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The Acid-catalyzed Condensation of 2-Propylresorcinol with Formaldehyde Diethyl Acetal. The Formation and Isomerization of Calix[4]resorcinarene, Calix[5]resorcinarene, and Calix[6]resorcinarene.

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Abstract: The title reaction initially produced a mixture of three cyclic oligomers, calix[n]resorcinarenes (n= 4, 5, 6), as the major products. Under the conditions of their formation, the pentamer rapidly isomerized to the tetramer and the hexamer, while the hexamer slowly isomerized to the tetramer. A new cyclic oligomer, calix[5]resorcinarene, was isolated and characterized.

Calix[n]resorcinarenes belong to a class of [1_n]metacyclophanes, in which resorcinol units are linked by methylene bridges at their 4- and 6-positions. Among them, calix[4]resorcinarenes are readily prepared by the acid-catalyzed cyclocondensation of resorcinols with alkyl or aromatic aldehydes, without using high dilution conditions, in moderate to high yields.[1-3] The cyclic tetramers can, in principle, exist in the four diastereomers due to the presence of substituents at the bridge positions. However, when alkyl aldehydes were used as condensation agents, the thermodynamically most stable isomers were usually isolated as single predominant products. The pathway for the macrocyclic formation with high selectivity has already been reported.[4]

In our study on the cyclocondensation of 2-alkylresorcinols with formaldehyde or its equivalents, cyclic tetramers are prepared in high yield.[5,6] However, when the reaction was stopped before its completion, the cyclic tetramer and cyclic hexamer were isolated from the reaction mixture.[7] The yields of the cyclic oligomers were dependent on the reaction conditions such as temperature, time, solvent, and condensation agent. In order to clarify the formation pathway for the cyclic oligomers, we examined the acid-catalyzed reaction of 2-propylresorcinol with formaldehyde diethyl acetal by HPLC and ^{1}H NMR spectroscopy. Thus, we have found a new cyclic oligomer, calix[5]resorcinarene.[8] Here, we report the formation and isomerization of these three cyclic oligomers.

2-Propylresorcinol (**1**, 1.40 g, 9 mmol) and formaldehyde diethyl acetal (0.94 g, 9 mmol) were dissolved in ethanol (12 ml). To this was added concd. HCl (3 ml). The solution was maintained at 80 °C with stirring, and periodically analyzed using HPLC[9] and ^{1}H NMR spectroscopy. After 15 min of reaction, a decrease in **1** and the appearance of many linear oligomers were observed. At 30 min, we detected three major products and traces of several products. The three major products were identified as the cyclic tetramer **2**, the cyclic pentamer **3** and the cyclic hexamer **4** by comparison with authentic samples. At this time, the relative composition is **4** > **3** > **2**. After 2 h, the amount of **2** is larger than that of the **4**, while the amount of **3** is small.

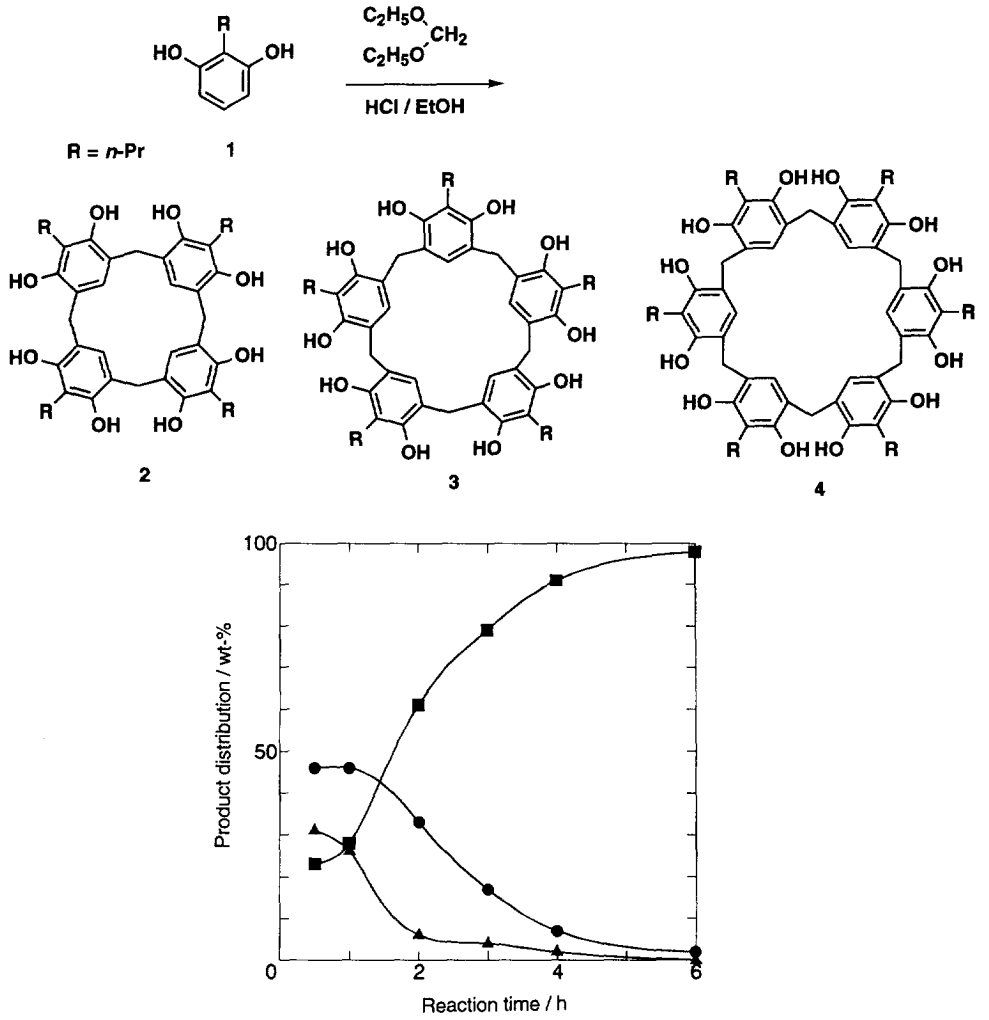
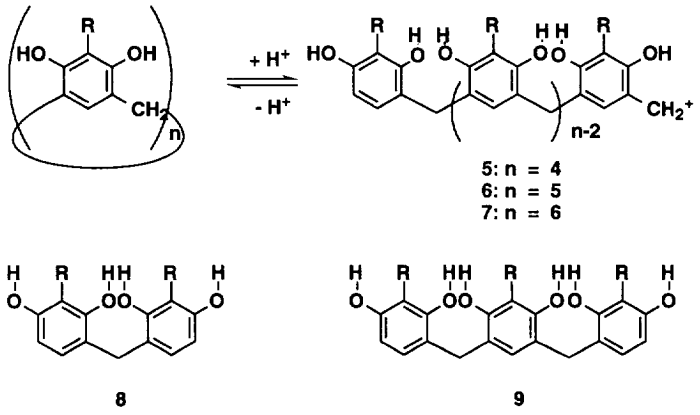


Figure 1. Relationship between time and product distribution in the cyclocondensation of **1** with formaldehyde diethyl acetal at 80 °C in ethanol/concd. HCl (4:1 v/v); (■) **2**, (▲) **3**, (●) **4**.

At 6 h, the yield of **2** is nearly quantitative. The product distribution determined by HPLC is shown in Figure 1. In order to elucidate the pathway for the isomerization of the cyclic oligomers, we examined several acid-catalyzed reactions of the cyclic oligomers under the conditions of their formation.

The acid catalyzed reaction of the hexamer yielded only the tetramer. During this isomerization, we could not detect the formation of the linear oligomers or the pentamer by ^{1}H NMR. Next, the isomerization of a 1:1 mixture of the two types of hexamers (methyl and propyl derivatives) gave all six possible types of cyclic tetramers. However, their isomer distribution was different from that of the cyclic tetramers obtained from the



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cyclocondensation of an equimolar mixture of 2-methylresorcinol and 2-propylresorcinol. A comparison of these isomer distributions indicated that the linear hexamer **7** generated by the protodealkylation of the cyclic hexamer produces lower linear oligomers from which the cyclic tetramer is constructed.

On the other hand, the cyclic pentamer initially isomerized to the cyclic hexamer and the cyclic tetramer, and finally to the cyclic tetramer. This result suggests that the degradation and the propagation of the linear pentamer **6** are much faster than the cyclization to the cyclic pentamer.

In contrast, the cyclic tetramer did not give any isomerization products. However, in the presence of a large amount of **1**, the major products were the linear dimer **8** and liner trimer **9**. The formation of these oligomers can be presumed as follows. The linear tetramer **5**, derived from **2**, reacts with **1** to yield a linear pentamer, which has no terminal methylene group for the formation of a new C-C bond, and hence is degraded to the lower oligomers such as **8** or **9**.

The pathways for the formation of the cyclic oligomers and the ring contraction and enlargement are explained as follows. During the initial stage, the acid-catalyzed reaction of **1** with a bridging agent rapidly produces linear oligomers, which readily polymerize or depolymerize to the linear tetramer, pentamer or hexamer, and these oligomers cyclize to the corresponding calix[n]resorcinarenes. After the consumption of **1**, the reconstruction of **3** and **4** is predominant. The ring-opening of these cyclic oligomers gave the linear oligomers, which propagate or degrade to produce precursors for the cyclic oligomers of different ring sizes. In conclusion, the selective formation of the cyclic tetramer **2** is attributable to the fast cyclization of the linear tetramer **5**.

Isolation of the calix[5]resorcinarene.

To a solution of 2-propylresorcinol (**1,** 1.40 g, 9 mmol) and formaldehyde diethyl acetal (0.94 g, 9 mmol) in ethanol (12 ml) was added concd. HCl (3 ml). The solution was stirred at 80 °C for 1h, diluted with ice-water, and then extracted with diethyl ether. The organic layer was washed with water, and the solvent was evaporated. The crude product was dried at 80°C for 2 h *in vacuo,* and triturated with methanol leaving the crude cyclic tetramer **2** (0.40 g, 27%). The methanol solution was concentrated to dryness and the resulting material was suspended in diethyl ether. Most of the cyclic hexamer **4** (0.43 g, 29%) was separated as insoluble material. The soluble fraction was recrystallized from chloroform to remove some impurities. Finally, the soluble fraction was recrystallized several times from dichloromethane to give the cyclic pentamer (**3,** 0.08 g, 5%), m.p. 160 °C(dec.). Its molecular formula was confirmed by elemental analysis and by its FAB mass

spectrum (diethanolamine matrix). In the ^1H NMR spectrum (DMSO-d_6, at 100 °C), **3** showed three singlets in the ratio of 2:1:2, which are assigned to the bridge methylenes, aromatic protons and OH protons.[10] The simplicity of the spectrum indicates the conformational flexibility of the cyclic oligomer in this solvent.[11]

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8. A [1_5]metacyclophane incorporating resorcinol units via their 2- and 4-positions was prepared. M. Tabatabai, M.; Vogt, W.; Böhmer, V.; Ferguson, G.; Paulus, E.F. *Supramol. Chem.*, **1994,** 4, 147-152.
9. The samples were analyzed on 20 cm x 4.6 mm Wakosil 5C18 using ethanol-water (2:1 v/v) as the mobile phase at a flow rate of 0.5 ml/min. The retention times are as follows: **2** (26.7 min), **3** (16.7 min), **4** (23.4 min).
10. ^1H NMR (DMSO-d_6, 100 °C) δ 0.878 (*t*, 12H, CH_3), 1.449 (8H), 2.571 (8H), 3.537 (*s*, 8H, bridge CH_2), 6.457 (*s*, 4H, ArH), 7.802 (s, 8H, OH). ^{13}C NMR (DMSO-d_6, 100 °C) δ 13.5 (CH_3), 21.6 (CH_2), 25.2 (CH_2), 30.1 (bridge CH_2), 116.9, 119.2, 127.3, 150.3. IR (KBr, cm^{-1}) 3360 (OH)
11. Since a completely dried sample of the calix[5]resorcinarene is not soluble in nonpolar solvents such as $CDCl_3$, we could not obtain its low temperature NMR spectrum for conformational analysis.

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