Acid-Catalyzed Formation of Hexahomooxacalix[3]arenes

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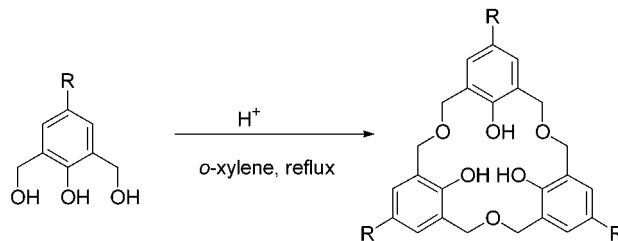
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Abstract: The role of acid catalysis in oxacalix[3]arene synthesis has been investigated. A range of acids were used to optimize the yield of *tert*-butyloxacalix[3]arene, the most efficient being *p*-toluenesulfonic acid, which, with local symmetry complementary with that of the lower rim of the calixarene, provides a templating effect.

The cyclic organic ligands known as hexahomooxacalix-[3]arenes are a subgroup of the calixarene family of macrocycles. The first synthesis of *t*-butylhexahomooxacalix[3]arene (**1**) was reported in 1962,[1] yet it took over twenty years for a more accessible method to be published.[2] Since these initial reports on oxacalix[3]arene synthesis, there have been several attempts to improve the yields and derivatives available.[3]

The most straightforward approach to oxacalix[3]arene synthesis remains that of Dhawan and Gutsche: cyclization of the appropriate 4-substituted bis(methylol)phenol in refluxing xylene. Despite its simplicity, there have been a number of comments in the literature regarding the reproducibility of this method.[3b,4] We have found that the yield of oxacalix[3]arene depends on the degree of purification of the bis(methylol)phenol precursor. Surprisingly, the more carefully the precursor is purified, the poorer the yield of the oxacalix[3]arene.

Published preparations of *p*-substituted bis(methylol)-phenols often involve neutralization of the sodium phenolate salt by acetic acid as the final step.[3b,5] If the resulting bis(methylol)phenol is cyclized under conditions shown in Scheme 1, without further purification, the corresponding oxacalix[3]arene may be obtained in yields up to 30%.[2] Assuming that the mechanism by which cyclotrimerization occurs is initiated by a catalytic amount of acid, removal of trace acetic acid from the bis-(methylol)phenol monomer through purification will result in only small amounts of oxacalix[3]arenes being

(1) Hultzsch, K. *Kunststoffe* **1962**, *52*, 19.
(2) Dhawan, B.; Gutsche, C. D. *J. Org. Chem.* **1983**, *48*, 1536.
(3) (a) Zerr, P.; Mussrabi, M.; Vicens, J. *Tetrahedron Lett.* **1991**, *32*, 1879. (b) Hampton, P. D.; Bencze, Z.; Tong, W.; Daitch, C. E. *J. Org. Chem.* **1994**, *59*, 4838. (c) Tsubaki, K.; Otsubo, T.; Tanaka, K.; Fuji, K. *J. Org. Chem.* **1998**, *63*, 3260. (d) Atwood, J. L.; Barbour, L. J.; Nichols, P. J.; Raston, C. L.; Sandoval, C. A. *Chem. Eur. J.* **1999**, *5*, 990. (e) Komatsu, N. *Tetrahedron Lett.* **2001**, *42*, 1733. (f) Ashram, M.; Mizyed, S.; Georghiou, P. E. *J. Org. Chem.* **2001**, *66*, 1473.
(4) Masci, B. *J. Org. Chem.* **2001**, *66*, 1487.
(5) Freeman, J. H. *J. Am. Chem. Soc.* **1952**, *74*, 6257.

Scheme 1.   Acid-Catalyzed Formation of Oxacalix[3]arenes

detected. Although other workers have used acids in the synthesis of oxacalix[3]arenes,[3b,c] we wished to demonstrate unequivocally the effects of acid catalysis in improving the yield of **1**. To verify our hypothesis and discover the effects of organic acids other than acetic acid on the yields of oxacalix[3]arenes via the acid-catalyzed route, we analyzed the formation of **1** from 4-*tert*-butylbis-(methylol)phenol ($\mathbf{5}_0$) under a variety of conditions.

Several species were observed during the reaction of the unpurified monomer, including oxacalix[3]arene **1**. As expected, no oxacalix[3]arene was observed under the strictly acid-free conditions b in Figure 2 with only calix-[4]arene isolated and a trace of calix[6]arene identified by NMR in the crude mixture. This implies that thermal dehydration alone is required to prepare calixarenes **3** and **4** from $\mathbf{5}_0$ but the presence of acid is necessary for oxacalixarene synthesis. Variation in the organic acid shows that optimum formation of the oxacalix[3]arene is achieved with TsOH, i.e., when the conjugate base has 3-fold symmetry to complement that of the desired product. These results are in general agreement with Hampton, who reported that both TsOH and MsOH catalyzed the formation of **1** in DME.[3b] Unexpectedly, addition of acetic acid to recrystallized $\mathbf{5}_0$ was more efficient than MsOH in producing **1**. Inspection of the reaction profile for these conditions, c and d, respectively, reveals that the latter also catalyzed the formation of linear polymer $\mathbf{6}_3$, which reduced the potential yield of **1**. Analysis of the crude product isolated from the latter conditions indicated that **3** was also present, presumably through cyclization and dehydration of $\mathbf{6}_3$.

The proposed formation of compounds **1** and **2** via the acid-catalyzed route is shown in Scheme 2. Once the carbocation of the monomer has been formed, it can react to form a dimer, $\mathbf{5}_1$. A number of paths may then be followed, all catalytic in H$^+$, through which the formation of **1** and **2** can be envisaged.

From the strong network of hydrogen bonds observed for oxacalixarenes, in both solution and the solid state,[6] one of the driving forces behind the formation of **1** from acyclic precursors is likely to be attraction between phenolic oxygens and the hydrogens from adjacent phenols. Preorganization by the catalyst will bring the termini of linear oligomers $\mathbf{5}_n$ or $\mathbf{6}_n$ close enough to facilitate cyclization. Thus, the use of MsOH or TsOH, where complementarity exists between the 3-fold symmetry presented by their conjugate bases and the geometry of the oxacalix[3]arene, may be expected to optimize the yield of **1** over other products.

(6) Suzuki, K.; Minami, H.; Yamagata, Y.; Fuji, S.; Tomita, K.; Asfari, Z.; Vicens, J. *Acta Crystallogr.* **1992**, *C48*, 350.
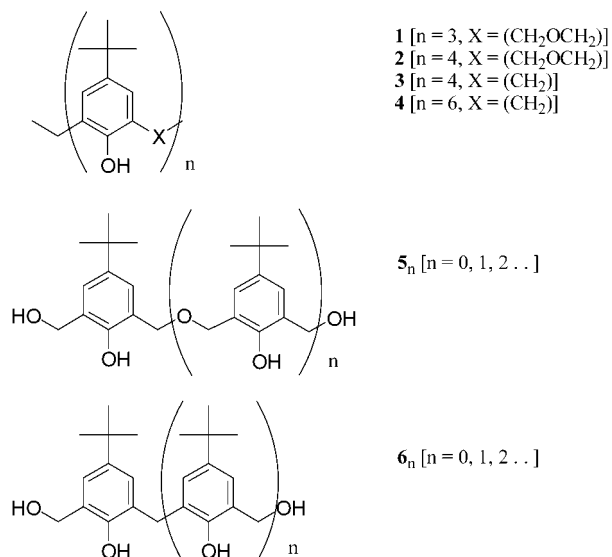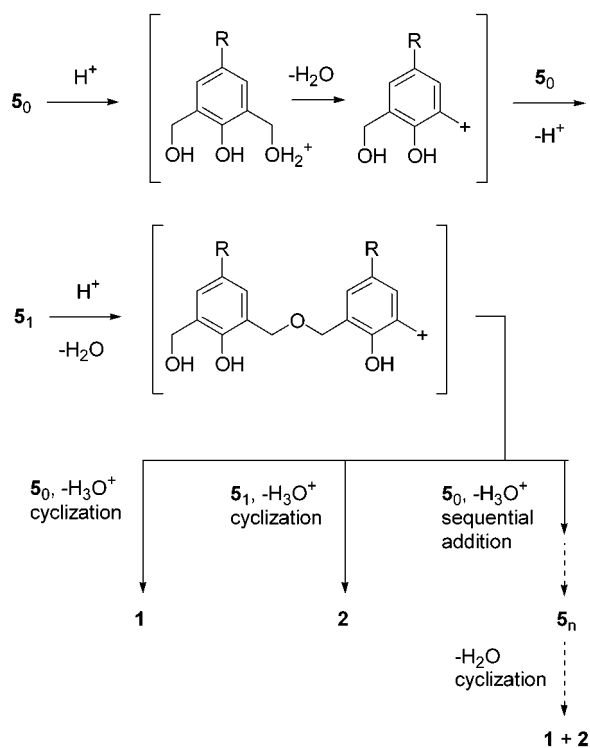
Figure 1. Structures of compounds discussed: oxacalix[3]-arene **1**, oxacalix[4]arene **2**, calix[4]arene **3**, calix[6]arene **4**, linear polymers $\mathbf{5}_n$ and $\mathbf{6}_n$ (R = *tert*-butyl).

Scheme 2. Formation of Oxacalix[n]arenes

In summary, we have shown that the formation of **1** relies on acid catalysis when the simple method in Scheme 1 is followed. The presence of trace acid in inadequately purified bis(methylol)phenols explains the variable results obtained by other workers when attempting to prepare oxacalix[3]arenes by this route.

Experimental Section

General Conditions. All materials were used as received without further purification. *tert*-Butylbis(methylol)phenol, $\mathbf{5}_0$, was prepared as reported in the literature[5] and used without purification in experiment a. Compound $\mathbf{5}_0$ was recrystallized from the minimum amount of hot benzene for use in experiments
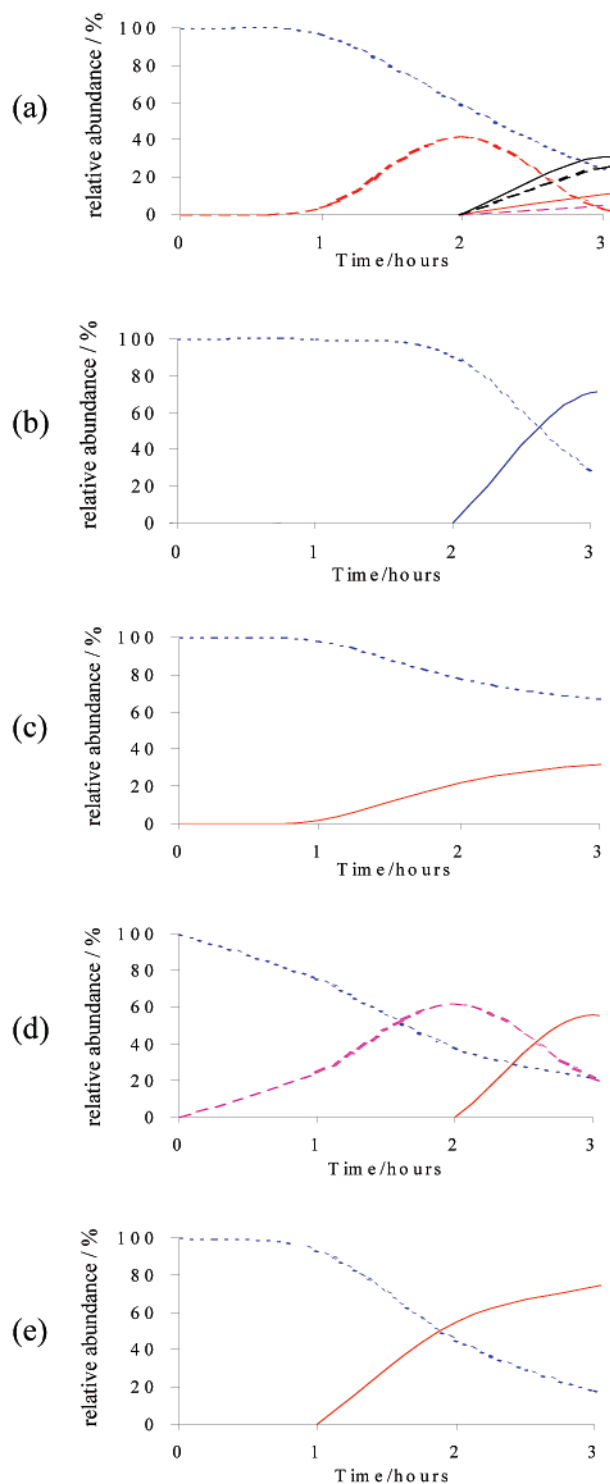
Figure 2. Profiles of cyclization reactions under conditions a−e: (red solid line) **1**; (blue solid line) **3**; (black solid line) **4**; (blue dashed line) $\mathbf{5}_0$; (red dashed line) $\mathbf{5}_2$; (black dashed line) $\mathbf{6}_1$; (purple dashed line) $\mathbf{6}_3$.

b−e. Reactions were monitored using a combination of Maldi-TOF mass spectrometry and ^{1}H NMR (360 MHz, CDCl$_3$ solution).

t-**Butylhexahomooxacalix[3]arene** (**1**). In a slight variation to the published procedure,[2] 4-*tert*-butylbis(methylol)phenol ($\mathbf{5}_0$, 5.00 g, 23.5 mmol) was refluxed in *o*-xylene (100 mL), under nitrogen, using a Dean−Stark trap to remove any water formed during the reaction. In experiments c−e, an aliquot of acid (8.7 mmol) was added prior to reflux (see text for details). Samples, taken at 0, 1, 2, and 3 h, were analyzed by mass spectrometry

to monitor the relative ratios of reactants, intermediates, and products. After 4 h, the reaction mixtures were left to cool to room temperature. Solvent was removed under reduced pressure to leave viscous oily residues. Diethyl ether (20 mL) was added to the residues and subsequently removed under reduced pressure to eliminate trace *o*-xylene. The resulting sticky solids were analyzed by ^{1}H NMR to identify any calixarenes present in the crude products (using assignments of 8.54, 9.62, and 10.34 ppm for the shift in phenolic protons of **1**, **3**, and **4**, respectively)[2,7] before being dissolved in the minimum dichloromethane. Methanol was added until slight opacity was observed and the mixtures left at 4 °C overnight to precipitate **1**, which was isolated by filtration. Reaction conditions are given in Table 1, which also gives isolated yields of **1**, and Figure 2 illustrates the changes in the abundances of detectable species over time.

(7) Gutsche, C. D.; Dhawan, B.; No, K. H.; Murthukrishnan, R. *J. Org. Chem.* **1981**, *103*, 3782.

Table 1. Isolated Yield of 1

conditions	% yield
crude 5_0, no added acid	26
recrystallized 5_0, no added acid	trace
recrystallized 5_0, acetic acid	41
recrystallized 5_0, methanesulfonic acid	23
recrystallized 5_0, *p*-toluenesulfonic acid	64

Supporting Information Available: Complete data and assignments for each species for experimental conditions a−e. This material is available free of charge via the Internet at http://pubs.acs.org.

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