Pathways for the Reversion of *p-tert*-Butylcalix[8]arene to *p-tert*-Butylcalix[4]arene[1]

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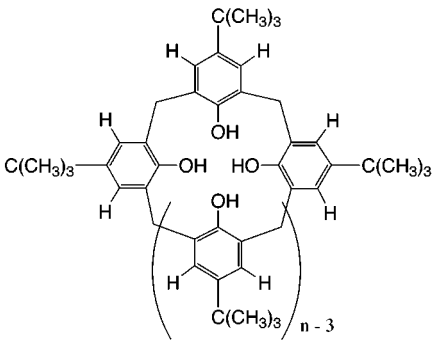
The conditions under which base-induced condensations of *p-tert*-butylphenol with formaldehyde are carried out can be controlled so that *p-tert*-butylcalix[4]arene (**1**),[2] *p-tert*-butylcalix[6]arene (**2**),[3] or *p-tert*-butylcalix[8]arene (**3**)[4] is the major product isolable in good to excellent yield. However, the pathways by which these three

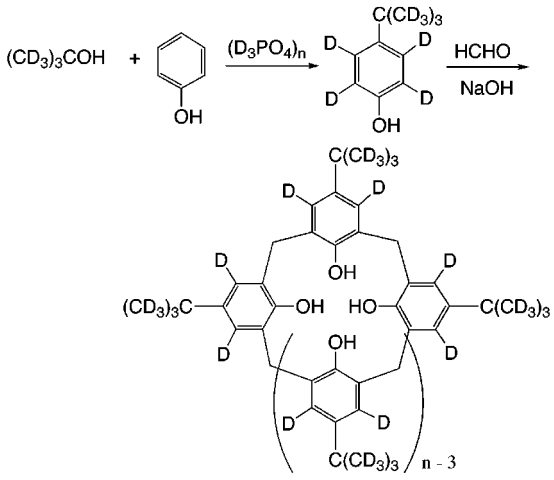


1 n = 4
2 n = 6
3 n = 8

compounds (designated as the "major" calixarenes[5]) are formed are quite unclear. A study carried out in this laboratory several years ago aimed at gaining insight into this question arrived at the conclusion that the cyclic octamer **3** and cyclic tetramer **1** are kinetic and thermodynamic products, respectively. This was based on the facts that (a) the cyclic octamer is formed under considerably milder conditions than the cyclic tetramer and (b) the cyclic octamer can be converted to the cyclic tetramer (referred to as a "reversion reaction" in this discussion) under the high-temperature conditions that are used to prepare the latter directly from *p-tert*-butylphenol.[6] It was postulated that the transformation of **3** to **1** might take place via an intramolecular pathway, whimsically called "molecular mitosis".[7] The incentive for the present work, the results of which have appeared elsewhere in abbreviated form,[5] was to test the viability of this postulate. Another study that endeavored to probe these pathways was carried out by Vocanson and Lamartine[8] who came to the conclusion that both the calix[4]arene and calix[8]arene are probably formed by cyclization of the corresponding linear oligomer (i.e., the pseudocalixarene).

The test that was used to reveal the presence or absence of "molecular mitosis" involves the conversion of a 1:1 mixture of the cyclic octamer **3** (designated as the protonated species) and its deuterium-labeled counterpart **5** (designated as the deuterated species) to a mixture of protonated cyclic tetramer (**1**) and deuterated cyclic tetramer (**4**). If the conversion is strictly intramolecular (i.e., "molecular mitosis") the cyclic tetramer that is formed should be a mixture of only two compounds, viz. **1** and **4**. On the other hand, if fragmentation/recombination pathways are involved the cyclic tetramer mixture will also include cyclic tetramers containing both protonated and deuterated residues, as depicted in Figure 1.

The deuterated *tert*-butylphenol required for the synthesis of **5** was prepared by treatment of acetone-d_6 with CD_3MgI followed by condensation of the resulting *tert*-butyl alcohol-d_9 with phenol using deuterated polyphosphoric acid (from P_2O_5 and D_2O) as the catalyst and solvent. The *tert*-butylphenol-d_{13} that was obtained was almost completely deuterated at the methyl groups as well as the aromatic ring. Condensation of this material with HCHO following the literature procedure[2] gave a 69% yield of **5**. A sample of deuterated cyclic tetramer **4** was obtained by treating **5** with NaOH in boiling diphenyl ether to effect the reversion reaction.



4 n = 4
5 n = 8

The mass spectrum of a 1:1 mixture (by weight) of **3** and **5** (see Figure 2) shows a pair of strong signals at *m/e* 1296 for **3** and 1383 for **5** in a ratio of l.08:1 (calcd for a 1:1 mixture by weight, 1.09:1). Treatment of this mixture with NaOH in boiling diphenyl ether afforded a product from which the cyclic tetramer was isolated in 42% yield. Its mass spectrum (see Figure 3) shows five

(1) Paper 53 in a series entitled Calixarenes. For paper 52, see: Stewart, D. R.; Gutsche, C. D. *J. Am. Chem. Soc.* **1999**, *121*, in press.
(2) Gutsche, C. D.; Iqbal, M. *Org. Synth.* **1990**, *68*, 234.
(3) Gutsche, C. D.; Dhawan, B.; Leonis, M.; Stewart, D. *Org. Synth.* **1990**, *68*, 2238.
(4) Munch, J. H.; Gutsche, C. D. *Org. Synth.* **1990**, *68*, 243.
(5) Gutsche, C. D. Calixarenes Revisited in *Monographs in Supramolecular Chemistry*; Stoddard, J. F., Ed.; Royal Society of Chemistry: Cambridge, 1998.
(6) Gutsche, C. D.; Iqbal, M.; Stewart, D. R. *J. Org. Chem.* **1986**, *51*, 742.
(7) Dhawan, B.; Chen, S.-I.; Gutsche, C. D. *Makromol. Chem.* **1987**, *188*, 921.
(8) Vocanson, F.; Lamartine, R. *Supramol. Chem.* **1996**, *7*, 19. It should be noted that the pathway proposed by Gutsche and co-workers for the formation of calix[4]arene is incorrectly stated in this paper "to involve a hemicalix[8]arene which yields calix[4]arene by molecular mitosis". It should instead have read "to involve a calix[8]arene which yields calix[4]arene by molecular mitosis", the latter pathway being the subject of the present paper.

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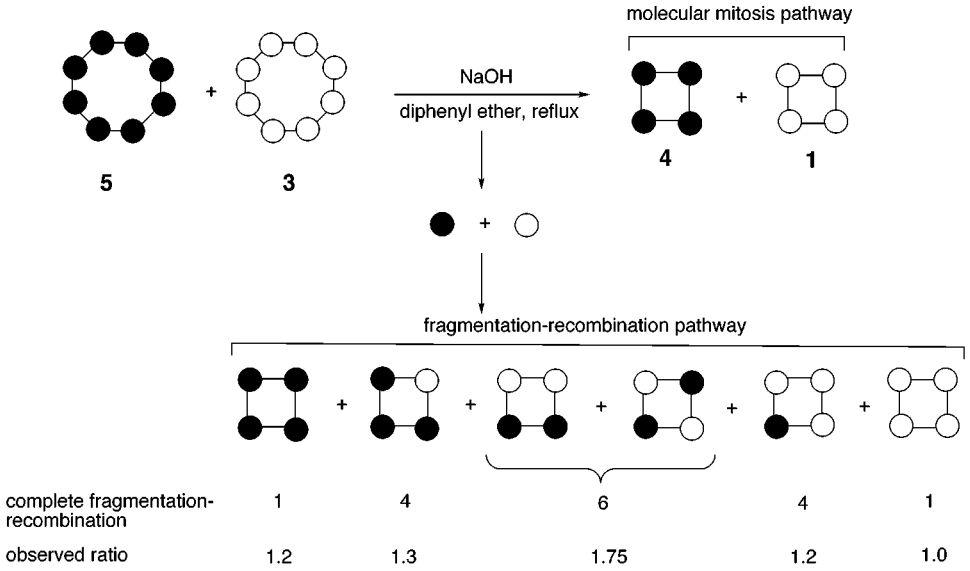

Figure 1. Pathways for the reversion reaction of *p-tert*-butylcalix[8]arene to *p-tert*-butylcalix[4]arene.

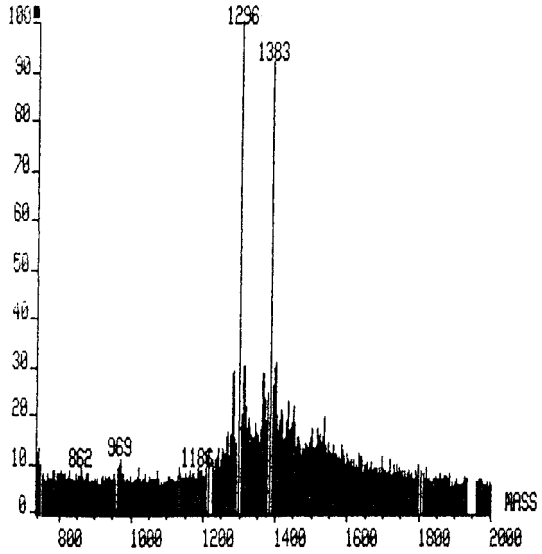

Figure 2. Mass spectrum of a 1:1 mixture of protonated *p-tert*-butylcalix[8]arene (**3**) and deuterated *p-tert*-butylcalix[8]arene (**5**).

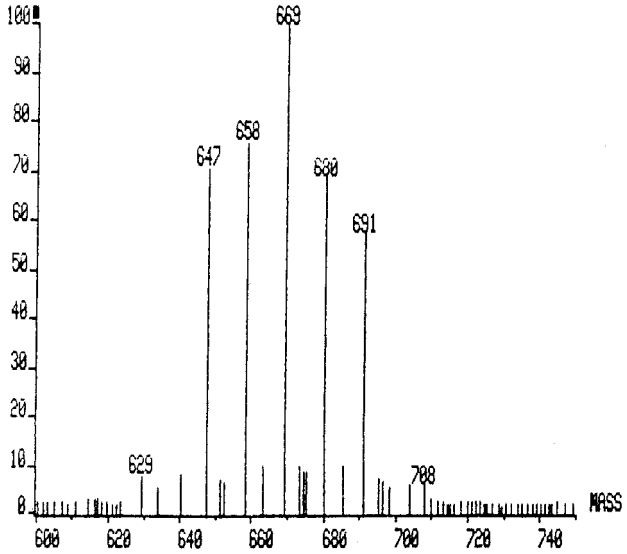

Figure 3. Mass spectrum of *p-tert*-butylcalix[4]arene obtained by reversion reaction of a 1:1 mixture of protonated and deuterated *p-tert*-butylcalix[8]arene (**3** and **5**).

strong signals corresponding to the fully protonated **1** at *m/e* 647, the fully deuterated **4** at *m/e* 691, and partially protonated and deuterated species at *m/e* 658, 669, and 680. If the pathway for the reversion reaction is molecular mitosis, the mass spectrum should show signals only at *m/e* 647 and 691 (see Figure 4 for mass spectrum of a 1:1 mixture {by weight} of **4** and **1**). If the pathway is completely fragmentation/recombination the mass spectrum should show five signals in the ratio of 1:4:6:4:1. The observed ratio (see Figure 1) of 1.1:1.2:1.7:1.2:1.0 for the five lines[9] falls between these extremes and indicates that the molecular mitosis pathway can account for only a fraction of the product. If three molecules undergo fragmentation/recombination for every molecule that undergoes molecular mitosis, the product ratio should be 1:1.1:1.64:1.1:1.0, which is reasonably close to that observed. That fragmentation/recombination is a major event[7] is also indicated by the mass spectra (see Figures 5 and 6) of the cyclic octamer and cyclic hexamer isolated in small amount from the reversion reaction product mixture. Of course, there is the possibility—indeed probability—that some or even all of the fragmentation/recombination occurs *after* the deuterated and protonated calix[4]arenes have been produced. The extent to which this is the case will alter the ratio between the two pathways in favor of molecular mitosis. Even when fragmentation/recombination does occur, it appears to be considerably less than complete. For complete fragmentation/recombination (i.e., fragmentation to monomeric residues), the signals in the mass spectra corresponding to the calixarenes containing even numbers of deuterated and protonated residues (see Figures 3, 5, and 6) would be considerably stronger relative to those arising from the completely deuterated and completely protonated

(9) Values are corrected to accord with the use of a 1:1 mixture by weight of **3** and **5**. Reference 5 (page 29) shows a slightly different ratio of mass spectral intensities (obtained from a companion experiment) but provides the same conclusion that the partition between the molecular mitosis and fragmentation/recombination pathways is ca. 1:3.

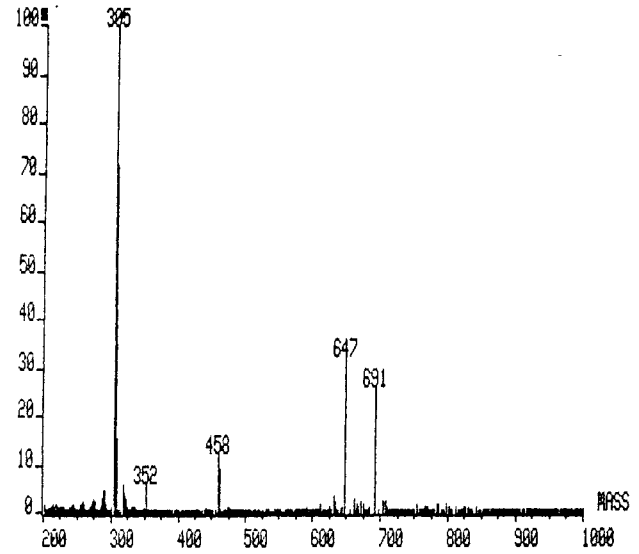

Figure 4. Mass spectrum of a 1:1 mixture (by weight) of protonated and deuterated *p-tert*-butylcalix[4]arene (**4** and **1**).

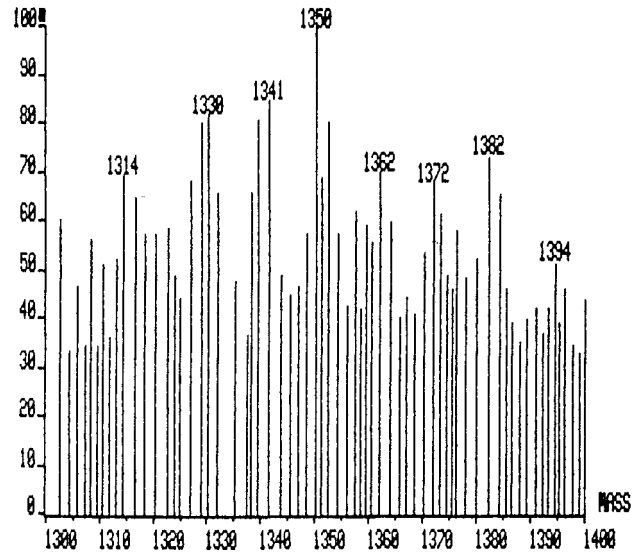

Figure 5. Mass spectrum of *p-tert*-butylcalix[8]arene present in the reversion reaction mixture.

species than is observed. In presenting so mixed a picture, Nature has chosen complexity over simplicity, oblivious to Occam's razor.

Experimental Section

Deuterium-Labeled *p-tert*-Butylphenol. Deuterated polyphosphoric acid was made by placing 7.24 g (0.051 mole) of fresh P_2O_5 in a well-dried flask equipped with a condenser and a septum, flushing the flask with N_2, placing the flask in an ice bath, and adding (via syringe) 3.07 g (0.153 mole) of 99.9% pure D_2O. The reaction mixture was stirred and heated at 230 °C for 20 min and then allowed to cool to room temperature. To the reaction mixture was added a slurry comprising 3.1 mL of toluene, 2.80 g (0.0338 mole) of *tert*-butyl alcohol-d_9 (prepared by the reaction of $(CD_3)_2C{=}O$ and CD_3MgI), and 4.76 g (0.051 mol) of phenol. The stirred mixture was heated at 80−85 °C for 15 min, cooled, and added to 75 mL of water contained in a 125 mL separatory funnel. The contents were washed three times with water and then worked up in conventional fashion to yield 4.19 g (78%) of an almost colorless liquid shown by TLC to be a mixture containing mostly the *para*-substituted phenol but accompanied by smaller amounts of the *ortho*-substituted and disubstituted phenols. A 3.00 g sample of this mixture was subjected to flash chromatography on a 25 mm × 25 cm column using $CHCl_3$ as the eluent and a flow rate of 5 cm/min. The fractions containing the desired *para*-substituted product amounted to 1.47 g, corresponding to an overall yield of 50%. The ^{1}H NMR spectrum of this material indicated it to be ca. 20% deuterated at the *ortho* positions and ca. 88% deuterated on the *tert*-butyl groups. A 2.51 g sample of the initial product mixture described above was re-treated with deuterated polyphosphoric acid obtained from 50 g of fresh P_2O_5 and 21.4 g of D_2O. The mixture was stirred and heated at 70−80 °C for 5 h and then worked up to give 2.08 g of material which was chromatographed as described above to afford 1.00 g of *p-tert*-butylphenol-d_{13}, the ^{1}H NMR spectrum of which indicated that almost all of the Ar−H and $C(CH_3)_3$ protons had been replaced by deuteriums.

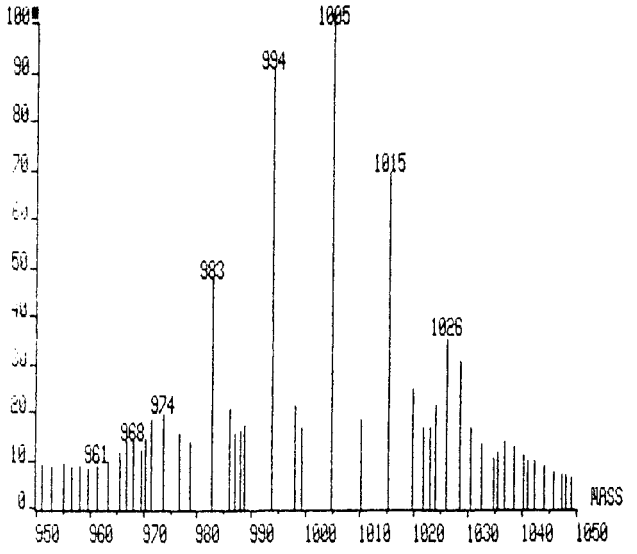

Figure 6. Mass spectrum of *p-tert*-butylcalix[6]arene present in the reversion reaction mixture.

Deuterium-Labeled *p-tert*-Butylcalix[8]arene (5). A 1.13 g (6.70 mmol) sample of *p-tert*-butylphenol-d_{13} was dissolved in 6.2 mL of xylene contained in a 50 mL round-bottomed flask equipped for magnetic stirring and fitted with a small Dean−Stark trap and condenser. To the solution were added 0.66 g (22 mmol) of paraformaldehyde and 20 μL of freshly prepared 10 N NaOH. The mixture was refluxed for 4 h and then worked up to yield a crude product that was recrystallized from $CHCl_3$ to give 0.83 g (69%) of *p-tert*-butylcalix[8]arene shown by HPLC analysis to be greater than 98% pure and by ^{1}H NMR analysis to be greater than 98% deuterated on the aromatic rings and the *tert*-butyl methyl groups. A FAB negative ion mass spectrum showed an M − 1 peak at *m/e* 1383 (calcd parent peak *m/e* 1384).

Deuterium-Labeled *p-tert*-Butylcalix[4]arene (4). A slurry containing 250 mg of deuterium-labeled *p-tert*-butylcalix[8]arene (**5**) and 3.5 μL of freshly prepared 10 N NaOH in 2 mL of diphenyl ether was refluxed, with stirring, for l.5 h. The cooled reaction mixture was treated with 4 mL of ethyl acetate and worked up to afford 156 mg (62%) of *p-tert*-butylcalix[4]arene as a colorless solid shown by HPLC analysis to be greater than 99% pure and by ^{1}H NMR analysis to be greater than 96% deuterated. A FAB negative ion mass spectrum showed a strong M − 1 peak at *m/e* 691 (calcd parent peak *m/e* 692).

Reversion Reaction with Mixture of Protonated and Deuterated *p-tert*-Butylcalix[8]arenes. A slurry containing 0.474 g (0.342 mmol) of *p-tert*-butylcalix[8]arene (**3**), 0.474 g of deuterium-labeled *p-tert*-butylcalix[8]arene (**5**) (FAB negative ion mass spectrum of mixture shown in Figure 4), and 14 μL of freshly prepared 10 N NaOH in 8 mL of xylene was treated as described above but with only 15 min refluxing to give 0.394 g (42%) of *p-tert*-butylcalix[4]arene as a mixture of the unlabeled and labeled materials. From the diphenyl ether−ethyl acetate filtrate, *p-tert*-butylcalix[6]arene and *p-tert*-butylcalix[8]arene were isolated in a manner similar to that of mixtures of the

unlabeled and labeled materials. The FAB negative ion mass spectra of these three products are shown in Figures 3, 5, and 6.

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