

Eight-ring Monomeric and Sixteen-ring Dimeric Formals and Ketals

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1,3-Dioxacyclooctanes and 1,3,9,11-tetraoxacyclohexadecanes, with and without *gem*-dimethyl substituents in the 2- or 6- (and 10- or 14-) positions, have been synthesized. They are all conformationally homogeneous, and the observed low dipole moments show that the 2- (and 10-) carbon atoms must be in "corner" positions. Two of the 16-membered rings must therefore have "square" diamond-lattice conformations, while the other two may be "square" or "rectangular".

Cyclohexadecane itself is conformationally heterogeneous in solution, and its lowest-enthalpy "square" diamond-lattice conformation becomes exclusive only in the low-temperature crystal phase.¹ One might therefore have expected the conformational situation in a corresponding tetra-ether, 1,5,9,13-tetraoxacyclohexadecane, to be even more complex, since on each type of ring skeleton there should be several possible dispositions of the oxygen atoms, for example the three shown in Fig. 1 for the square ring conformation.

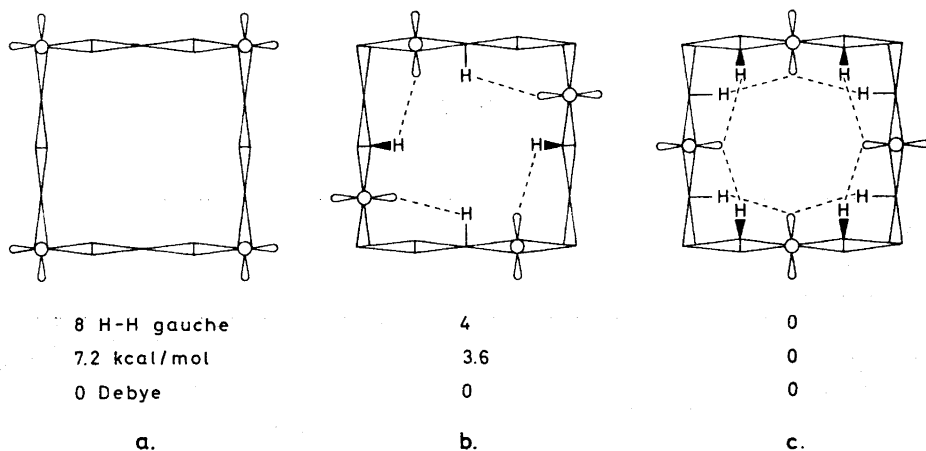


Fig. 1.

Nevertheless, this tetraether turned out¹ to have a single conformation in solution, the same as in the crystal. The rationale of this was that when the ether oxygens are β to all corners (Fig. 1c), all eight repulsive *gauche* CH...CH interactions of the hydrocarbon, two at each corner, are changed into *gauche* CH...O interactions, which must be less repulsive and perhaps even slightly attractive. This conformation was subsequently verified by Groth for the crystal.² * The measured dipole moment was extremely low for this tetraether (0.3 D) and for the 3,3,7,7,11,11,15,15-octamethyl derivative (~ 0) which has this oxygen location imposed by the restriction of the substituents to corner positions; however, a zero dipole moment is also expected for the other two conformers (a and b) in Fig. 1.

For 1,3,9,11-tetraoxacyclohexadecane a stability argument in terms of number of CH...O *gauche* interactions cannot predict the best location of the oxygen atoms on the "square" ring conformation; in each of the three possible conformers (Fig. 2) only four *gauche* interactions are improved. On the other hand, the expected dipole moments are vastly different and should allow experimental identification.

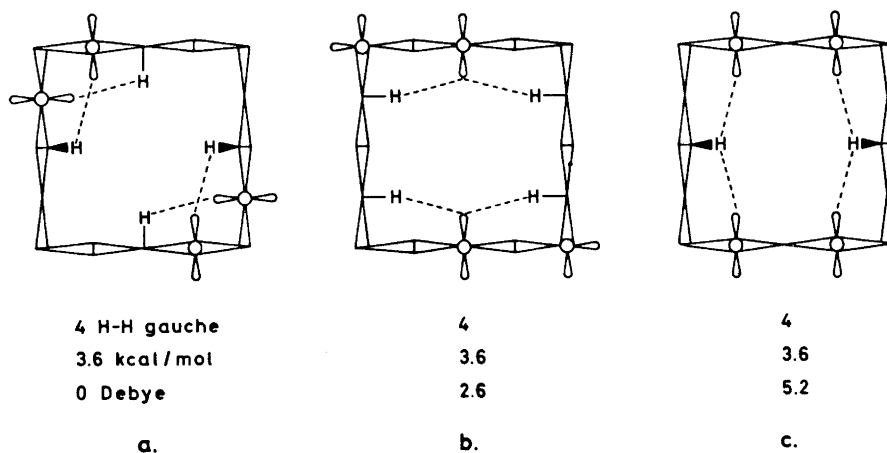
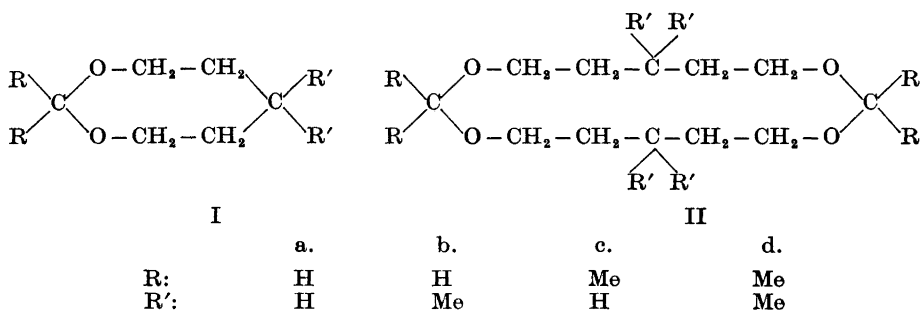


Fig. 2.

To examine this conformational problem, and at the same time study the related 1,3-dioxacyclooctanes, four pairs of compounds (I and II) were synthesized:

* It is interesting that the chemically related poly(trimethylene oxide) in the crystalline state has a helical conformation built up of the same *anti*, *anti*, +*gauche*, +*gauche* CH₂-O-CH₂-CH₂-repeat unit (Takokoro, H., Takahashi, Y. and Chatani, Y. Cited by Mark, J. E. *J. Polymer Sci. B* 4 (1966) 825). Even 1,3-dibromopropane and 1,3-dichloropropane, as well as the 2,2-dimethyl derivative, show a remarkable preference ($\sim 60\%$) for the +*gauche*, +*gauche* conformation in the gas phase, as shown by electron diffraction (Stølevik, R., unpublished).



Some of these carry *gem*-dimethyl substituents in order to define "corner" positions.

SYNTHETIC ASPECTS

The cyclic formals (Ia, b; IIa, b) were prepared from paraformaldehyde and pentane-1,5-diol (or 3,3-dimethylpentane-1,5-diol) in benzene solution in the presence of an acid ion-exchange resin,³ removing formed water as an azeotrope with benzene. A relatively small yield of the crystalline dimeric cyclic formal was obtained. The main product was a polymer which could be pyrolyzed in the presence of an acid catalyst to give in good yield the liquid monomeric cyclic formal. The unsubstituted rings (Ia; IIa) have been prepared by Hill and Carothers⁴ by a different method.

The cyclic ketals (Ic, d; IIc, d) were prepared from 2,2-dimethoxypropane and the same diols in benzene solution in the presence of an acid ion-exchange resin; formed methanol was removed as an azeotrope with benzene. The liquid monomeric cyclic ketal was obtained directly in 60–70 % yield. This could be converted in 70–80 % yield to the crystalline dimeric cyclic ketal by simply stirring a solution in hexane in the presence of the same acid resin. Presumably, the strain in the 8-membered ring is the driving force for its conversion to the unstrained 16-membered ring. A further reaction to still larger rings provides no additional strain relief and would even be thermodynamically disfavoured, since the entropy of the whole system must thereby decrease.

CONFORMATIONS OF THE 1,3-DIOXACYCLOOCTANES

The conformations of the 8-membered rings have already been discussed in a preliminary communication.⁵ First of all, the temperature-invariant infrared spectra of these liquids on cooling suggest conformational homogeneity. Secondly, the observed low values of their molecular dipole moments (Table 1) are very close to those of the simplest aliphatic analogs, 2,2-dimethoxypropane and dimethoxymethane, and the preferred conformation of the latter has been established⁶ as *+gauche*, *+gauche*. A much larger value (Table 1) is found⁷ for 1,3-dioxan, where the corresponding bonds are *+gauche*, *-gauche*,

Table 1. Data for 1,3-dioxacyclooctanes.

| | B.p. | Found | | Analysis Formula | Calc. | | Dipole moment in benzene at 25°C |
|-----------------|-----------------|-------|-------|--|-------|-------|-------------------------------------|
| | | C | H | | C | H | |
| Ia ⁴ | 130–140°/760 mm | | | C ₈ H ₁₂ O ₂ | | | 0.73 D ^a |
| Ib | 164–168°/765 mm | 66.83 | 11.49 | C ₈ H ₁₆ O ₂ | 66.70 | 11.10 | 1.00 D ^a |
| Ic | 40–41°/9 mm | 67.31 | 10.63 | C ₈ H ₁₆ O ₂ | 66.70 | 11.10 | 0.58 D ^b |
| Id | 58–60°/10 mm | 69.98 | 11.72 | C ₁₀ H ₂₀ O ₂ | 69.97 | 11.63 | 0.61 D ^b |

^a To be compared with 0.99 D for dimethoxymethane and 1.9 D for 1,3-dioxan.⁷

^b To be compared with 0.61 D for 2,2-dimethoxypropane.

and still higher values are expected for *anti*, *gauche* and *anti*, *anti*. This means that the oxygen atoms must be adjoining a nearly perfect corner formed by two staggered C–O bonds, which thus limits the possibilities to the boat-boat and boat-chair (Fig. 3).

In our preliminary publication,⁵ 100 MHz ¹H NMR-spectroscopic data were taken to indicate that the boat-chair was chosen by the two compounds lacking substituents in the diol component (Ia,c) and the boat-boat by the two that carry such substituents (Ib,d). However, more recent 251 MHz ¹H and 63 MHz ¹³C data⁸ suggest that all four adopt the boat-chair conformation and also confirm by an independent method that the –O–CR₂–O–group is straddling the perfect corner position (Fig. 3b). This is of course expected for the ketal group because of the bulk of the substituents (R = Me) but is a surprising and most important conclusion for the formal group (R = H). In this ring system, one explanation may be that transannular H–H interactions are relieved. In addition, the favourable antiparallel dipole orientation may play a role, since also open-chain systems prefer this +*gauche*, +*gauche* geometry. Thus, not only the already mentioned dimethoxymethane,⁶ but also the oxymethylene polymer has, at least in the crystal, a helix conformation with all bonds *gauche* of the same sign.⁹

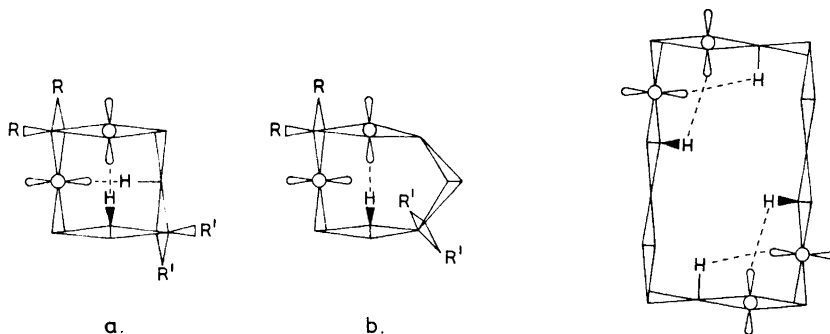


Fig. 3.

Fig. 4.

CONFORMATIONS OF THE 1,3,9,11-TETRAOXACYCLOHEXADECANES

All four sixteen-membered rings are conformationally homogeneous by the criterion that their infrared spectra have sharp bands and are practically identical in the solid and in solution. The unsubstituted ring shows a few crystal splittings suggesting a tighter packing in the crystal; this may also be concluded from its higher enthalpy (and entropy) of melting (Table 2).

Table 2. Data for 1,3,9,11-tetraoxacyclohexadecanes.

| | M.p. (°C) | ΔH_m (kcal/mol) | ΔS_m (cal/deg.mol) | Found | | Analysis Formula | Calc. | | Dipole moment in benzene at 25°C |
|------------------|--------------|----------------------------|-------------------------------|-------|-------|--|-------|-------|---|
| | | | | C | H | | C | H | |
| IIa ⁴ | 56–58 | 8.5 | 25.6 | | | C ₁₂ H ₂₄ O ₄ | | | 0.9 D |
| IIb | 82–85 | 7.1 | 19.8 | 66.55 | 11.19 | C ₁₆ H ₃₂ O ₄ | 66.70 | 11.10 | ~0 |
| IIc | 102–104 | 6.2 | 16.7 | 66.85 | 11.25 | C ₁₆ H ₃₂ O ₄ | 66.70 | 11.10 | 0 |
| IId | 138–140 | 5.9 | 14.5 | 69.08 | 11.39 | C ₂₀ H ₄₀ O ₄ | 69.97 | 11.63 | 0 |

Conformational homogeneity is in itself surprising when no substituents are present, since the number of *gauche* H–H interactions is the same in all three possible conformers of the square ring skeleton (Fig. 2). That we have again a preference for the conformer with both –O–CH₂–O– systems across corners* is unequivocally demonstrated by the low observed dipole moment (Table 2) of this compound (as of the substituted compounds). Whether it is in fact the “square” ring skeleton (Fig. 2a) cannot be definitely decided from these data. A “rectangular” non-diamond-lattice type of ring conformation, calculated¹⁰ to be only about 1 kcal/mol higher in enthalpy of cyclohexadecane, would also allow both –O–CR₂–O– groups to be at diametric corners and have cancelled dipole moments (Fig. 4) in the two cases when there is no substituent R' in the diol component (IIa,c). In the other cases (IIb,d) all corners are fixed, so as to impose the square ring skeleton, by the bulk of the *gem*-dimethyl groups and by the dipole-favoured orientation of the 1,3-dioxa-grouping across a corner.**

The strong conformational preference and the apparent rigidity of these four 1,3,9,11-tetraoxacyclohexadecanes, as well as of the two 1,5,9,13-tetraoxacyclohexadecanes discussed in the introduction, is very striking and in contrast both to cyclohexadecane on the one hand and to other macrocyclic oligoethers on the other hand. Thus, the hydrocarbon is a conformer mixture in solution,¹ and 15- and 18-ring homologues of ethylene oxide have broad infrared bands and dipole moments close to the statistical value calculated for

* A very recent crystal structure determination of 1,3,8,10-tetraoxacyclotetradecane reveals the same feature of corner location of both formal groups on the unique 14-ring diamond-lattice conformation (Bassi, I. W., Scordamaglia, R. and Fiore, L. *J. Chem. Soc. Perkin 2* 1972 1726).

** Anet and Krane⁸ have recently shown by 251 MHz ¹H and 63 MHz ¹³C NMR spectroscopy that not only the latter two compounds (IIb, d) but also one of the former (IIa) are indeed square, whereas the ketal IIc is rectangular.

independently oriented ether dipoles.¹¹ When it is considered that the calculated value for four ether dipoles is as high as $\sqrt{4} \times 1.3 D = 2.6 D$, the observed near-zero values for our 16-membered rings force us to believe that the interaction between CH α and oxygen β to the same corner (or *vice versa*), indicated by pointed lines in Figs. 1, 2, and 4, has a certain attractive character and so acts to stiffen the whole ring. This is in contrast with the transannular CH...O interaction (Fig. 3), one step closer on the diamond lattice, which in 8-membered rings seems to be repulsive.

EXPERIMENTAL

Preparation of cyclic formals (Ia,b; IIa,b). A mixture of pentane-1,5-diol or 3,3-dimethylpentane-1,5-diol¹² (0.5 mol), paraformaldehyde (0.5 mol), benzene (150 ml), and Amberlite IR-120 cation-exchange resin (3 g) in its acid form³ was boiled for 2–3 h, when the calculated quantity of formed water had been collected from the distilled azeotrope in a water separator. The catalyst was filtered off and remaining benzene evaporated *in vacuo*. Distillation of the residue at reduced pressure gave a small quantity of the dimeric formal which distilled as a liquid and crystallized partly (IIa) or sublimed directly (IIb). If necessary, the solid can be washed free of diol with water and recrystallized from water/ethanol containing a trace of KOH.

The non-distillable solid residue was mixed with a trace of sulfuric or *p*-toluene-sulfonic acid and pyrolysed at 100–200°. The camphor-smelling liquid pyrolysate was collected over potassium carbonate, redistilled at atmospheric pressure and identified as the monomeric formal (Ia,b).

Analytical and physical data are given in Tables 1 and 2.

Preparation of cyclic ketals (Ic,d; IIc,d). A mixture of pentane-1,5-diol or 3,3-dimethylpentane-1,5-diol¹² (0.5 mol), 2,2-dimethoxypropane (0.5 mol), benzene (150 ml), and Amberlite IR-120 resin (3 g) was heated in a flask fitted with a 60 cm Vigreux column. Formed methanol started to distil as an azeotrope with benzene at 58°, and heating was continued until the b.p. was 80°. After cooling, the catalyst was filtered off and the benzene evaporated. Distillation of the residue at 10 mmHg gave the liquid monomeric ketal and left a residue which at further reduced pressure (0.1 mmHg) gave more monomer, before finally some dimeric ketal sublimed.

The monomeric ketal was dissolved in hexane or pentane and stirred for 4 h with the same Amberlite resin. The catalyst was filtered off, the solution then filtered through potassium carbonate, and the solvent evaporated. The solid residue was taken up in warm ethanol, and the dimeric ketal crystallized on cooling.

Analytical and physical data are given in Tables 1 and 2.

Calorimetric measurements. These were performed in a Perkin-Elmer Differential Scanning Calorimeter DSC-1B.

Determination of dipole moments. Dielectric constants were measured at 25° in a Weillheim Dipolmeter DM 01 on four different benzene solutions of each compound. Refractive indices were measured on the same solutions in a Brice-Phoenix Differential Refractometer. Dipole moments were calculated according to Hedestrand¹³ using no correction for atomic polarization.

Infrared spectra. These were recorded in a Perkin-Elmer Grating Infrared Spectrophotometer 457 as KBr pellets and in CS₂- and CCl₄-solutions. Low-temperature spectra were obtained in an R11C low-temperature cell cooled with methanol/dry-ice mixture.

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