

## Syntheses and Conformations of Monomeric and Dimeric Cyclic Dimethylketals

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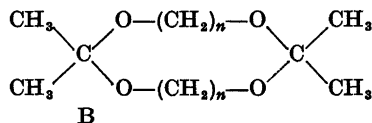
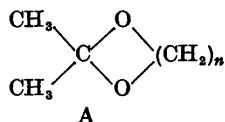
The syntheses of dimeric cyclic ketals of ring size 12–22 are described.

The monomeric 9–12 membered cyclic ketals were unstable and could not be isolated unless substituted with *gem*-dimethyl groups in conformationally stabilizing positions.

In contrast to the corresponding formals, long chain polymers were not formed, probably because of the *gem*-dimethyl-effect of the 2,2-dimethyl-1,3-dioxa group.

The 12-membered cyclic ketal was shown by low temperature NMR to take a square conformation. Three-bond bridged rectangular conformations were assumed for the dimeric cyclic ketals, with the 1,3-dioxa group + *gauche*+*gauche* across corners.

Cyclic compounds with *gem*-dimethyl groups in the 2-position of 1,3-dioxa systems, A and B, were of interest for conformational studies. We



were also interested in the effect exercised by *gem*-dimethyl groups in other positions of cyclic ketals on their conformations and synthetic yield.

For the preparation of most of the cyclic ketals the following method was used: a mixture of a diol and an acid ion exchange resin in benzene was boiled with equivalent amounts of dimethoxypropane, and an azeotropic mixture of methanol and benzene was distilled out.

The yields and the melting or boiling points of the monomeric and dimeric cyclic ketals prepared, and analytical data of new compounds are shown in Table 1. From propane-1,3 and butane-1,4 diol only the monomeric cyclic ketals were formed by this method, as expected because of the general tendency for formation of 6- and 7-membered rings. The dimeric cyclic ketal of butanediol, a 14-membered ring, was therefore synthesized from but-2-yne-1,4-diol by the same ketalization method. Formation of the 7-membered ring is then excluded because of the triple bond. The mixture of oligomers of the acetylenic cyclic ketal was hydrogenated and the saturated 14-membered ring isolated by distillation. This compound has now also been synthesized by oligomerisation of 2,2-dimethyl-1,3-dioxepan.<sup>1</sup> The monomeric and dimeric cyclic ketals of pentane-1,5-diol have been described earlier.<sup>2</sup>

We did not succeed in preparing the 9-, 10- and 11-membered cyclic ketals by the general method, nor was it possible to prepare them from the dimeric compounds by sublimation or by pyrolysis with *p*-toluenesulfonic acid. The 12-membered ring monomer from nonane-1,9-diol was most probably formed, but hydrolyzed immediately. However, with *gem*-dimethyl groups in the 6- and 9-positions even the 11-membered cyclic ketal was stable. With *gem*-dimethyl groups in the 6- and 10-positions the 12-membered ring was unstable, and only the dimeric compound was isolated.

The dimeric cyclic ketal of propane-1,3-diol was obtained in a small yield by oligomerization of 2,2-dimethyl-1,3-dioxane with boron trifluoride.

Table 1.

Diol	Homologue <sup>a</sup>	M.p. (b.p.) °C/mmHg	Yield %	Analytical data Formula	Calc. C	H	Mol. wt.	Found C	H	Mol. wt. osm.
Propane-1,3-diol	Monomer	124/760	~35							
Propane-1,3-diol	Dimer <sup>b</sup>	115	2	C <sub>12</sub> H <sub>24</sub> O <sub>4</sub>	62.04	10.41	232	62.77	10.02	231
2,2-Dimethylpropane-1,3-diol	Monomer	35/15	~80							
Butane-1,4-diol	Monomer	137/760	~30							
But-2-yne-1,4-diol (Hydrogenated ketal)	Dimer	145	3							
Hexane-1,6-diol	Dimer	106	34	C <sub>18</sub> H <sub>36</sub> O <sub>4</sub>	63.31	11.47	316	68.19	11.28	316
Heptane-1,7-diol	Dimer	99	5	C <sub>30</sub> H <sub>40</sub> O <sub>4</sub>	69.72	11.70	344	69.97	11.55	343
Octane-1,8-diol	Dimer	106	30	C <sub>22</sub> H <sub>44</sub> O <sub>4</sub>	70.92	11.90	372	71.16	11.80	372
3,3,6,6-Tetramethyloctane-1,8-diol <sup>14</sup>	Monomer	~106/14	~20	C <sub>15</sub> H <sub>30</sub> O <sub>2</sub>			242			265
3,3,6,6-Tetramethyloctane-1,8-diol	Dimer	135	8	C <sub>30</sub> H <sub>60</sub> O <sub>4</sub>	74.32	12.48	484	74.52	12.40	478
3,3,7,7-Tetramethylnonane-1,9-diol <sup>15</sup>	Dimer	70	8	C <sub>33</sub> H <sub>64</sub> O <sub>4</sub>	74.94	12.58	512	74.38	12.44	517

<sup>a</sup> Number of ring atoms of ketal. <sup>b</sup> Prepared by dimerization of the monomer.

Table 2.

Cyclic ketal	Number of ring atoms	Dipole moment in benzene (D)	$\Delta H_m$ (kcal/mol)	$\Delta S_m$ (e.u.)	Infrared spectrum in $CCl_4$ solution as compared with solid
2,2,6,6-Tetramethyl-1,3-dioxan	6	1.7	2.6	10.4	Some small differences
2,2-Dimethyldioxepan	7		2.9	12.6	Identical
2,2,6,6,9,9-Hexamethyl-1,3-dioxacycloundecane	11				
2,2,8,8-Tetramethyl-1,3,7,9-tetraoxacyclododecane	12		5.6	14.6	Identical
2,2,9,9-Tetramethyl-1,3,8,10-tetraoxacyclotetradecane	14	0	7.3	17.8	Only intensity differences
2,2,11,11-Tetramethyl-1,3,10,12-tetraoxacyclo-octadecane	18	0.6	8.4	22.5	Fairly similar
2,2,12,12-Tetramethyl-1,3,11,13-tetraoxacycloicosane	20	0	10.9	29.5	Crystal conf. + others in solution
2,2,13,13-Tetramethyl-1,3,12,14-tetraoxacyclodocosane	22	0	14.8	39.5	Different
2,2,6,6,9,9,13,13,17,17,20,20-Dodecamethyl-1,3,12,14-tetraoxacyclodocosane	22	0	13.7	33.7	Fairly similar
2,2,6,6,10,14,14,18,18,22,22-Dodecamethyl-1,3,13,15-tetraoxacyclotetracosane	24	0	9.5	27.7	Different

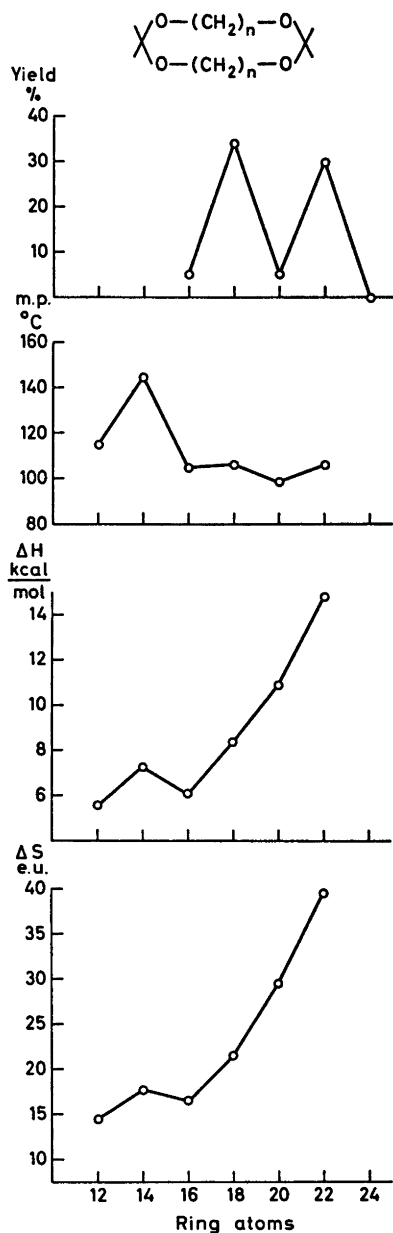


Fig. 1. Yields, melting points, enthalpies and entropies of fusion of dimeric cyclic dimethyl ketals.

The dimeric cyclic dimethyl ketals of butane-, pentane-,<sup>2</sup> hexane-, heptane- and octane- $\alpha,\omega$ -diols are crystalline, stable compounds. Solid polymers were not formed, to the contrary of what is described for the corresponding formals.<sup>3</sup>

The physical properties of the cyclic ketals were investigated by IR and NMR-spectroscopy, dipole moments and differential calorimetry. The results are given in Table 2.

For the unsubstituted dimeric ketals, the values for the melting point and enthalpy and entropy of fusion are compared graphically in Fig. 1. Also given are the yields for those compounds that are synthesized by the same method and are therefore comparable.

## DISCUSSION

The 2,2-dimethyl-1,3-dioxepan had identical IR-spectra in the solid phase (below  $-37^\circ\text{C}$ ) and as liquid; this indicates a single low-energy conformation, the same in both phases. For 1,1-dimethylcycloheptane the lowest-energy conformation is found by calculations<sup>4,5</sup> to be a twist-chair with isoclinal methyl groups. Most probably this is also the conformation for 2,2-dimethyl-1,3-dioxepan (Fig. 2). The NMR-spectra of this compound at  $-130^\circ\text{C}$  indicate the expected equivalence of the methyl groups.

For cycloundecane Dale<sup>6</sup> has found by semi-quantitative calculations a low-energy triangular conformation which can accommodate *gem*-dimethyl groups in the 1 and 4 positions. Also on the third corner of this conformation, position 8, *gem*-dimethyl groups may be accommodated without steric hindrance. These corners are the substitution positions for 1,3-dioxo-2,2,6,6,9,9-hexamethylcycloundecane as shown in Fig. 3 and the conformation therefore possible for this compound. However, low-temperature spectra at  $-130^\circ\text{C}$  did not indicate equivalence of the methyls in the dioxo group and could not prove this assumption.

A 5,5,9,9-tetramethyl-substituted 12-membered cyclic ketal does not suit any of the

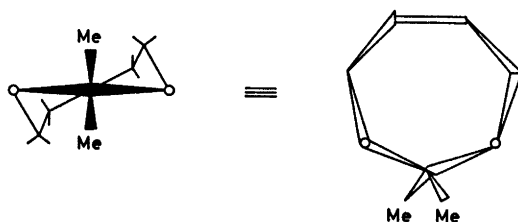


Fig. 2. Conformation of 2,2-dimethyl-1,3-dioxepan.

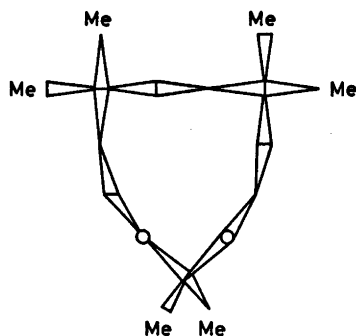


Fig. 3. Conformation of 1,3-dioxo-2,2,6,6,9,9-hexamethylcycloundecane.

calculated low-energy conformations,<sup>6</sup> and so it may be understood why it is not formed. On the other hand, for the monomeric 12-membered cyclic ketal from unsubstituted nonane-1,9-diol there should exist a low-energy square conformation, but we did not succeed in isolating this molecule.

The 1,3-dioxo-group is known to prefer a *+gauche+gauche* conformation across a "corner",

as found by NMR in 1,3,7,9-tetraoxacyclododecane<sup>7</sup> and by X-ray structure analysis in 1,3,8,10-tetraoxacyclotetradecane.<sup>8</sup> For the dimeric ketals, with *gem*-dimethyl groups in position 2 this tendency should be even more pronounced because the *gem*-dimethyl groups in large rings generally prefer corner positions because of their steric requirements.<sup>9</sup> All the dimeric cyclic ketals should therefore prefer to have the oxygens across corners. This is clearly demonstrated for the new compound 2,2,8,8-tetramethyl-1,3,7,9-tetraoxacyclododecane. The IR spectra were identical in the solid phase and in solution (Fig. 4), and this indicates high conformational stability. The NMR spectra (Fig. 5) show a single peak for the methyl groups which persists by lowering the temperature to  $-100^{\circ}\text{C}$ , as expected when the methyl groups are on corners of the square conformation, Fig. 6A. For the  $\beta$ -hydrogens, also on corners of the square conformation and therefore equivalent, no broadening occurs in the low temperature spectrum, only the small changes in the coupling expected because of the splitting

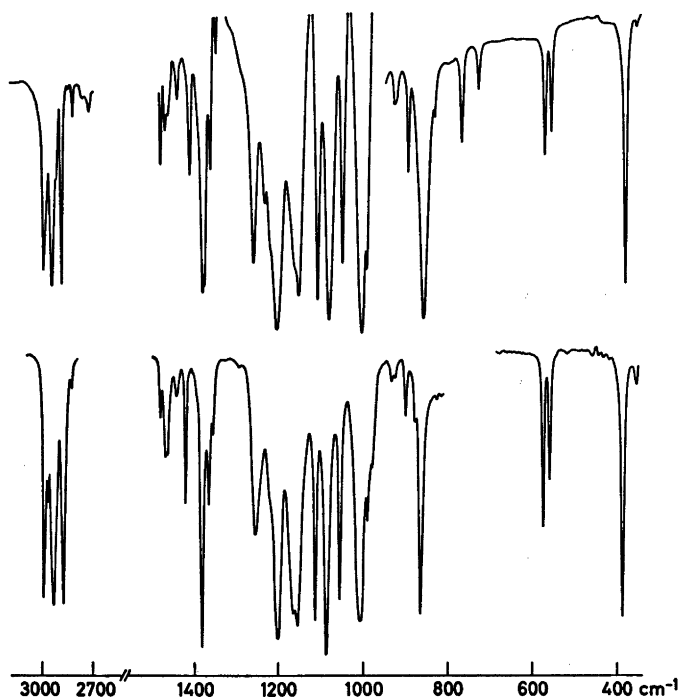


Fig. 4. Infrared spectra of 2,2,8,8-tetramethyl-1,3,7,9-tetraoxacyclododecane as solid in KI (top) and in solution in  $\text{CCl}_4$  (bottom).

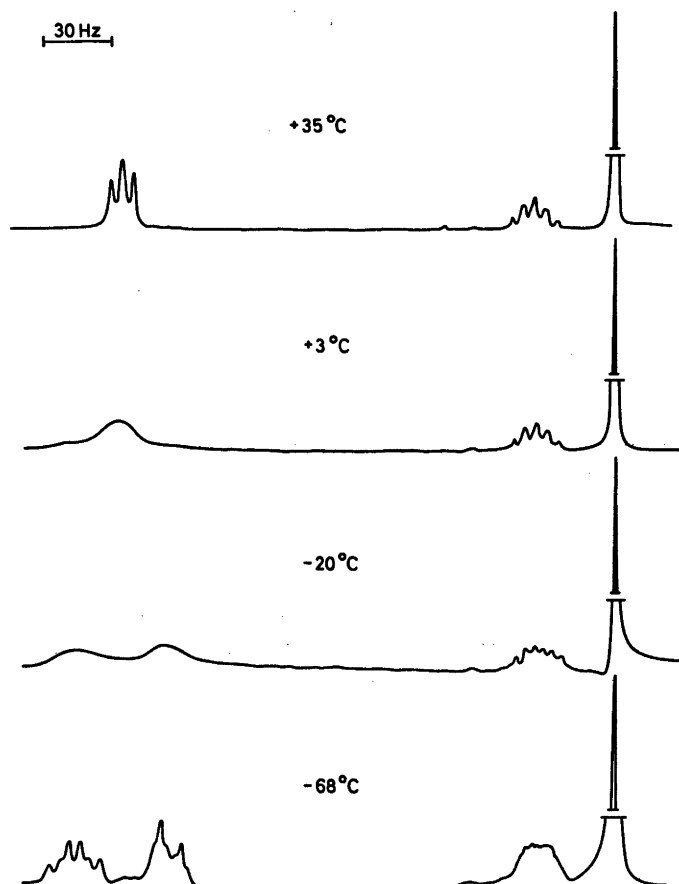


Fig. 5. <sup>1</sup>H NMR spectra at 100 MHz of 2,2,8,8-tetramethyl-1,3,7,9-tetraoxacyclododecane at various temperatures in CHFCl<sub>2</sub> (top curve in CDCl<sub>3</sub>).

of the  $\alpha$ -hydrogens. There is also a striking resemblance in coupling pattern between this low temperature NMR-spectrum and that of the dimer of 1,3-dioxane, which we have earlier found<sup>7</sup> to take the same square conformation. Notable is the high coalescence temperatures in these two twelve membered rings,  $-52^\circ\text{C}$  for the diformal and  $-5^\circ\text{C}$  for the diketal.

The tendency for C-C-bond,  $\alpha$ - $\beta$  to the 1,3-dioxa group, to be *gauche*, as pointed out by Dale<sup>10</sup> and found in all known crystal structures, will tend to give the dimeric cyclic ketals compact conformations, with three-bond "bridges" and close van der Waals contact between the parallel chains. This is shown in Fig. 6B for 2,2,12,12-tetramethyl-1,3,11,13-tetraoxacycloeicosane. This is the same three-

bond bridge as in the above mentioned 12-membered and 14-membered ring diformals and the 12-membered ring dimeric ketal. The same is also found by low temperature <sup>13</sup>C NMR of 2,2,10,10-tetramethyl-1,3,9,11-tetraoxacyclohexadecane<sup>11</sup> and recently by crystal structure determination of 1,3,9,11-tetraoxacyclohexadecane.<sup>12</sup> The fact that our new 20-membered ring, 2,2,12,12-tetramethyl-1,3,11,13-tetraoxacycloeicosane does not show the tendency to absorb solvent molecules, as we have found earlier in 20-membered rings when four-bond bridge open conformations are imposed<sup>13</sup> is an indication of the compact conformation also for the 20-membered cyclic diketal.

The dimeric, large ring ketals therefore all seem to prefer the rectangular conformation

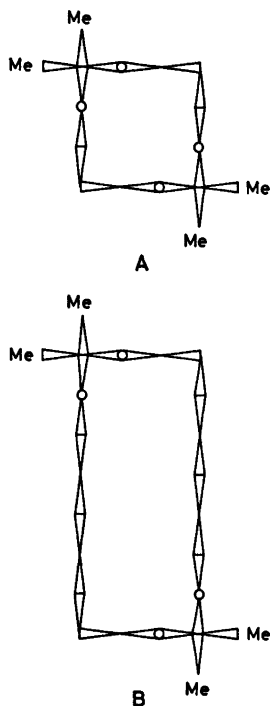


Fig. 6. Conformation of A: 2,2,8,8-tetramethyl-1,3,7,9-tetraoxacyclododecane and B: 2,2,12,12-tetramethyl-1,3,11,13-tetraoxacycloicosane.

in the crystal with the dioxa groups across opposite corners and three-bond "bridges" between the parallel chains. The 12-, 16- and 20-membered rings will thereby leave the diamond lattice, and this results in lower stability which shows up in a lower yield and also in slightly lower melting points than for the 14-, 18- and 22-membered rings.

## EXPERIMENTAL

All the monomeric and dimeric cyclic ketals except 2,2,8,8-tetramethyl-1,3,7,9-tetraoxacyclododecane were synthesized in the following way:

A mixture of the diol (0.25 mol), benzene (300 ml) and Amberlite IR-120 resin in its acid form was heated and moisture distilled out together with some benzene. 2,2-Dimethoxypropane (0.27 mol) was added dropwise and the methanol formed during the reaction was distilled out as an azeotrope with benzene, b.p. 59°C. Distillation was continued slowly until b.p. 80°C (7–10 h). The catalyst was filtered off and the filtrate stirred with sodium hydrogen carbonate (5 g)

for 2 h. After filtration the benzene was evaporated and the residue dissolved or extracted with pentane. By cooling of the pentane solution the dimeric ketals crystallized out and was recrystallized from pentane. An exception was the tetraoxadodecamethylcyclotetacosan which was isolated by vacuum distillation (b.p. 190–200°C/0.1 mmHg) and recrystallized from methanol.

The stable monomeric cyclic ketals were isolated by vacuum distillation of the pentane solution after precipitation of the dimers. The distillation residues contained higher homologues of the cyclic ketals and some open-chain reaction products.

Butane-1,4-diol gave only the monomeric cyclic ketal by this procedure, besides some tetrahydrofuran. Recrystallized but-2-yne-1,4-diol gave, however, a mixture of cyclic ketals with triple bonds which were hydrogenated with palladium catalyst in benzene solution at 2.5 kg/cm<sup>2</sup> for 20 h. After vacuum distillation the saturated dimeric cyclic ketal, a 14-membered ring, was isolated from a fraction boiling at 115°C/0.2 mmHg. The main yield was higher-boiling cyclic ketals. Some monomeric cyclic ketal was formed during the hydrogenation.

The 2,2,8,8-tetramethyl-1,3,7,9-tetraoxacyclododecane was synthesized from 2,2-dimethyl-1,3-dioxan by adding dry, gaseous boron trifluoride (1%). After 2 days at room temperature the mixture was refluxed for one hour, neutralized with gaseous ammonia and distilled in vacuum. Crystals in a fraction boiling at 100–110°C/18 mmHg was separated from accompanying liquid by absorption on filter paper. Sublimation gave the clean 2,2,8,8-tetramethyl-1,3,7,9-tetraoxacyclododecane.

*Determination of dipole moments.* Dielectric constants were measured at 20°C in a Weilheim Dipolmeter DM 01.

*Infrared spectra.* These were recorded in a Perkin-Elmer Grating Infrared Spectrophotometer 457.

*Calorimetric measurements.* A Perkin-Elmer Differential Scanning Calorimeter IB was used down to a temperature of –90°C.

*<sup>1</sup>H NMR spectroscopy.* The NMR spectra were recorded with a Varian HA 100 15 D instrument.

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