

'Stapled' Calix[4]arenes: Immobilization of the Calix[4]arene Conformation by Cross-linking on the Upper Rim

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The calix[4]arene conformation can be immobilized by stapling the upper rim with catechol, resorcinol or salicylic acid: in certain cases novel molecular asymmetry is generated.

There are four different conformations in calix[4]arenes: cone, partial-cone, 1,2-alternate and 1,3-alternate.¹ It is known that interconversion among these conformations, which occurs through the oxygen-through-the-annulus rotation, can be suppressed by introduction of bulky substituents onto the OH groups and isolation of four conformers becomes possible.²⁻⁴ It has been demonstrated that these conformers show quite different physical and chemical properties and therefore act as novel basic skeletons for molecular design of functionalized materials.⁴⁻⁷ In this class of conformationally-immobile calix[4]arenes, however, the OH groups have been used for the purpose of inhibiting the conformational isomerism, further functionalization of the lower rim is impossible. Is there any other method to immobilize the conformation? Meanwhile, we have currently been interested in the synthesis of molecular capsules from two half-bowl-shaped calix[4]arenes.⁸ Examin-

ation of Corey-Pauling-Koltun (CPK) molecular models suggested that compound **1** would be a nice synthetic target without any steric distortion. Since **2** has been synthesized,⁹ we considered that the reaction of two moles of **2** with four moles of catechol (or resorcinol) under high dilution conditions would yield **1**. Unexpectedly, however, the product isolated from the reaction mixture was **3** (or **4**): that is, an intramolecular cross-link at the upper rim occurred in preference to an intermolecular cross-link. Although the reaction was found not to be useful for the synthesis of a molecular capsule, we noticed that this might be applicable to the immobilization of the conformation. We address here a new method to immobilize the calix[4]arene conformation by cross-linking on the upper rim.

Compound **3** (or **4**) was synthesized by the treatment of catechol (or resorcinol) in refluxing acetone in the presence of M_2CO_3 ($M^+ = Na^+, K^+ \text{ or } Cs^+$). The products were isolated

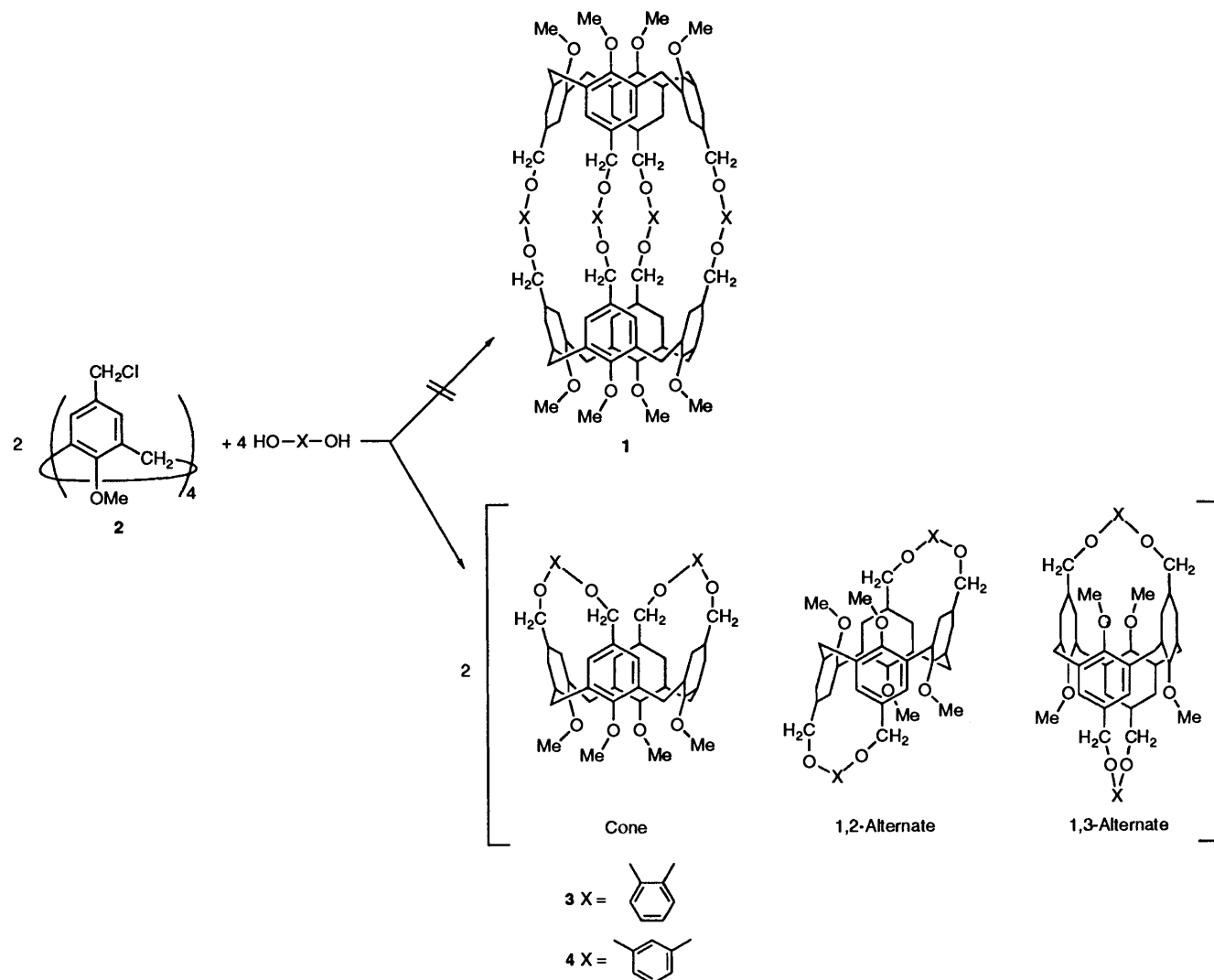
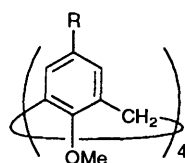


Table 1 Conformer distribution of 'stapled' calix[4]arenes 3 and 4

Product	Base	Additive	Yield (%)	Distribution (%)		
				Cone	1,2-Alternate	1,3-Alternate
3	Na ₂ CO ₃	—	0	0	0	0
3	Na ₂ CO ₃	NaI	76	0	15	85
3	K ₂ CO ₃	—	16	0	4	96
3	K ₂ CO ₃	KI	89	0	4	96
3	Cs ₂ CO ₃	—	71	0	99	1
3	Cs ₂ CO ₃	CsI	21	0	99	1
4	Na ₂ CO ₃	—	0	0	0	0
4	Na ₂ CO ₃	NaI	5	0	38	62
4	K ₂ CO ₃	—	26	27	58	15
4	K ₂ CO ₃	KI	88	10	25	65
4	Cs ₂ CO ₃	—	40	68	32	0
4	Cs ₂ CO ₃	CsI	28	79	21	0

by preparative TLC (silica gel, chloroform) and identified by IR, ¹H NMR and mass spectral evidence and elemental analysis. The conformer distribution was determined by HPLC analysis (Inertsil ODS column, chloroform-methanol, 1:8 v/v) of the raw products.

When Na₂CO₃ was used as base, the yield was significantly enhanced by the addition of NaI. For 3 (*i.e.* the cross-linker is catechol) only 1,2-alternate-3 and 1,3-alternate-3 resulted and the production of cone-3 was not detected. For 4 (*i.e.* the cross-linker is resorcinol), in contrast, cone-4 was produced in addition to 1,2-alternate-4 and 1,3-alternate-4. This implies that the distance between the *para*-position in the cone conformation is too far to cross-link with catechol. It is also seen from Table 1 that the conformer distribution is significantly affected by the metal cation present in the base. For 3 1,3-alternate-3 was predominantly produced in the presence of Na⁺ and K⁺ whereas 1,2-alternate-3 was predominantly produced in the presence of Cs⁺. For 4, on the other hand, the major conformer is 1,3-alternate in the presence of Na⁺, 1,2-alternate in the presence of K⁺ and cone in the presence of Cs⁺. If the first cross-link occurs between proximal phenyl units, the resultant product is either cone or 1,2-alternate. If the first cross-link occurs between distal phenyl units, the resultant product is 1,3-alternate. Thus, the metal effect is explained as such that Na⁺ facilitates the distal cross-link whereas Cs⁺ facilitates the proximal cross-link. In general, tetramethoxycalix[4]arenes 5 tend to adopt a partial-cone conformation.^{2,10-12} Only when template metal cations (*e.g.*, Li⁺ and Na⁺) which can interact with four oxygens are present, do they change into a cone conformation. Hence, distal cross-linking to yield 1,3-alternate should occur from cone-2 whereas proximal cross-linking to yield cone or 1,2-alternate should occur from partial-cone-2.



5a R = H
5b R = Bu^t

To confirm if the three conformers of 3 and 4 isomerize, we heated them in Cl₂CDCDCl₂ at 100 °C for 12 h. Analysis by ¹H NMR spectroscopy and HPLC established that they do not isomerize. One can conclude, therefore, that although compounds 5 are conformationally mobile, 'stapled' 3 and 4 are conformationally immobile.

We also found that salicylic acid is useful as a cross-linker.

Judging from the basicity, the chloromethyl groups in 6 should first react with the phenolate anion followed by the reaction with the carboxylate anion in salicylic acid. If the reaction occurs at the proximal phenyl units, the *syn* isomer 7 is formed. On the other hand, if the reaction occurs at the distal phenyl units, the *anti* isomer 8 is formed. The reaction was carried out in DMF at 70 °C in the presence of Cs₂CO₃. The product analysis established that only the *anti* isomer is produced (m.p. 218–219 °C, yield 36%). This indicates that the reaction occurs only at the distal phenyl units. Very interestingly, 8 has no plane of symmetry and therefore is a racemate. The ¹H NMR signals split into a pair in the presence of the Pirkle's reagent [(*S*)-(+)2,2,2-trifluoro-1-(9-anthryl)ethanol].

In conclusion, the present paper demonstrates for the first time that the calix[4]arene conformation can be readily immobilized by stapling the upper rim with catechol, resorcinol or salicylic acid. In some cases one can make the calix[4]arene optically-active.

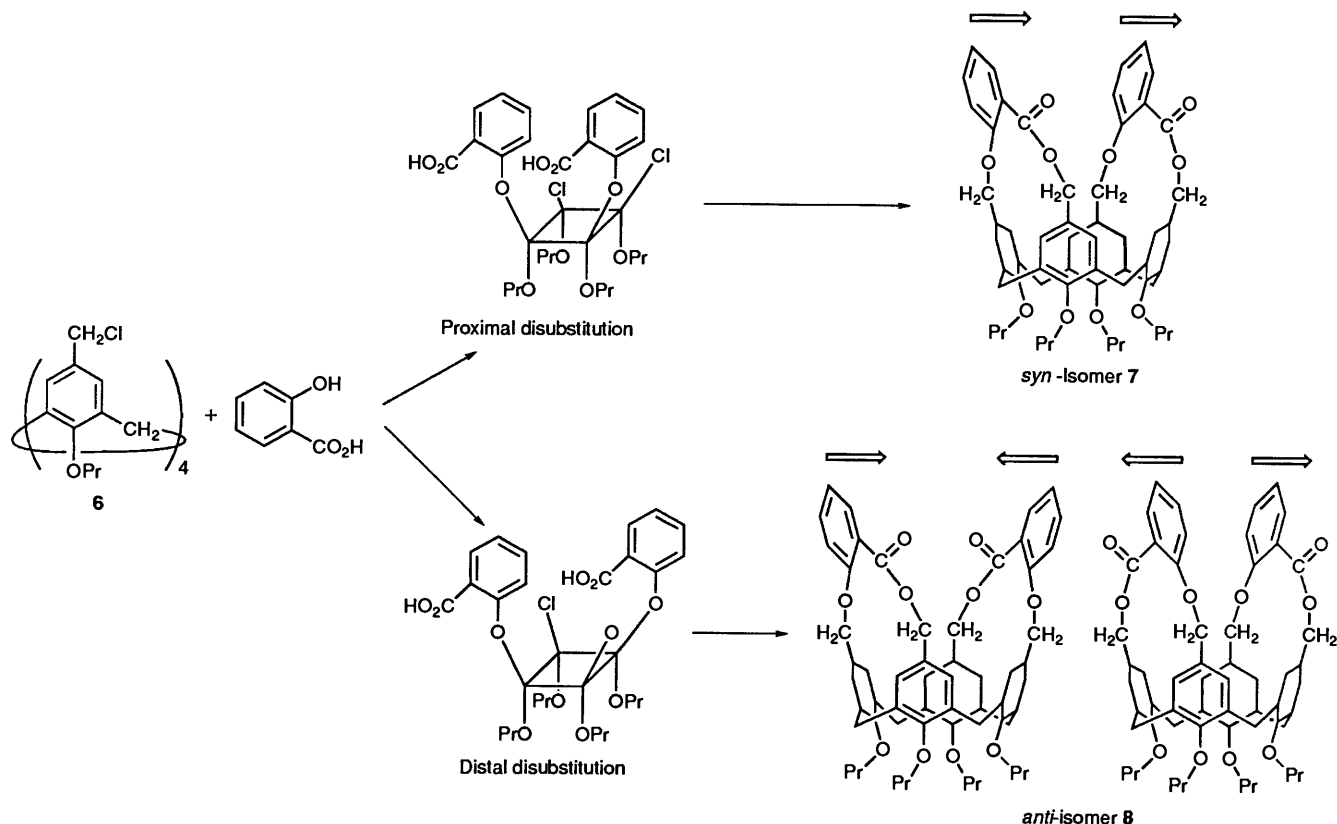
Experimental

General Procedure A: Synthesis of Calix[4]arenes 3 and 4.—Compound 2 (0.20 g, 0.30 mmol) was dissolved in acetone (60 cm³) and treated with M₂CO₃ (M⁺ = Na⁺, K⁺ or Cs⁺) (29.7 mmol). The reaction mixture was stirred at reflux temperature for 1 h and a solution of catechol (or resorcinol) (0.20 g, 1.78 mmol) in acetone (60 cm³) was added from a dropping funnel over 12 h. The mixture was stirred at reflux temperature for 36 h. After cooling, the mixture was diluted with ice-water and extracted with dichloromethane. The organic layer was washed twice with water and dried over MgSO₄. After filtration, the filtrate was concentrated to dryness. The residue was subjected to TLC separation (silica gel; chloroform).

General Procedure B: Synthesis of Calix[4]arenes 3 and 4.—The work-up was similar to that described for general procedure A but was carried out in the presence of MI (M⁺ = Na⁺, K⁺ or Cs⁺). The difference between A and B is discussed in Table 1.

1,2-Alternate-3. M.p. > 270 °C (decomp.); *m/z* 748; δ_H-(CDCl₃; 25 °C) 2.31 (12 H, s, CH₃O), 3.33, 3.54 and 3.79 (2, 4 and 2 H, resp., d, s and d, resp., ArCH₂Ar), 5.16 and 5.25 (each 4 H, each d, ArCH₂O), 6.83–6.91, 6.96–7.08 and 7.89 (8, 4 and 4 H, resp., m, m and s, resp., ArH) (Found: C, 68.9; H, 5.35. Calc. for C₄₈H₄₄O₈·0.85CHCl₃: C, 69.00; H, 5.32%).

1,3-Alternate-3. M.p. > 300 °C (decomp.); *m/z* 748; δ_H-(CDCl₃; 25 °C) 3.48 (8 H, s, ArCH₂Ar), 3.65 (12 H, s, CH₃O), 4.85 (8 H, s, ArCH₂O), 6.99–7.08 and 7.12–7.22 (12 and 4 H, resp., each m, ArH) (Found: 75.5; H, 5.8. Calc. for C₄₈H₄₄O₈·0.14CHCl₃: C, 75.53; H, 5.81%).



Cone-4. M.p. $>270^\circ\text{C}$ (decomp.); m/z 748; δ_{H} (CDCl_3 ; 25°C) 3.07, 3.08, 4.26 and 4.29 (each 2 H, each d, ArCH_2Ar), 3.79 (12 H, s, CH_3O), 4.84 and 4.89 (each 4 H, each d, ArCH_2O), 6.01, 6.56, 6.72, 6.75 and 7.25 (2, 8, 2, 2 and 4 H, resp., t, s, d, d and t, resp., ArH) (Found: C, 75.8; H, 5.8. Calc. for $\text{C}_{48}\text{H}_{44}\text{O}_8 \cdot 0.11\text{CHCl}_3$: C, 75.83; H, 5.83%).

1,2-Alternate-4. M.p. $>280^\circ\text{C}$ (decomp.); m/z 748; δ_{H} (CDCl_3 ; 25°C) 2.71 (12 H, s, CH_3O), 3.14, 3.70 and 4.02 (2, 4 and 2 H, resp., d, s and d, resp., ArCH_2Ar), 5.11 (8 H, s, ArCH_2O), 6.48, 6.52, 6.63, 6.96, 7.01 and 7.21 (2, 2, 2, 4, 2 and 4 H, resp., d, t, d, t and d, resp., ArH) (Found: C, 73.45; H, 6.1. Calc. for $\text{C}_{48}\text{H}_{44}\text{O}_8 \cdot 2\text{H}_2\text{O}$: C, 73.45; H, 6.16%).

1,3-Alternate-4. M.p. $>300^\circ\text{C}$ (decomp.); m/z 748; δ_{H} (CDCl_3 ; 25°C) 3.30 (12 H, s, CH_3O), 3.44 (8 H, s, ArCH_2Ar), 5.12 (8 H, s, ArCH_2O), 6.04, 6.71, 6.74, 6.86 and 7.21 (2, 2, 2, 8 and 2 H, resp., t, d, d, s and t, resp., ArH) (Found: C, 76.6; H, 6.0. Calc. for $\text{C}_{48}\text{H}_{44}\text{O}_8 \cdot 0.03\text{CHCl}_3$: C, 76.67; H, 5.90%).

Synthesis of Calix[4]arene 8.—Salicylic acid (1.18 g, 8.52 mmol) was dissolved in dimethylformamide (DMF) (50 cm^3) and the solution was treated with Cs_2CO_3 (2.78 g, 8.52 mmol). The reaction mixture was stirred at 80°C for 1 h and compound 6 (0.50 g, 0.64 mmol) was added. The mixture was stirred at 80°C for 7 h. After cooling, the mixture was diluted with ice-water and extracted with dichloromethane. The organic layer was washed twice with water and dried over MgSO_4 . After filtration, the filtrate was concentrated to dryness. The residue was subjected to TLC separation (silica gel; chloroform); m.p. $218\text{--}219^\circ\text{C}$; yield 36%; ν_{max} (Nujol)/ cm^{-1} 1720 (C=O) no ν_{OH} ; δ_{H} (CDCl_3 ; 30°C) 1.01 and 1.11 (each 3 H, each t, $\text{CH}_3\text{CH}_2\text{CH}_2$), 1.82–1.93 and 1.99–2.10 (each 2 H, each m, $\text{CH}_3\text{CH}_2\text{CH}_2$), 3.07, 3.20, 4.39 and 4.40 (each 1 H, each d, ArCH_2Ar), 3.61–3.73 and 3.93–4.04 (2 H and 3 H, resp., each m, $\text{CH}_3\text{CH}_2\text{CH}_2$ and ArCH_2O), 4.48, 5.24 and 5.41 (each 1 H, each d, ArCH_2O), 6.16, 6.21, 6.56, 6.92, 7.02–7.09 and 7.31–7.44 (1, 1, 1, 1, 1 and 3 H, resp., d, d, d, t, m and m, resp., ArH)

(Found: C, 76.0; H, 6.6. Calc. for $\text{C}_{58}\text{H}_{60}\text{O}_{10}$: C, 75.96; H, 6.59%).

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