



Self-assembly of calix[4]arene amine derivatives



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ABSTRACT

Self-assembly can occur spontaneously in solution for calix[4]arenes substituted at both the upper and lower rims with flexible pendant groups containing aromatic rings. This self-assembly occurs in both a head-to-tail and head-to-head manner, as proven by NOESY experiments.

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1. Introduction

The concept behind self-assembly is the spontaneous and reversible association of building blocks into well-defined structures via non-covalent interactions.¹ The study of these non-covalent interactions has been greatly enhanced by research into macrocyclic calixarene molecules.^{2–6} Calix[4]arenes are one of the most versatile building blocks in supramolecular chemistry, in the fabrication of molecular devices and supramolecular architectures, as they possess a framework, which allows the introduction of appropriate binding cores at either the upper or the lower rim.^{7–14} Indeed, over the past 20 years, a great deal of interest has been generated in the self-assembly of calix[4]arenes resulting in the inclusion of small molecules, which can then be separated from the bulk solution.^{15–22} As part of our on-going research into calix[4]arene derivatives as potential ligands for energy transfer studies,^{23,24} we targeted the attachment of functional groups containing nitrogen donor atoms to both the upper and lower rims of our calix[4]arene scaffolds directly, without using the nitration route we had previously published.²³ This paper reports on the unexpected and spontaneous self-assembly in solution of these calix[4]arene derivatives.

2. Results and discussion

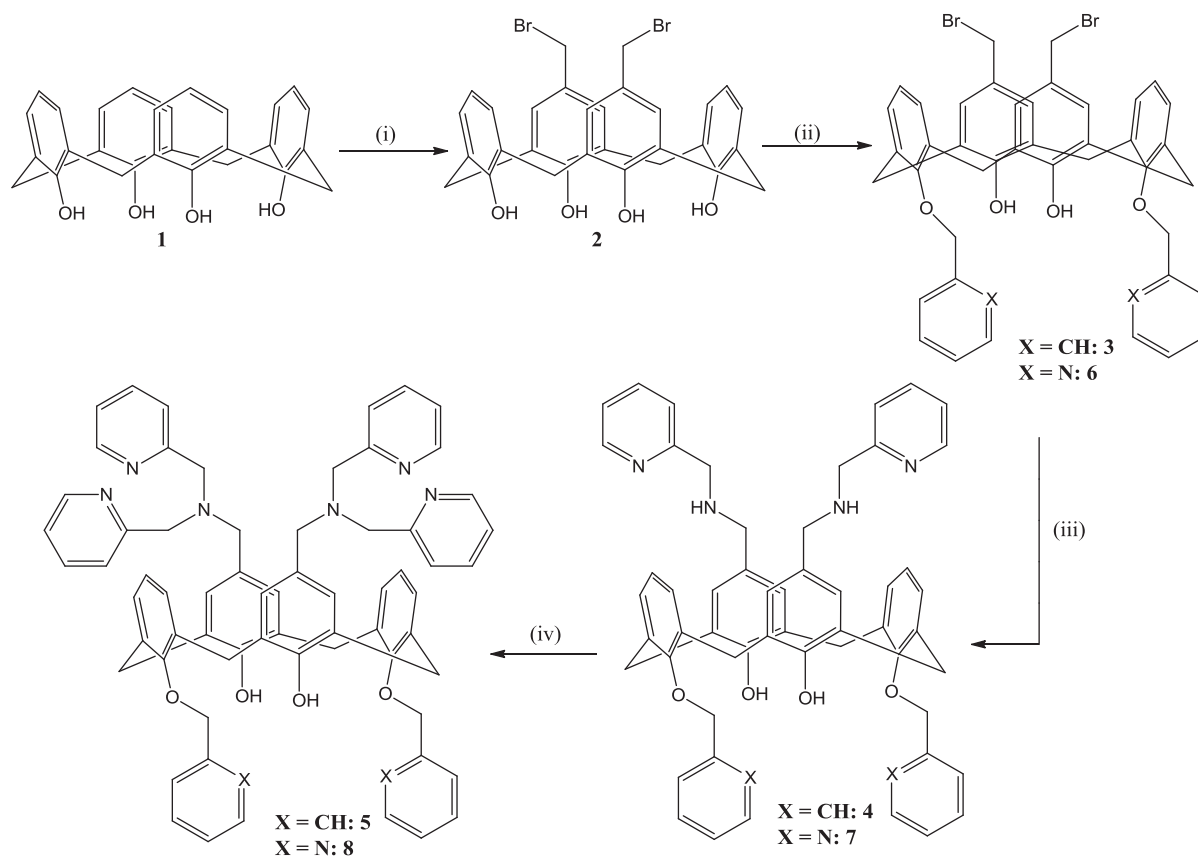
Scheme 1 shows the synthetic approach chosen for the benzyl (**3–5**) and pyridyl (**6–8**) derivatives. The upper rim chloromethylation

of calix[4]arenes has been reported by Gutsche,²⁵ Ungaro²⁶ and Pochini²⁷ for calix[4]arene derivatives containing two *tert*-butyl groups on the upper rim and alkyl derivatives on the lower rim. These methods involved the use of either SnCl₄ with chloromethyl *n*-octyl ether or the formation of the methyl alcohol and its conversion to the chloromethyl derivative with thionyl chloride. However, neither of these reactions was successful when we started with tetrahydroxycalix[4]arene (**1**). On the other hand, the reaction of **1** with formaldehyde in the presence of Zn–HBr in glacial acetic acid^{28–30} resulted in the formation of **2** in almost quantitative yield. The ¹H NMR spectrum of **2** shows sharp signals for the aromatic and hydroxyl protons but broad signals for both the methylene bridges and bromomethylene group, which was taken to be an indication of conformational change in solution since the lower rim and two positions of the upper rim are unsubstituted. The signal for the hydroxyl protons is almost the same in compounds **1** and **2**, indicating that hydrogen bonding between the hydroxyl groups is occurring in both cases, which would suggest that the major form of **2** in solution is the cone conformation.

Derivatisation of the lower rim of **2** with either benzyl groups or methylpyridine groups, using previously reported methods,²³ resulted in the formation of the cone conformers of both **3** and **6**. The attachment of both of those groups was evident in the ¹H NMR spectra of both **3** and **6** as a result of the OCH₂ signal at 5.12 and 5.16 ppm, respectively. We have ascertained that the benzyl or pyridylmethyl groups are not attached to the oxygen atom *para* to the bromomethyl substituents through an HMBC NMR experiment.

The reaction at the upper rim of either **3** or **6** with 2-aminomethylpyridine resulted in **4** and **7**, which were waxy

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Scheme 1. Reaction conditions: (i) formaldehyde, Zn–HBr, glacial acetic acid, 90 °C, 72 h; (ii) K₂CO₃, benzyl bromide or 2-aminomethylpyridine hydrochloride, MeCN, Δ, 18 h; (iii) 2-aminomethylpyridine, MeCN, Δ, 6 h; (iv) 2-aminomethylpyridine hydrochloride, DCM, Δ, 8 h.

solids in both cases. CHN analyses confirmed the formation of **4** and **7**. However, the ¹H NMR spectra of both **4** and **7** did not show the expected signals for the proposed structures (see Fig. 1). There appeared to be several species present in solution, which could not be accounted for, given the CHN results. Furthermore, TLC analysis suggested the presence of a single species. Therefore, two possibilities that could explain this unexpected increase in signals in the ¹H NMR spectra of **4** and **7** were (i) conformational change in solution, that is, forming the partial cone, 1,2-alternate or 1,3-alternate conformers in solution, or (ii) self-assembly. We did not believe that conformational change was occurring, as such a change had never been previously observed in our laboratory and there was no metal ion present in the reaction to initiate that type of transformation. The alternative explanation of self-assembly was a possibility but required further investigation.

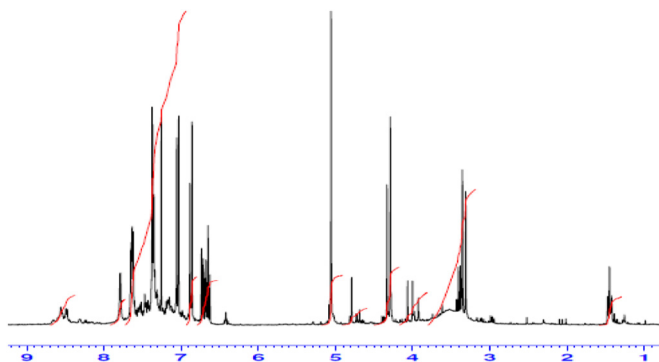


Fig. 1. The ¹H NMR spectrum of **4** obtained in CHCl₃.

We decided to react **3** and **6** with 2-aminoethylpyridine to give **9** and **10** (see Scheme 2) to see if the ¹H NMR spectra obtained would be similar to those obtained for **4** and **7**. We synthesised **9** and **10** in good yields using similar procedures to those for **4** and **7** (see Scheme 2). A similar increase in the number of signals observed in the ¹H NMR spectra of compounds **9** and **10** were observed. Again, CHN analyses confirmed the formation of **9** and **10**.

These observations led us to believe that some kind of self-assembly was occurring in solution. To investigate how this self-assembly was occurring, we began by carried out a dilution experiment on **9** using ¹H NMR spectroscopy on a 500 MHz instrument to see whether the self-assembly could be prevented if a very dilute solution of the compound was present. We started off with a 1 mM solution of **9** in CDCl₃ and obtained the ¹H NMR spectrum. Then we carried out a 10-fold dilution and re-ran the spectrum. We repeated this until we had a 1 μM solution. The results of the dilutions are shown in Fig. 2.

It is clearly evident, from Fig. 2, that as the concentration of **9** decreases, so also does the number of signals in each spectrum until the spectrum is simplified to what should be expected for the cone conformation of **9** (Fig. 2). Two distinct doublets for the methylene bridges can be clearly seen as well as four other signals (singlet, doublet, triplet and multiplet) for the remaining methylene groups. A similar effect was observed when this experiment was carried out on either of the compounds **4**, **7** or **10**, which showed this similar phenomenon in solution.

Using NOESY experiments, it should be possible to ascertain whether the self-assembly is occurring in a head-to-tail manner or in a head-to-head/tail-to-tail manner (see Fig. 3). We will define the processes as being either a Homo process, where like ends are connected together, either head-to-head or tail-to-tail, or a Hetero

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