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Structurally-Unusual Calix[4]arene Derivatives Generated by Intra- and Intermolecular McMurry Reactions

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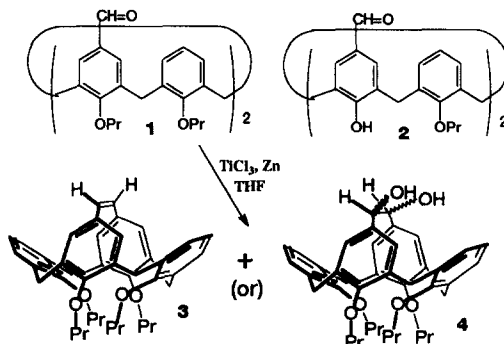
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Abstract: A new class of calix[4]arene derivatives with highly strained structures has been synthesized by intramolecular reductive dimerization of appropriate formyl groups in the presence of low-valent titanium agents (so-called McMurry reaction). New derivatives possessed very interesting molecular structures with upper rims intramolecularly connected by a CH=CH bond and are immobilized either in cone or in 1,3-alternate conformation. The cage compound with inner space perfectly closed by four aromatic units has been obtained from a tetraformyl derivative in 1,3-alternate conformation. Intermolecular reductive coupling of two monoformylcalix[4]arenes has yielded a bis-calixarene derivative which was found to behave as a good host molecule for quaternary ammonium salts.

Calix[4]arenes^{1,2} are very well known for their unique molecular architecture and they have been frequently used as building blocks for the construction of more elaborated molecular systems possessing interesting functions. We have realized that by the application of so-called McMurry reaction to the formyl calix[4]arene derivatives, we can prepare very interesting compounds with unusual molecular topology and/or with unusual properties. The cavity of such molecules is created by fully conjugated π -systems suitable for cation- π interactions and hence is useful for complexation of appropriate molecules.

The McMurry reaction^{3,4} enables reductive dimerization of aldehydes and ketones to yield olefins on treatment with low-valent titanium reagents and generally is performed in two consecutive steps: first the low-valent titanium agent is prepared by reduction of TiCl_n ($n=3,4$) with a strong reducing agent, and then the carbonyl compound is added to the mixture thus obtained. The first step seems to be a drawback of whole reaction due to the usage of highly-reactive species such as C_8K , TiCl_3/K , TiCl_3/Li . Very recently,^{5,6} a new improvement of this reaction with very high reproducibility has been described, where a much easier protocol can be used. Two steps are done together ("instant procedure") by heating of the oxo-compound with TiCl_3 and Zn dust in DME or THF.

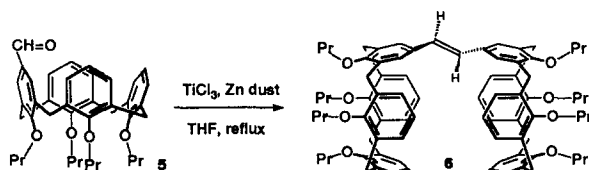
The reaction carried out according to Scheme 1 (heating of **1**⁷ in the presence of 6 eq. of TiCl_3 and 8 eq. of Zn dust in THF) did not lead to the proposed dimeric form but derivative **3** (30%) was isolated from the reaction mixture⁸ as a sole product. This compound has very interesting molecular architecture with two



Scheme 1. Preparation of derivatives **3** and **4**.

opposite aromatic rings connected by a *cis*-double bond while their lower rims are pushed outwards from the cavity. The same reaction carried out at room temperature¹⁰ yielded two diastereomeric structures **4A** and **4B** in 43% yield. The McMurry reaction of calix[4]arene derivative **2** did not yield any similar product of intramolecular coupling, probably due to the incompatibility of free hydroxyl groups with the reaction conditions or, what is more possible, due to the non-immobilized conformation leading preferentially to the polymers. Surprisingly, very recently (during the preparation of this manuscript) the similar synthesis of compounds of type **3** and **4** (EtOCH₂CH₂, instead of Pr) has been published by an Italian group.⁹ In their study, low-valent titanium was generated from Mg/Hg amalgam and TiCl₄ at room temperature. In this paper we demonstrate the versatility of the McMurry reaction for the synthesis of various intramolecularly- or intermolecularly-bridged calix[4]arene derivatives, which is not predicted by the Italian group.

To obtain a compound with the cavity suitable for cation- π interactions we have carried out the McMurry reaction of monoformyl-calix[4]arene **5**¹¹ according to Scheme 2. Dimeric structure **6** has been



Scheme 2. Preparation of derivative **6**.

isolated¹² in 35% yield as a *trans*-isomer (the model reaction of 4-ethoxybenzaldehyde has yielded a mixture of *trans* and *cis* isomers in 95:5 ratio). The determination of the CH=CH configuration by ¹H or ¹³C NMR was difficult. Judging from CPK models, the *cis*-configuration is impossible because of the steric crowding of two calix[4]arenes.

Its complexation ability towards 1-methylquinolinium iodide (1-MQ), which seems to fit the size of **6** in a *syn*-conformation, has been measured by ¹H NMR spectroscopy. Figure 1 shows typical a titration curve obtained by the plotting of $\delta_{\text{CH}_3\text{N}}$ versus 1/[Guest] in CDCl₃, CD₃CN=4:1 v:v at 25 °C. The calix[4]arene concentration was kept constant (5.0 mmol dm⁻³) while the concentration of guest was varied (1-50 mmol dm⁻³). It is obvious from Figure 1 that the N-CH₃ signal of guest molecule is shifted up-field in the presence of calix[4]arene derivative.

The complexation constant was estimated assuming the formation of a 1:1 complex using the original program for curve fitting of the data.¹¹ Due to the fact that the signal of 1-MQ itself is concentration dependent (although slightly) because of self-association (the upper curve in Figure 1) the difference between both curves was used for the computation of K_c . It was found that bis-calixarene **6** acts as a much better host molecule ($\log K_c=2.64 \text{ mol}^{-1}\text{dm}^3$) than simple 25,26,27,28-tetrapropoxycalix[4]arene **7** ($\log K_c=1.96 \text{ mol}^{-1}\text{dm}^3$) used as a reference compound. The inner space of **6** is created by two calix[4]arene subunits that can cooperatively "catch" the guest molecule like tweezers with the help of cation- π interactions.¹¹ At the same time the double bond bridge may also contribute to this binding, thus enforcing the complexation constant. This fact is also demonstrated by large up-field shift of the double bond signal in the presence of guest - $\Delta\delta=0.70 \text{ ppm}$ (H:G = 50), while the signals of other protons are only scarcely shifted. The complexation constant ($\log K_c=1.35 \text{ mol}^{-1}\text{dm}^3$) of an isomeric guest molecule 2-methylisoquinolinium iodide (2-MIQ) is

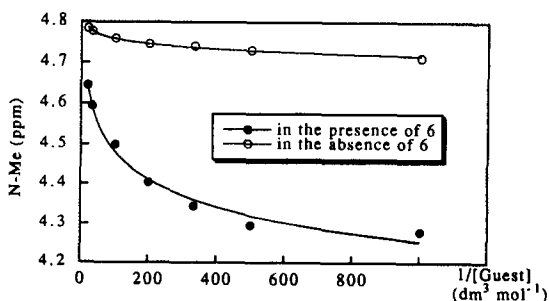
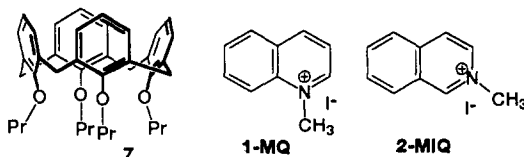
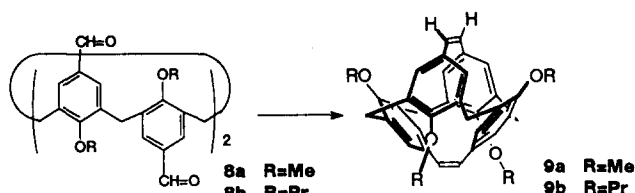


Figure 1. Titration curve of **6** with 1-MQ.

much lower than that of 1-MQ. The results indicate that **6** has the size-selective recognition ability.

We have realized that the McMurry reaction can offer us very interesting compounds based on 1,3-



Scheme 3. Preparation of cage derivative **9**.

alternate conformation. When tetrapropoxy derivative **8b**¹³ was submitted to the McMurry reaction according to Scheme 3, the intramolecular double-coupling product **9b** was isolated¹⁴ in 25% yield. A similar reaction of **8a**¹³ yielded derivative **9a** only in trace amount (<0.5%), again probably on account of polymeric products due to the non-

immobilized starting structure. ¹H NMR spectrum of **9b** (Figure 2) reflects high molecular symmetry of this compound without any unusual chemical shifts. The inner cavity of **9b** is perfectly closed by four aromatic units and represents a cage that can be suitable for complexation of small cations or molecules.

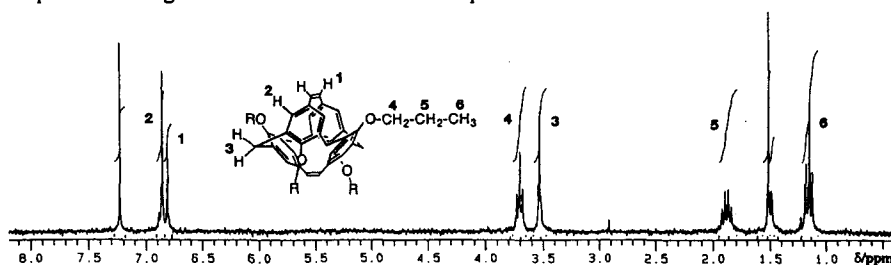


Figure 2. ¹H NMR spectrum of cage molecule **9b** (CDCl₃, 250 MHz, 25 °C).

In conclusion, we have demonstrated the usefulness of the McMurry reaction in the construction of calix[4]arene-derived supramolecular systems with unusual molecular structures, which can provide well delineated inner spaces useful for molecular recognition of quaternary ammonium salts.

References and notes

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- Diformyl derivative **1** was prepared by bromination of 26, 27-dipropoxycalix[4]arene with Br₂ in CHCl₃ at room temperature (96% yield), additional alkylation with propyl iodide/NaH in DMF at -5 °C (95%), lithiation with BuLi in THF and reaction with DMF (52%).
- Preparation of **3**: A solution of deriv. **1** (0.30 g, 4.62×10⁻⁴ mol) in 25 ml of THF was added dropwise during 2 h under reflux to the stirred suspension of TiCl₃ (0.43 g, 2.77×10⁻³ mol) and zinc dust (0.24 g, 3.70 ×10⁻³ mol) in 25 ml THF. Reaction mixture was then refluxed for 15 h, solvent was partly evaporated and filtered through the short column of silica-gel (CHCl₃) to remove inorganic materials. Filtrate was concentrated and submitted to preparative TLC (silica-gel, hexane:CHCl₃=6:1) to yield 0.070 g (30%) of product as a fraction with highest R_f, m.p. 170-172.5 °C (acetone). ¹H NMR spectrum (250 MHz, CDCl₃): δ 0.82 (t, 6H, J=7.5 Hz, O-CH₂CH₂CH₃); 1.10 (t, 6H, J=7.4 Hz, O-CH₂CH₂CH₃); 1.80 (m,

- 8H, O-CH₂CH₂CH₃); 3.15 (d, 4H, J=14.4 Hz, Ar-CH₂-Ar, eq); 3.68 (t, 4H, J=6.4 Hz, O-CH₂CH₂CH₃); 3.84 (t, 4H, J=6.4 Hz, O-CH₂CH₂CH₃); 4.42 (d, 4H, J=14.4 Hz, Ar-CH₂-Ar, ax); 5.41 (s, 4H, H-Ar); 6.53 (s, 2H, CH=CH); 6.94 (t, 2H, J=6.9 Hz, H-meta); 7.11 (d, 4H, J=7.4 Hz, H-para). EA calcd. for C₄₂H₄₈O₄: C, 81.77; H, 7.86%. Found C, 81.46; H, 7.80%.
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 10. Preparation of **4**: A mixture of **1** (0.30 g, 4.62×10⁻⁴ mol), TiCl₃ (0.43 g, 2.77×10⁻³ mol) and zinc dust (0.24 g, 3.70 ×10⁻³ mol) in 50 ml of THF was stirred at room temperature for 19 h and then filtered through the short column of silica-gel (CHCl₃) to remove inorganic materials. Filtrate was evaporated and purified by preparative TLC (silica-gel, hexane:CHCl₃=4:1) to yield 0.070 g (23%) of isomer **4A** (higher R_f) and 0.061 g (20%) of isomer **4B** (lower R_f). **4A**: m.p. 169-172 °C (acetone). ¹H NMR spectrum (250 MHz, CDCl₃): δ 0.88 (t, 6H, J=7.4 Hz, O-CH₂CH₂CH₃); 1.16 (t, 6H, J=7.4 Hz, O-CH₂CH₂CH₃); 1.86 (m, 8H, O-CH₂CH₂CH₃); 2.71 (s, 2H, CH-OH); 3.20 (d, 2H, J=14.2 Hz, Ar-CH₂-Ar, eq); 3.21 (d, 2H, J=14.2 Hz, Ar-CH₂-Ar, eq); 3.73 (t, 4H, J=6.3 Hz, O-CH₂CH₂CH₃); 3.90 (4H, J=7.8 Hz, O-CH₂CH₂CH₃); 4.47 (d, 2H, J=14.5 Hz, Ar-CH₂-Ar, ax); 4.49 (d, 2H, J=14.2 Hz, Ar-CH₂-Ar, ax); 4.60 (s, 2H, CH-OH); 5.44 (s, 2H, H-Ar); 6.02 (s, 2H, H-Ar); 7.05 (m, 2H, H-para); 7.21 (m, 4H, H-meta). EA calcd. for C₄₂H₅₀O₆: C, 77.49; H, 7.76%. Found C, 77.87; H, 7.75%. **4B**: m.p. 155-158 °C (acetone). ¹H NMR spectrum (250 MHz, CDCl₃): δ 0.81 (t, 6H, J=7.4 Hz, O-CH₂CH₂CH₃); 1.09 (t, 6H, J=7.4 Hz, O-CH₂CH₂CH₃); 1.79 (m, 8H, O-CH₂CH₂CH₃); 2.32 (brs, 2H, CH-OH); 3.13 (d, 2H, J=14.3 Hz, Ar-CH₂-Ar, eq); 3.15 (d, 2H, J=14.6 Hz, Ar-CH₂-Ar, eq); 3.64 (t, 4H, J=6.2 Hz, O-CH₂CH₂CH₃); 3.82 (t, 4H, J=7.9 Hz, O-CH₂CH₂CH₃); 4.14 (s, 2H, CH-OH); 4.36 (d, 2H, J=14.3 Hz, Ar-CH₂-Ar, ax); 4.42 (d, 2H, J=14.0 Hz, Ar-CH₂-Ar, ax); 5.28 (s, 2H, H-Ar); 5.87 (s, 2H, H-Ar); 6.96 (t, 2H, J=7.4 Hz, H-para); 7.13 (d, 4H, J=6.8 Hz, H-meta). EA calcd. for C₄₂H₅₀O₆: C, 77.49; H, 7.76%. Found C, 77.76; H, 7.75%.
 11. Araki, K.; Hisaichi, K.; Kanai, T.; Shinkai, S. *Chem. Lett.*, **1995**, 569-570. The association constant with 1-methylquinolinium iodide has been reported here for the similar bis-calixarene derivative (CH₂ group instead of CH=CH bond): K_c = 47 mol⁻¹ dm³, ¹H NMR spectroscopy, CDCl₃:CD₃CN=10:2 v/v, 24 °C.
 12. Preparation of **6**: The same procedure as for **3**, yield 35% m.p. 310-312 °C (EtOH-CHCl₃). ¹H NMR spectrum (400 MHz, CD₂Cl₂): δ 0.81 (t, 12H, J=7.4 Hz, O-CH₂CH₂CH₃); 1.02 (t, 12H, J=7.6 Hz, O-CH₂CH₂CH₃); 1.93 (m, 16H, O-CH₂CH₂CH₃); 3.16 (d, 4H, J=13.1 Hz, Ar-CH₂-Ar, eq); 3.18 (d, 4H, J=13.1 Hz, Ar-CH₂-Ar, eq); 3.81 (t, 8H, J=7.3 Hz, O-CH₂CH₂CH₃); 3.88 (m, 8H, O-CH₂CH₂CH₃); 4.45 (d, 8H, J=13.4 Hz, Ar-CH₂-Ar, ax); 6.50-6.60 (m, 16H, H-Ar, CH=CH); 6.66 (d, 4H, J=7.3 Hz, H-Ar); 6.77 (s, 4H, H-Ar). EA calcd. for C₆₂H₉₆O₈: C, 81.40; H, 8.01%. Found C, 81.08; H, 8.00%.
 13. Compound **8b** was prepared in 76% yield by the reaction of 25,26,27,28-tetrapropoxycalix[4]arene 1,3-alternate derivative with CF₃COOH and (CH₂)₆N₄. Derivative **8a** has been obtained analogously from 25,26,27,28-tetramethoxycalix[4]arene in 65% yield.
 14. Preparation of **9b**: The same procedure as for **3**, yield 30%, m.p. 280-281 °C (AcOEt) ¹H NMR spectrum (250 MHz, CDCl₃): δ 1.18 (t, 12H, J=7.3 Hz, O-CH₂CH₂CH₃); 1.91 (m, 8H, O-CH₂CH₂CH₃); 3.57 (s, 8H, Ar-CH₂-Ar); 3.74 (t, 8H, O-CH₂CH₂CH₃); 6.84 (s, 4H, CH=CH); 6.89 (s, 8H, H-Ar). MS (SIMS) 640 (M⁺).

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