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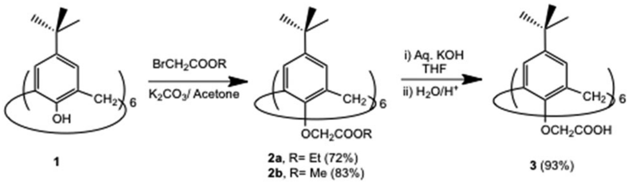
p-tert-Butylcalix[6]arene hexacarboxylic acid conformational switching and octahedral coordination with Pb(II) and Sr(II)†

Birendra Babu Adhikari,[ab] Keisuke Ohto[b] and Michael P. Schramm*[a]

p-tert-Butylcalix[6]arene hexaacetic acid is in a symmetric cone conformation in $CHCl_3$, but it becomes conformationally flexible in $CHCl_3/CH_3CN$ (1 : 1). In this mixture the host has a strong binding affinity towards Pb(II) and instantly forms a complex of low symmetry – shortly thereafter structural reorganization occurs resulting in a high symmetry complex of Pb(II) in an octahedral cage of carboxylates. Sr(II) and Ba(II) display similar behavior over a longer period of time.



Scheme 1 Synthesis of *p-tert*-butylcalix[6]arene hexacarboxylic acid **3**.

Recent attention has been devoted to the functionalization of calix[4]arenes resulting in supramolecular species with diverse functional properties. Cation binding of calix[4]arene derivatives is one area that has been well developed.[1] Unlike calix[4]arene whose thermodynamic preference is for a rigid C_{4v} cone conformation, calix[6]arene is flexible and of lower symmetry with phenyl groups alternating orientation in solution presenting challenges to characterization.[2] Only a few reports are available regarding the conformational behavior and solution structure of lower rim modified non-bridged calix[6]arene derivatives and their metal complexes.[3–7]

The *tert*-butyl ester of *p-tert*-butylcalix[6]arene (**2**, where R = *t*-butyl, Scheme 1) adopts a 1,2,3-alternate conformation in solution but changes to C_{6v} cone conformation upon complexation with K^+ and Cs^+.[5] For the corresponding ethyl ester (**2a**), no identifiable conformation was observed even at low temperatures,[6] but again this changed upon the addition of alkali metal cations.[5] The *p-tert*-butylcalix[6]arene hexaamide adopts a 1,2,3-alternate conformation in solution, two Na^+ ions fix the conformation as a cone.[7]

The specific role of carboxylic acid groups in the extraction of Pb(II) with calix[4]arene derivatives has been well addressed.[8] Recently, we reported on the very strong binding of *p-tert*-butylcalix[5]arene pentacarboxylic acid with Pb(II). The size-match effect resulted in a fixed cone conformation of the complex. Additionally, positive allosteric effects were observed as the host extracts two Pb(II) ions in stepwise.[9] We became interested in the behavior of the higher order *p-tert*-butylcalix[6]arene hexacarboxylic acid ligand **3** (Scheme 1).

The synthesis of *p-tert*-butylcalix[6]arene **1** and its ethoxycarbonylmethyl derivative **2a** has been described.[10] Compound **2b** was prepared in high yield following analogous methods. Alkaline hydrolysis of **2a** with aq KOH in THF and acidification afforded the corresponding hexacarboxylic acid **3**[10] in 93% yield.

The ^1H NMR of **3** in $CDCl_3$ suggests a regular cone conformation (distinct doublets at 3.41 and 4.49 ppm). Presumably this conformation is due to hydrogen bond interactions among six carboxylic acid groups.[11] In polar solvents loss of resolution and broadening occur (see ESI† for spectra in several polar solvents).

We titrated host **3** in $CDCl_3/CD_3CN$ (Fig. 1a) with Pb(II) and observed changes to the spectra. With 0.25 equivalents a new series of small peaks emerged (Fig. 1b). An additional 0.25 equivalents provided a more clear, yet complex spectra with numerous *sharp* resonances (Fig. 1c). The following were notable: (a) three pairs of doublets for Ar*H* protons with 1 : 1 : 1 : 1 : 1 : 1 integration, (b) six pairs of doublets for ArOCH_2 and ArCH_2Ar, (c) three *tert*-butyl peaks with 1 : 1 : 1 integration (see ESI†). These patterns, in particular the splitting of Ar*H* protons, are consistent with the observed K^+ complexed **2a** "lozenge" conformation.[5] The new signals coexist with those of the unbound ligand in a 1 : 1 ratio, indicating a strong 1 : 1 host guest complex. Addition of 1.0 equivalent Pb(II) resulted in the disappearance of the free ligand.

A few new, weak signals appeared (Fig. 1d) and at 1.5 equivalents (Fig. 1e) these new peaks were easier to identify.

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[a] *Department of Chemistry and Biochemistry, California State University Long Beach, 1250 Bellflower Blvd., Long Beach, 90840, CA, USA. E-mail: michael.schramm@csulb.edu; Fax: +1-562-985-8557*
[b] *Department of Chemistry and Applied Chemistry, Saga University, Honjo-1, 840-8502, Saga, Japan*

† Electronic supplementary information (ESI) available: All preparative procedures, titrations and CIF data are provided. CCDC 970239. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3cc48465c

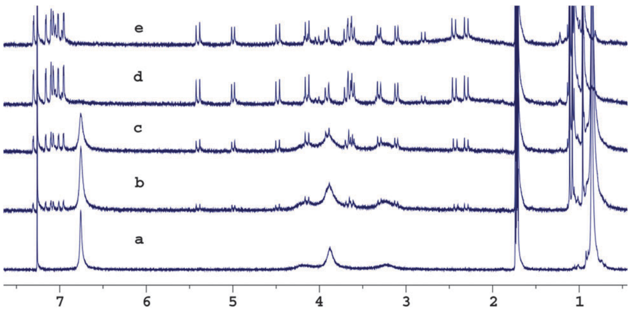

Fig. 1 ^{1}H NMR titration of **3** (5 mM) with various equivalents of $Pb(ClO_4)_2$ in $CDCl_3/CD_3CN$ = 1/1 at 300 MHz. (a) Free host and (b)–(e) in presence of 0.25, 0.5, 1.0 and 1.5 equivalents Pb(II), respectively. Residual solvent peaks $CHCl_3$ (7.26 ppm), CH_3CN (1.73 ppm), H_2O from $Pb(ClO_4)_2{\cdot}3H_2O$ (2.4 ppm, very broad).

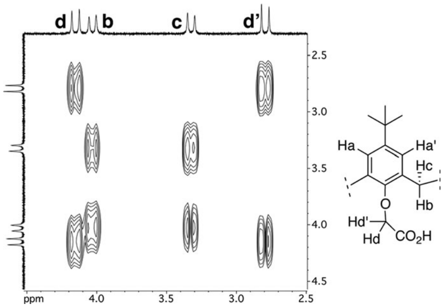

Fig. 3 Partial COSY NMR of **3** (5 mM) with 1 equivalent of $Pb(ClO_4)_2{\cdot}3H_2O$ at equilibrium in $CDCl_3/CD_3CN$ at 300 MHz.

Curious, we next acquired ^{1}H NMR spectrum of **3** in the presence of one equivalent Pb(II) over a period of one day and observed the shift from the initial spectra (Fig. 2a) to a new spectra comprised exclusively of the small peaks we initially observed in Fig. 1d. After 15 hours this new, sole species is of significantly higher symmetry than the initial lozenge (Fig. 2d); the Ar*H* region exhibits two doublets with *meta* coupling, the Ar*CH*$_2$Ar protons exist as a pair of sharp doublets indicative of a rigid conformation and the ArO*CH*$_2$ protons also exist as a pair of sharp diastereotopic doublets. The *tert*-butyl groups required 26 hours to come to equilibrium as one sharp signal and the ^{1}H NMR spectra remained the same after 15 days.

The carboxylic acid groups play a crucial role in this reorganization – ^{1}H NMR titrations of Pb(II) with ester **2b** exhibited a strong 1 : 1 host : guest complex at 1 equivalent of Pb(II) with similar spectral features as Fig. 1d – but no further changes were observed with additional Pb(II) or time (see ESI†).

Some similarities exist for **3**·Pb(II) with the site exchange of two identical complexes adopting C_{3v} symmetry of **2a**·Cs(I) complex at −30 °C.[5] However, in our case, the *tert*-butyl signal does not split into two and the spectrum remained the same in the temperature range of −20 °C to 60 °C (ESI†) indicating that all the phenyl units are arranged identically with respect to the metal ion. The Ar*CH*$_2$Ar protons in our case are separated by 0.71 ppm, far smaller than the separation of 1.15 ppm in C_{3v} flattened cone conformation[12] but close to the separation by 0.87 ppm for C_6 symmetrical cone conformation.[5] Furthermore, the six aryl carbons were non-equivalent as indicated by six ^{13}C signals and only one signal was observed for Ar*CH*$_2$Ar carbon at around 33 ppm.

The appearance of two distinct AB doublets for calixarene Ar*CH*$_2$Ar protons was consistent with a highly C_6 symmetrical cone conformation, but the diastereotopic ArO*CH*$_2$ protons and the *meta* coupling of Ar*H* posed a problem with assignment of such a simple structure. COSY and NOSEY afforded a complete assignment of protons for the **3**·Pb(II) complex – Hb and Hc were assigned as the Ar*CH*$_2$Ar protons (Fig. 3). Of the pair, Hb exhibits a more intense coupling to the aromatic Ha/Ha′ protons, consistent with the illustrated dihedral angle; the Ha/Ha′ to Hc cross peak was less intense. NOSEY on the other hand displayed a through space correlation between Ha/Ha′ and Hc but not Hb. Hd and Hd′ have a significantly large chemical shift difference for diastereotopic nuclei (J = 16 Hz, $\Delta\delta$ = 1.37 ppm) and NOE cross peaks between Hd′ and one of the Ha/Ha′ nuclei were observed. A small opposite phase peak that could indicate chemical exchange between d/d′ coexists within a larger NOE signal. No NOE cross peaks between Hd and neither Ha or Ha′ were observed, thus d and d′ are in distinct chemical environments (ESI† contains full COSY and NOESY).

High accuracy electrospray mass data of a 1 : 1 host : guest complex at equilibrium gave a base peak at *m*/*z* 3054.2599 corresponding to a dimeric structure [$C_{156}H_{189}O_{36}Pb_2$ (dimer + H^+) = 3054.2491]. The expected molecular ion was observed with a *m*/*z* 1527.6349 [$C_{78}H_{95}O_{18}Pb$ (host:guest + H^+) = 1527.6285] with 40% intensity of the base peak. Our initial thought was to explore the possibility of the formation of a dimeric solution structure with time. The ^{1}H and 2D NMR evidences along with changes to simple features such as the carboxylic acid resonance[13] in conjunction with MS data gave some support for this idea. Indeed similar NMR features are observed in other H-bonded dimeric structure at equilibrium including splitting patterns for a assemblies of calix[4]arene urea hydrogen bond dimers[14,15] and a calix[6]arene dimer formed by hydrogen bonded interactions of leucine amino acid groups introduced at the lower rim.[16]

We attempted to confirm this solution structure with DOSY NMR. A sample of **3** in the presence of 0.5 equivalents Pb(II) was allowed to come to equilibrium resulting in a 1 : 1 mixture of free **3** and the **3**·Pb(II) complex. The free ligand **3** had an average diffusion coefficient of 4.823×10^{-10} m^2 s^{-1} (average of 3 signals), while the signals from the host–guest complex had an average of 4.716×10^{-10} m^2 s^{-1} (average of 5) (uncorrected $CDCl_3$ = 2.324×10^{-9} m^2 s^{-1}) (see ESI†). Based on the observed molecular weight differences these results were

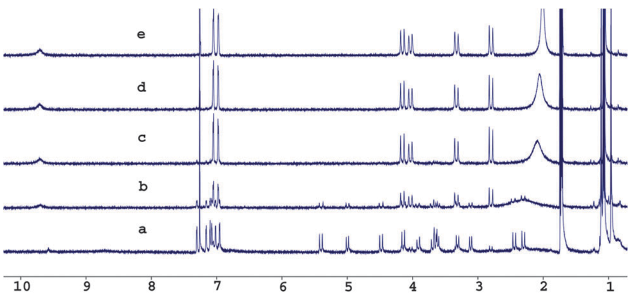

Fig. 2 ^{1}H NMR of **3** (5 mM) with 1 equivalents of $Pb(ClO_4)_2{\cdot}3H_2O$ in $CDCl_3/CD_3CN$ = 1/1 at 300 MHz. (a) At the time of mixing and (b)–(e) after 4, 12, 15, 24 hours respectively. Residual solvent peaks $CHCl_3$ (7.26 ppm) and CH_3CN (1.73 ppm). The broad signal at around 2 ppm is due to H_2O from $Pb(ClO_4)_2{\cdot}3H_2O$.

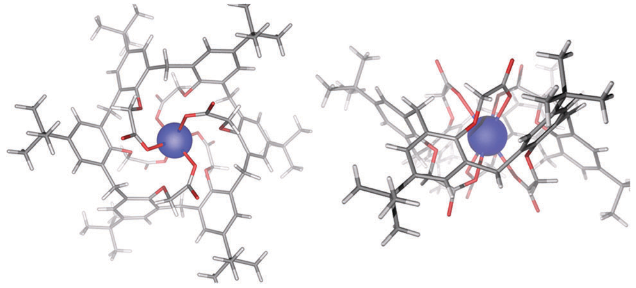

Fig. 4 Rendered X-ray crystal structure of equilibrium host **3**–Pb(II) guest complex. Cropped top side views.

not consistent with a dimeric structure. Curious we reran the high accuracy MS experiment at time of mixing and then again at 24 hours and observed the same MS data at both time points – a dimeric MS structure prevailed in both experiments and the molecular ion for the monomer was 40% the intensity of the base peak (see ESI†). The observed dimer is likely an artifact of the measurement and unrelated to structure as we observed two distinctly different species by ^{1}H NMR in solution at time of mixing (Fig. 2a) and after 24 hours only one (Fig. 2d).

Single crystal X-ray difraction data (Fig. 4)‡ resolved the incongruous NMR and MS data – a newly observed octahedral cage of carboxylates formed around Pb(II)! The aromatic rings of calix[6]arene **3** alternate up and down with respect to the plane of the metal center – the carboxylate oxygens poised perfectly at 2.725 Å to provide an octahedral coordination environment for Pb(II). The six ethers also point inward with oxygen–Pb distances of 2.887 Å (see ESI†). Careful inspection of the solid state structure fully resolved our ^{1}H and 2D NMR observations – the aromatic Ha and Ha′ resonances become non-equivalent due to an in *vs.* out twist in the solid state structure. The Ar*CH*$_2$Ar are sharp and fully consistent in this alternating arrangement. The diastereotopic ArO*CH*$_2$ along with NOSEY correlation between Hd′ and the aromatic protons Ha/Ha′ is now easily understood.

This newly observed geometry and behavior for calix[6]arene is the result of an initially fast and strong binding event that gives rise to a low symmetry structure; this slowly undergoes conformational switching to a very high symmetry and stable structure.[17] Hexacoordinate Pb(II) has an ionic radius of 133 pm and we found that hexacoordinate Sr(II) with a radius of 132 pm undergoes the same initial binding event, but coerces calix[6]arene into an octahedral cage rather slowly – the NMR solution structure after 360 hours has all the same H NMR features that we observed for Pb(II) after 15 hours. Preliminary single crystal X-ray data reveals an identical space group and unit cell (see ESI†). The larger (149 pm) hexacoordinate Ba(II) again binds strongly to **3**, but undergoes conformational reorganization even slower than the **3**·Sr(II) complex. After 360 hours there exists a 1 : 1 mixture of the initially formed low symmetry complex and the high symmetry cage structure (see ESI†). These effects are likely a combination of both size of the cation and their affinity for carboxylates.[18] No evidences of strong binding of **3** with Ca(II), Cu(II), Bi(III), Y(III), Gd(III) and UO$_2$(II) in CDCl$_3$/CD$_3$CN exists at this time (see ESI†). Work with these cations in other solvent systems is ongoing.

The application of calixarenes to separation and extraction sciences can be used to address environmental challenges. Remediation of heavy metals and radionuclides is one such ongoing challenge – a highly selective host may provide new opportunities to extract and/or transport those cations. In this regard, **3** holds great potential for applications to the environmentally malevolent Pb(II) as well as ^{90}Sr(II) polluted nuclear wastes. The events of conformational change with time and this newly observed octahedral cage geometry for calix[6]arene add to an already rich field of supramolecular science but may also hold promise for the development of novel metal organic frameworks.

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Notes and references

‡ Single-crystal X-ray analysis was performed on a Bruker Smart APEX II CCD area diffractometer using MoKα radiation ($\lambda = 0.71073$ Å), operating in the ω and φ scan mode over a range of $1.02 \leq \theta \leq 25.01$, SADABS was used and the structure was solved by direct methods, all non-hydrogen atoms were refined anisotropically and disordered solvent was resolved with SQUEEZE[19] and ascribed to one H_2O per unit formula, SHELXTL 97 was used for final full-matrix refinements were against F^2. $C_{78}H_{96}O_{18}Pb(H_2O)$, 1546.65 g mol^{-1}, cubic, 28.3035(7) Å, 90.00°, 22673.6(17) Å^3, su max = 0.000, su mean = 0.000, 150 K, $Pn\bar{3}n$, $Z = 8$, independent reflections = 3367, $R = 0.0424$, w$R = 0.1243$ and $S = 1.080$.

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