Approaches to polymetallated calixarene derivatives

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Abstract
Tetrabrominated calix[4]arene analogue 4 was subjected to lithium-halogen exchange with tert-butyl lithium to give a tetra-lithium salt which could be silylated with chlorotrimethylsilane to give tetrasilylated derivative 5 and the trisilylated analogue 6. However, attempts to use boron electrophiles resulted in only partial boronation. Attempts to brominate calix[6]arene 12 proved surprisingly difficult, which prevented the isolation of 13 and hence generation of the corresponding hexa-lithium salt. Bromination of calix[8]arene 14b was possible and the octa-lithium salt was generated by lithium-halogen exchange of 15 with tert-butyl lithium. Subsequent reaction with chlorotrimethylsilane though, only resulted in partial silylation to give 16.

Keywords: Calixarene, metallation, silylation, boronation

Introduction

Calixarenes1, the cyclic products of the condensation of molecules such as para-substituted phenol and formaldehyde, represent a class of receptor which is readily available in varying ring sizes, particularly 1a-c. These receptors have been widely used for ligating cations and neutral organic molecules in solution, due to: (i) their ease of access via simple one-pot processes; (ii) their formation of well defined stable cyclic derivatives possessing varying cavity sizes suitable for binding different guests; (iii) their ease of chemical modification, and functionalisation. However, the synthesis of anion binding derivatives of benzenoid calixarenes has been much less studied2, with no reported examples of calixarenes containing Lewis-acid metals directly attached to the benzene rings. The only examples of the construction of calixarene-based Lewis-acidic receptors have relied upon attaching the metals to the oxygen moieties of calixarenes such as 1a3, for example bis-tetraalkoxy silanes3a which can act as anion or Lewis-base acceptors.

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Poly-Lewis-acidic receptors\(^4\) have been applied as selective binding agents for various Lewis-basic systems, such as carbonyl groups\(^5\) and anions\(^6\) and have even been recently used as Diels-Alder catalysts\(^7\). However, systems containing four\(^5\) or more Lewis-acidic groups are extremely rare, despite the fact that it has been shown that the four mercury atoms of a [12]mercuracarborand can behave cooperatively to bind chloride ion\(^6\)\(^m\).

We became interested in developing new poly-Lewis-acid based receptors containing four, six and eight Lewis-acid functions and viewed calixarenes as suitable relatively rigid frameworks for the attachment of multiple metals, for example structures 2, with the expectation that such systems would behave cooperatively to bind anions as shown schematically by Figure 1. In this paper we report our approaches to the synthesis of polymetal-substituted calixarenes, using silicon to demonstrate the methods for poly-metal attachment.
Results and Discussion

The possibility of incorporating silicon, with a view to attaching Lewis-acidic atoms such as boron, onto the benzene rings of calixarenes was initially explored using the calix[4]arene ring system 1a since it possesses both minimal functionality and conformational flexibility\(^1,8\). Calixarene 1a\(^9\) was therefore subjected to removal of the tert-butyl groups, followed by O-methylation\(^9\) and bromination\(^10\) using similar methods to those reported in the literature. Thus, calixarene 1a was converted into compound 4 as shown in Scheme 1.

\[ \text{Scheme 1.} \text{ De-tert-butylation bromination on the calix[4]arene.} \]

After obtaining 4, it was possible to examine different methods for obtaining the tetra(trimethylsilylated)calix[4]arenes 5. After much experimentation, it was found that the lithiation of 4 was possible, but only by using an excess of tert-butyllithium (3 equivalents per bromine), followed by silylation with excess chlorotrimethylsilane (Equation 1). Silica gel
chromatography gave two compounds with similar mobility, which could be separated by fractional recrystallisation to give compound 5 (21%) and 6 (32%).

\[
\begin{align*}
\text{4} & \xrightarrow{\text{1BuLi, THF, -78 °C, then}} \text{Me}_3\text{SiCl, -78 °C to r.t.} \\
\text{SiMe}_3 & \quad + \quad \text{SiMe}_3 \\
\text{OMe} & \quad \text{5} & \quad \text{OMe} & \quad \text{4} & \quad \text{OMe} & \quad \text{6}
\end{align*}
\]


The successful synthesis of the silylated calixarenes 5 and 6 was then extended to boronation using standard methods consisting of lithiation of 4 followed by reaction with various boron electrophiles, such as trialkylborates and trihaloboranes. For example, 4 was reacted with excess tert-butyllithium, followed by addition of excess trimethylborate. In separate reactions, both pinacol and ethylene glycol were added to the reactions in order to isolate stable boronate esters of type 7 and 8 respectively. After the reaction, white solids were obtained, however, these solids (reactions A and B) were insoluble in organic solvents. The +ve ion f.a.b. mass spectrum of the solid from reaction B did show peaks at m/z 621, 620, 619, 618 (corresponding to M + H⁺ and M⁺ of 10 rather than 8), but when the experiments were repeated via the boronic acid intermediate¹¹ followed by addition of pinacol or ethylene glycol (reaction C and E, **Scheme 2**), no tractable material could be isolated. The main problem with reactions C and E (**Scheme 2**) seemed to be the high solubility of the reaction product in water.

In order to obtain more direct evidence for the attachment of boron to the benzene rings of the calix[4]arenes ring system, 4 was lithiated, quenched with trimethylborate, and the crude product subjected to oxidation with H₂O₂/NaOH¹². The crude products were then acylated to obtain 9 (reaction D, **Scheme 2**). A white solid was obtained, whose mass spectrum showed peaks at m/z 538 and 481 corresponding to (M + H⁺) of 11 and 3b respectively. This result suggests that intramolecular lithioaryl aggregation may be responsible for the formation of unreactive intermediates, which fail to react cleanly with the boron electrophiles.
The use of alternative boron electrophiles after lithiation of 4, i.e. boron trifluoride, boron trichloride and boron tribromide (to lead to 2a, X = F, Cl, and Br respectively), under a variety of reaction conditions, also led to the formation of complex product mixtures from which pure
materials could not be isolated. However, having produced the tetra(trimethylsilyl) derivative 5, an alternative route to boron Lewis-acid receptors 2a (X = Cl or Br) might involve a desilylation-boronation reaction of 5, with either boron trichloride or boron tribromide. Unfortunately, quantitative and rapid demethylation and desilylation occurred to give 3a in each case after hydrolysis.

Having been successful in incorporating trimethylsilyl groups onto the calix[4]arene ring system, attention was focused to the next larger member of the benzenoid calixarene family, i.e. the calix[6]arene ring system. The cavities of the calix[6]arenes are larger than those of the calix[4]arenes, and therefore should have better properties for the formation of inclusion complexes13. However, the calix[6]arenes have received little attention, mainly because of their higher degree of functionality and flexibility (which normally makes their chemistry more complex14,15 than that of the calix[4]arenes. To combat this problem, functionalization (e.g. hexa-O-alkylation) could be envisaged as a means of controlling the ring flexibility, and therefore modulating the properties of the calix[6]ene derivatives.

In order to prepare the trimethylsilyl derivatives of the calix[6]arenes, the bromo-derivative had to be prepared first for metalation and reaction with chlorotrimethylsilane. The starting material 1b9 was converted to 12b as shown in Scheme 3. However, compound 12b could not be brominated cleanly under a variety of conditions, such as N-bromosuccinimide in 2-butanone with sonication and bromine/iron(III) bromide. Failure to brominate 12b was thought to be largely due to the insolubility of this material, thus the more soluble calix[6]arene derivatives 12c and 12d were employed (Scheme 3) and subjected to bromination over extended periods in order to access 13c and 13d respectively.

\[
1b \quad \xrightarrow{1) \text{AlCl}_{3}, \text{phenol, toluene, 48 %}.} \quad 12 \quad \xrightarrow{2) \text{Base, RI, DMF, D, 41-87 %}.} \quad 13
\]

\[
\begin{align*}
12 & \quad \xrightarrow{\text{NBS, 2-butanone,}} \\
\text{a; } & \quad R = H \\
\text{b; } & \quad R = \text{Me} \\
\text{c; } & \quad R = (\text{CH}_2)_9\text{CH}_3 \\
\text{d; } & \quad R = (\text{CH}_2)_4\text{CH}_3 \\
13 & \quad \xrightarrow{\text{a; } R = H} \\
\text{b; } & \quad R = \text{Me} \\
\text{c; } & \quad R = (\text{CH}_2)_9\text{CH}_3 \\
\text{d; } & \quad R = (\text{CH}_2)_4\text{CH}_3
\end{align*}
\]


Since it was not possible to brominate the calix[6]arene ring system, the calix[8]arene ring system was then examined to find out it would prove more convenient to brominate and hence
access the trimethylsilylated derivative. Thus removal of the tert-butyl groups of 1c gave 14a, which was methylated to give 14b (Scheme 4).


Bromination of 14b was possible using N-bromosuccinimide in a 3:5 mixture of toluene and 2-butanone under sonication to give 15 in 53% yield. Lithiation of 15 with excess tert-butyl lithium followed by reaction with chlorotrimethylsilane (Equation 2) gave a major product 16, i.e. with only two trimethylsilyl groups attached. Considerable manipulation of the reaction conditions failed to improve the efficiency of this process, which again suggests that relatively stable, hindered intramolecular poly-lithium complexes are formed as intermediates, which are unreactive towards electrophiles larger than a proton.


Summary

Although calix[4]arene 3b was converted into the corresponding tetrakisylated derivative 5 using a bromination, lithiation, and silylation sequence, attempts to use boron electrophiles in place of silicon resulted in only partial boronation. Attempts to brominate calix[6]arenes 12 proved surprisingly difficult, which prevented the isolation of 13 and hence generation of the
corresponding hexa-lithium salt. However, bromination of calix[8]arene 14b was possible and the octa-lithium salt was generated by lithium-halogen exchange of 15. Subsequent reaction with chlorotrimethylsilane though, only resulted in partial silylation to give 16. Alternative strategies for the construction poly-Lewis-acid receptors are under investigation.

**Experimental Section**

**General Procedures.** Dichloromethane was distilled over calcium hydride. Light petroleum refers to the fraction boiling in the range 40-60 °C. Anhydrous tetrahydrofuran was distilled prior to use over benzophenone-ketyl. All other compounds were purchased from Aldrich and were used without further purification. T.l.c. was performed on Merck plastic or aluminium sheets coated with silica gel 60 F254 (Art. 5735); the chromatograms were initially examined under u.v. light and then developed either with iodine vapour or an ethanolic anisaldehyde (1.0 %) solution containing sulfuric acid (9%) used as a spray and visualised by heating with a heat gun. Column chromatography was achieved under medium pressure or under gravity, using Merck Kieselgel H (Type 60) or Prolabo neutral alumina (50-160 mm). All anhydrous, low temperature reactions were carried out in glassware which was dried prior to use by storage in a glass oven maintained at 140 °C and cooled under a stream of argon. All organic extractions were dried with anhydrous magnesium sulfate or anhydrous sodium sulfate. Evaporations were carried out using a Büchi rotary evaporator or Büchi cold-finger rotary evaporator, followed by evaporation under high vacuum (typically at approximately 2 mmHg). Kugelruhr distillations were carried out using a Büchi KGR-51 Kugelrohr apparatus. Melting points were determined using an Electrothermal melting point apparatus and were uncorrected. ¹H spectra were recorded at 200 or 300 MHz on a Bruker AC200 or AC300 n.m.r. spectrometer. ¹³C spectra were recorded at 75 MHz on a Bruker AC300. Both ¹H and ¹³C spectra were recorded using CDCl₃ and CHCl₃ as internal standards respectively. I.r. spectra were recorded on a Perkin-Elmer 783 equipped with a PE600 data station or Perkin-Elmer 598 and u.v. spectra were recorded on a Perkin-Elmer 115 spectrometer. Electron impact (e.i.) (70 e.v.) and chemical ionisation (c.i.) spectra were recorded with a Kratos MS25. Fast atom bombardment (f.a.b.) spectra were recorded on a Kratos MS50, using a meta-nitrobenzyl alcohol matrix and accurate mass determinations were carried out on a Kratos Concept IS spectrometer. Microanalyses were performed using a Carlo-Erba 1106 elemental analyser.

**Preparation of 5,11,17,23-tetra(trimethylsilyl)-25,26,27,28-tetramethoxycalix[4]arene (5a) and 5,11,17-tris(trimethylsilyl)-25,26,27,28-tetramethoxycalix[4]arene (6).** To a stirred solution of 4 (0.500g, 0.63mmol) in tetrahydrofuran (30 ml) was added tert-butyllithium (4.50 ml, 7.65 mmol) dropwise at -78 °C under argon. The reaction mixture was stirred at -78 °C for 0.5 h and a further 0.5 h at room temperature. Chlorotrimethylsilane (4.00ml, 31.70mmol) was added dropwise to the resulting yellow solution at -78 °C. After stirring for 0.5h at room temperature, the reaction mixture was heated under reflux for 45 min, washed with a saturated
aqueous solution of ammonium chloride (2 x 50 ml), dried, filtered and concentrated to yield a light yellow oil (0.510g). Purification by silica gel column chromatography (toluene as eluant) gave the first fraction as a white crystalline solid (0.290 g) which showed 2 spots by t.l.c. (toluene). Fractional recrystallisation from dichloromethane/methanol yielded compound 5a as white crystals (0.100g 21%): M.p. 238-240 °C; $\nu_{\text{max}}$ (KBr disc) inter alia 3020 (Ar-H), 2960, 2820 (C-H), 1585 (C=C); $\delta$ (1H, 300 MHz, CDCl3) 0.00-0.20 (36H, m, 12 x CH3Si); 2.71, 3.01, 3.16, 3.33, 3.51, 3.56, 3.76, 4.15 (20H, all br s, 4 x CH2 and 4 x CH3O), 6.86, 7.06, 7.13, 7.21, 7.88 (8H, all br s, aromatic); $\delta$ (13C, CDCl3) -1.2 (12 x CH3Si), 29.1, 30.3, 36.7 (4 x CH2), 60.0 (4 x CH3O), 132.7, 133.1, 133.5, 133.7, 134.4, 135.0, 135.5, 158.1 (aromatic); m/z (+ve e.i.) 768 (M+, base peak); Accurate mass, C44H64O4Si4; requires: m/z 768.3882, found: 768.3886.

Preparation of 37,38,39,40,41,42-hexapentyloxycalix[6]arene (12d). A mixture of 12a (0.100g, 0.16mmol), barium hydroxide octahydrate (1.500g, 4.76mmol), 1-iodopentane (1.60ml, 12.57mmol) in dimethylformamide (30ml) was stirred at room temperature for 4 d. Water (20ml) added, the mixture was extracted with chloroform (2 x 50ml), dried, filtered and concentrated to yield a light yellow liquid. Trituration with methanol (10ml) yielded a light yellow solid (0.120g). Recrystallization from chloroform/methanol gave compound 12d as light yellow crystals (0.090g, 51%): M.p. 181-183 °C; $\nu_{\text{max}}$ (KBr disc) inter alia 3060, 3020 (Ar-H), 2920, 2860 (C-H), 1585 (C=C) cm$^{-1}$; $\delta$ (1H, 300 MHz, CDCl3) 0.95 (18H, t, J 7.5 Hz, 6 x CH3), 1.32 (36H, m, 6 x (CH2)$_3$), 3.22 (12H, br s, 6 x OCH2), 3.92 (12H, br s, 6 x ArCH2Ar), 6.80 (6H, t, J 7.5 Hz, 6 x CCHCH), 7.02 (12H, br s, 12 x CCHCH); $\delta$ (13C, CDCl3) 14.2 (6 x CH3), 22.8, 26.5, 30.0 (6 x CH2)8, 32.1 (6 x ArCH2Ar), 72.8 (6 x OCH2), 123.4 (5 x COCH2), 132.4 (6 x CCHCH), 152.4 (6 x COCH2); Analysis, C72H96 O6.1/8CHCl3, requires: C, 80.7; H, 9.0; Cl, 1.2; found: C, 80.7; H, 9.2; Cl, 1.4%.

Preparation of 37,38,39,40,41,42-hexadecyloxycalix[6]arene (12c). A mixture of 12a (0.110g, 0.10mmol), barium hydroxide octahydrate (1.500g, 4.76mmol) and 1-iododecane (2.00ml, 9.36mmol), in dimethylformamide (30ml) was heated at 100 °C for 24h. Water (50ml) added and extracted with chloroform (3 x 50ml), dried, filtered and concentrated to yield a light yellow liquid. Trituration with methanol (10ml) yielded a light yellow solid (0.120g). Recrystallization from chloroform/methanol gave compound 12c as white crystals (0.090g, 64%): M.p. 66-68 °C; $\nu_{\text{max}}$ (KBr disc) inter alia 3060, 3020 (Ar-H), 2920, 2860 (C-H), 1585 (C=C) cm$^{-1}$; $\delta$ (1H, 300 MHz, CDCl3) 0.90 (18H, m, 6 x CH3), 1.30 (96H, s, 6 x (CH2)$_8$), 3.25 (12H, br s, 6 x COCH2), 3.92 (12H, br s, 6 x ArCH2Ar), 6.77 (6H, br m, 6 x CCHCH), 7.00 (12H, br s, 12 x CCHCH); $\delta$ (13C, CDCl3) 14.3 (6 x CH3), 22.9, 26.5, 30.0, 30.5 (6 x CH2), 32.1 (6 x ArCH2Ar), 73.0 (6 x OCH2), 123.4
(6 x CCHCH), 129.1 (12 x CCHCH), 134.8 (12 x CCHCH), 155.3 (6 x COCH2); Analysis, C102H15O6, requires: C, 82.9; H, 10.6; found: C, 82.6; H, 10.9%.

**Preparation of 5,11,17,23,29,35,41,47-octabromo-49,50,52,53,54,55,56-octamethoxyxycalix[8]arene (15).** A mixture of 14b (0.800g, 0.88mmol) and N-bromosuccinimide (2.070g, 11.63mmol) in 2-butanone (50ml) and toluene (30ml) was sonicated for 45min and stirred at room temperature for 3d. The reaction mixture was washed with a 10% aqueous solution of sodium bisulfite (70ml) and extracted with toluene (3 x 50ml), dried, filtered and concentrated to yield a white solid. Recrystallization from chloroform/methanol afforded 15 as white crystals (0.69 g, 53%): M.p. 295-297 °C; υ\text{max} (KBr disc) \textit{inter alia} 3020, 3000 (Ar-H), 2940, 2820 (C-H), 1510 (C=C) cm\textsuperscript{-1}; δ (\textsuperscript{1}H, 300 MHz,CDCl\textsubscript{3}) 3.54 (24H, s, 8 x CH\textsubscript{3}O), 3.94 (16H, s, 8 x ArCH\textsubscript{2}Ar), 7.01 (16H, s, 16 x CCHC); δ (\textsuperscript{13}C, CDCl\textsubscript{3}) 30.0 (8 x ArCH\textsubscript{2}Ar), 61.1 (8 x CH\textsubscript{2}O), 117.2 (8 x CBr), 132.0 (16 x CHCB\textsubscript{r}), 135.9 (16 x C\textsubscript{H}CH), 155.7 (8 x COCH\textsubscript{3}); m/z (e.i) \textit{inter alia} 1586, 1587, 1588, 1589, 1590, 1591, 1592, 1593 (base peaks), 1594, 1595, 1596, 1597, 1598, 1599 (all M + H\textsuperscript{+}); Analysis, C\textsubscript{64}H\textsubscript{56}O\textsubscript{8}.2CHCl\textsubscript{3}.MeOH, requires: C, 42.9; H, 3.3; Br, 34.1; Cl, 11.9; found: C, 42.8; H, 3.3; Br, 33.9 Cl, 12.2%.

**Preparation of calix[8]arene (16).** To a stirred solution of 15 (0.20 g, 0.13mmol) in tetrahydrofuran (20ml) was added tert-butyllithium (1.80 ml, 3.01 mmol) dropwise at -78 °C under argon. The reaction mixture was stirred at -78 °C for 1 h. Chlorotrimethylsilane (1.50 ml, 11.89 mmol) was added dropwise to the resulting yellow solution at -78 °C. After stirring for 0.5h at room temperature, the reaction mixture was heated under reflux for 3h, washed with a saturated aqueous solution of ammonium chloride (2 x 50ml), dried, filtered and concentrated to yield a light yellow oil (0.291g) which crystallized upon standing. Methanol (5ml) was added and filtered to yield the title compound as a cream solid (0.073g, 53%): δ (\textsuperscript{1}H, 300 MHz,CDCl\textsubscript{3}) 0.13 (18H, m, 6 x CH\textsubscript{3}Si), 3.53 (24H, m, 8 x CH\textsubscript{3}O), 4.05 (16H, s, 8 x ArCH\textsubscript{2}Ar), 6.80 and 7.10 (22H, m, aromatic); δ (\textsuperscript{13}C, CDCl\textsubscript{3}) -0.9 (6 x CH\textsubscript{3}Si), 29.9, 30.2, (8 x ArCH\textsubscript{2}Ar), 60.8 (8 x CH\textsubscript{3}O), 124.0, 129.0, 129.1, 133.2, 134.3, 134.4, 156.7, 157.7 (aromatic C’s).

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References


