. 54 °C (lit. 60 °C),[27] 242 mg (60 %) of *4*, m.p. 74 °C and 226 mg (56 %) of *5*, m.p. 195 °C. All melting points are corrected.

NMR experiments. The spectra were run on samples containing about 10 % (by weight) of the compound in question dissolved in CDCl₃. An exception is the spectrum of *3* at low temperature which was run in a mixture of CD₂Cl₂ and CF₂Cl₂ (3:1 by volume). The nuclear Overhauser experiment was carried out with a thoroughly degassed sample containing 75 mg (0.37 mmol) *3* plus 0.75 mmol CHCl₃ as internal standard in CDCl₃. Decoupling power was just sufficient to delete

any Hₓ (Hₐ) signal (gated decoupling). The spectrum simulations were performed with a modified LAOCOON program.[28]

Acid-equilibration. Ca. 2 mg of the tetramethyl compound (*4–O* or *5–H*) (*ca.* 10 µmol) were dissolved in 100 µl of solvent to which were added 0.1 µl BF₃–Et₂O (1 µmol) and 0.5 mg of naphthalene (4 µmol) as internal standard. The vessel was closed under N₂ and kept in a thermostated bath at 25.0 (±0.2) °C. After 2–3 days the equilibrium was established and 0.5 µl of the sample was injected on a 10 % polypropyleneglycol on Chromosorb W 60/80 column (180 cm, 4.0 mm Ø, flow=15 ml/min). Several runs were made on each sample. The same composition was obtained when starting from either isomer, thus assuring complete equilibration. The ratios *H/O* as calculated from the integrated GLC peaks were multiplied by a response factor of 0.951 to give the equilibrium constant with a reproducibility of ±4 % corresponding to standard errors on Δ*G* of *ca.* 0.02 kcal mol⁻¹. By comparison with the naphthalene peak in each run it was ascertained that no loss of *4* or *5* had occurred during the equilibration.

REFERENCES

1. Dahl, O., Dale, J., Frederiksen, N., Henriksen, H., Jensen, R.B., Jørgensen, S.E., Larsen, S., Nørskov, L. and Schroll, G. *Acta Chem. Scand. B 33* (1979) 197.
2. Mills, J.A. *Adv. Carbohydr. Chem. 10* (1955) 1.
3. Lemieux, R.U. and Howard, J. *Can. J. Chem. 41* (1963) 393.
4. Frederiksen, N., Jensen, R.B., Jørgensen, S.E., Nielsen, J.U.R., Nørskov, L. and Schroll, G. *Acta Chem. Scand. B 31* (1977) 694.
5. Kilburn, D.M., *M.Sc. Thesis,* Queens University, Kingston, Ontario 1969. Referenced by Burden, I. J., and Stoddard, J.F. *J. Chem. Soc. Perkin Trans. 1* (1975) 666.
6. Bernstein, J., Green, B.S. and Rejtö, M. *J. Am. Chem. Soc. 102* (1980) 323.
7. Sohar, P., Horvath, T. and Abraham, G. *Acta Chim. Acad. Sci. Hung. 103* (1980) 95.
8. Jensen, R.B., Buchardt, O., Jørgensen, S.E., Nielsen, J.U.R., Schroll, G. and Altona, C. *Acta Chem. Scand. B 29* (1975) 373.
9. Bell, R.A. and Saunders, J.K. *Top. Stereochem. 7* (1973) 1.
10. The structures of *3–H, 4–O* and *5–H* have since been confirmed by X-ray diffraction analysis. *To be published.*

11. Anteunis, M. and Swaelens, G. *Org. Magn. Res. 2* (1970) 389.
12. Eliel, E.L. and Hofer, O. *J. Am. Chem. Soc. 95* (1973) 8041.
13. Eliel, E.L. *Stereochemistry of Carbon Compounds,* McGraw-Hill, New York 1962, p. 208 ff.
14. Hirsch, J.A. *Top. Stereochem. 1* (1967) 199.
15. Eliel, E.L. and Gianni, M.H. *Tetrahedron Lett.* (1962) 97.
16. Nader, F.W. and Eliel, E.L. *J. Am. Chem. Soc. 92* (1970) 3050.
17. Kaloustian, M.K. Dennis, N., Mager, S., Evans, S.A., Alcudia, F. and Eliel, E.L. *J. Am. Chem. Soc. 98* (1976) 956.
18. Allinger, N.L. *Adv. Phys. Org. Chem. 13* (1976) 1.
19. *Quantum Chemistry Program Exchange 11* (1976) 318; *13* (1981) 395.
20. Allinger, N.L. and Chung, D.Y. *J. Am. Chem. Soc. 98* (1976) 6798.
21. Squillacote, M., Sheridan, R.S., Chapman, O.L. and Anet, F.A.L. *J. Am. Chem. Soc. 97* (1975) 3244.
22. Burkert, U. *J. Comput. Chem. 1* (1980) 192.
23. Borgen, G., Dale, J., Daasvatn, K. and Krane, J. *Acta Chem. Scand. B 34* (1980) 249.
24. Haworth, W.N., Heath, R.L. and Wiggins, L.F. *J. Chem. Soc.* (1944) 155.
25. Wiggins, L.F. *J. Chem. Soc.* (1946) 384.
26. Feit, P.W. *J. Med. Chem. 7* (1964) 14.
27. Micheel, F. *Justus Liebigs Ann. Chem. 496* (1932) 77.
28. Schaumburg, K., Manscher, O.H. and Jacobsen, J.P. *Quantum Chemistry Program Exchange 13* (1981) 394.