Induced-fit recognition by *p*-carboxylatocalix[4]arene hosts

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ABSTRACT

Calix[4]arene derivatives bearing anionic carboxylato groups at the upper rim (*p*-carboxylatocalix[4]arenes) are able to 'grab' paraquat dicationic guest through an induced-fit mechanism, which originates from the conformational mobility of calixarene skeleton.

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Molecular recognition[1] plays a pivotal role in many supramolecular phenomena. As part of molecular recognition, the induced-fit mechanism[2] has stimulated chemists to develop new biomimetic hosts that are able to give adaptive structural changes during the interaction with substrates. In this regard, calixarene[3] macrocycles have attracted a particular attention, thanks to their conformational mobility. In fact, it is well known that appropriate calix[4]arene derivatives can interconvert in solution between four discrete conformations (cone, partial-cone, 1,3-alternate, and 1,2-alternate)[4] and that the conformational equilibrium is profoundly influenced by the presence of suitable guests.[3b,5] Thus, while four different conformers are present in solution for tetramethoxycalix[4]arene,[4,6] it adopts a cone conformation after addition of Li⁺ or Na⁺, with oxygen atoms at the lower rim close to cationic guest.[7] In another interesting example, it has been shown that 1,3-dimethoxycalix[4]crown-6, which exists in solution mainly in the cone conformation, adopts a 1,3-alternate conformation after addition of Cs⁺,[8] leading the ArOMe rings to interact with the cationic guest. Analogously, our group has reported that larger calix[n]arene derivatives (*n* = 7[9] and 8[10]) show an induced-fit process in which an alkali cation guest induces a conformational templation of flexible calix[7 or 8]arene anion. In addition, mutually induced conformational changes were observed during the binding process between water-soluble *p*-sulfonatocalix[8]arene and cationic cholinergic guests.[11]

Among the calixarene derivatives featuring anionic groups at the upper rim, *p*-sulfonatocalixarenes[12] have been intensively investigated as concerns their binding properties, whereas largely less studied remain those bearing carboxylato groups at the upper rim (*p*-carboxylatocalixarenes).[13] In this regard, Gutsche has shown that such derivatives form moderately strong complexes with aromatic hydrocarbons,[14] while recently Dalgarno[15] has reported the formation of nanotubes based on the self-assembly of a *p*-carboxylatocalix[4]arene. In this Letter, we wish to report interesting examples of induced-fit recognition by *p*-carboxylatocalix[4]arene derivatives **1** and **2** in the complexation with an organic quaternary ammonium ion such as paraquat (*1,1′-dimethyl-4,4′-bipyridinium*, **3**) dichloride (Chart 1).
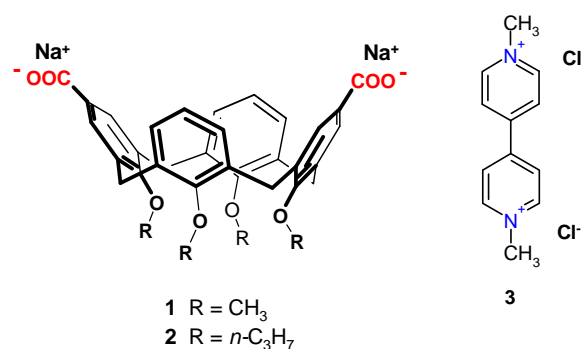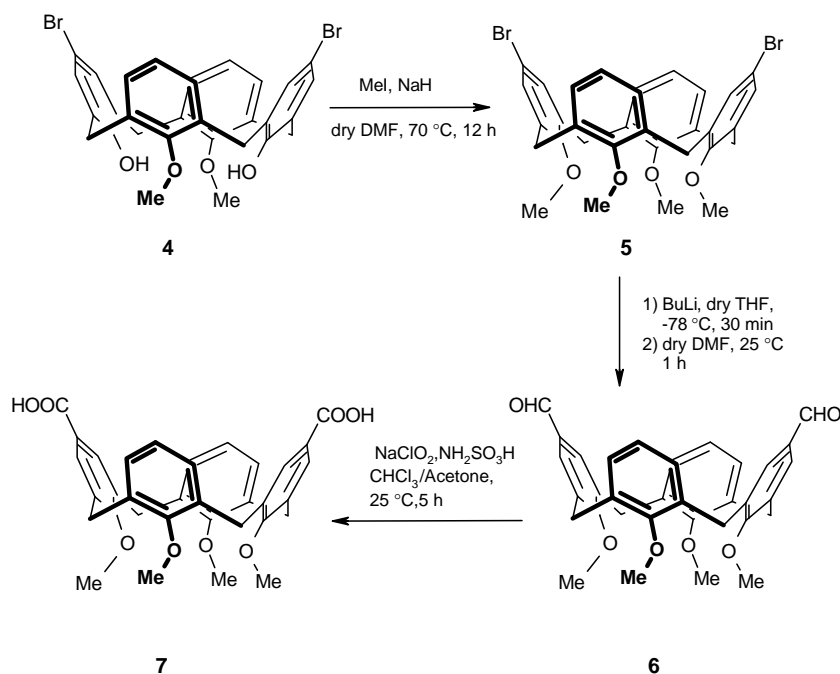

1 R = CH₃
2 R = *n*-C₃H₇

Chart 1.

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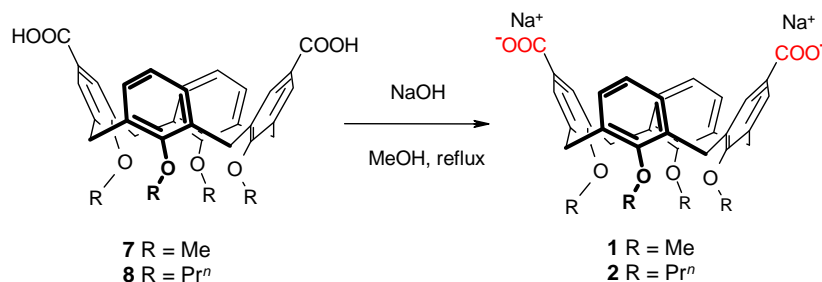**Scheme 1.** Synthesis of calix[4]arenedicarboxylic acid **7**.

Synthesis of calix[4]arenedicarboxylic acid **7** was obtained by means of halogen–lithium exchange reaction[16] of 11,23-dibromo-25,26,27,28-tetramethoxycalix[4]arene **5** as described in Scheme 1.[17]

In particular, alkylation of **4**[18] with MeI in DMF/NaH at 70 °C for 3 h gave **5** in 60% yield.[17] The latter was 5,17-dilithiated by reaction with *n*-BuLi in THF at −30 °C and quenched, after 30 min, with dry DMF to give dialdehyde **6** in 96% yield.[17] Then, oxidation of **6** with aqueous solution of NaClO$_2$ and NH$_2$SO$_3$H[19] gave calix[4]arenedicarboxylic acid **7** in 88% yield.[17] The ^{1}H NMR spectrum[17] (CDCl$_3$/CD$_3$OD, 45/1, v/v) of **7** showed the presence of both partial-cone and cone conformations in a 4/1 ratio.[20] In fact, the partial cone conformer was evidenced by an ArCH$_2$Ar AX system at 4.24/3.17 ppm, which correlates in the 2D HSQC spectrum[17] with a signal at 30.2 ppm relative to ArCH$_2$Ar carbons between *syn*-oriented phenol rings, while a cross-peak of equal intensity was present at 3.71/35.4 ppm between a broad singlet and the pertinent carbon signal relative to ArCH$_2$Ar groups between *anti*-oriented phenol rings.[17] The cone conformer was characterized by a second, less intense, ArCH$_2$Ar AX system at 4.03/3.13 ppm, which correlates in the 2D HSQC spectrum with a signal at 30.3 ppm relative to ArCH$_2$Ar carbons between *syn*-oriented phenol rings. Obviously, two possible partial-cone conformations, **7a** and **7b** (Fig. 1), are possible
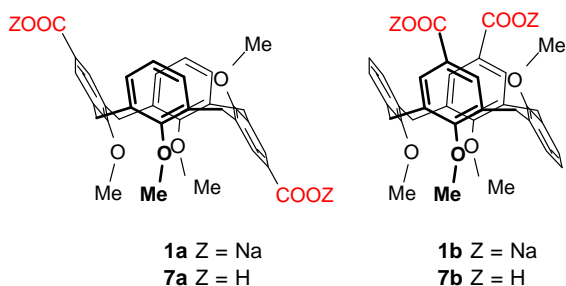
for derivative **7**. The first one, **7a**, presents the two distal carboxy-groups in *anti* orientation, whereas **7b** possesses these carboxy-groups in *syn* orientation, with an unsubstituted anisole ring inverted. Discrimination among them was obtained by simple symmetry considerations. In fact, the presence of two resonances at 170.2 and 169.6 ppm[17] relative to carboxy groups in the ^{13}C NMR[17] spectrum of **7** was fully consistent with partial-cone conformation **7a**.

p-Carboxylatocalix[4]arene **1** was easily obtained in 90% yield by treatment of **7** with an aqueous solution of NaOH in refluxing MeOH for 12 h (Scheme 2).[17] Analogously to derivative **7**, NMR analysis and molecular mechanic calculations[21] indicate that at room temperature *p*-carboxylatocalix[4]arene derivative **1** exists as a mixture of partial-cone and cone conformations in a 4/1 ratio.[20] Between the two possible partial-cone conformations (**1a** and **1b** in Fig. 1), NMR studies and molecular mechanic calculations[17] indicate that **1** adopts the partial-cone conformation **1a** with *anti*-oriented carboxylato groups. In analogy to **7**, tetrapropoxylated diacid **8**, obtained following the procedure reported by Ungaro and co-workers,[19] was deprotonated with aqueous solution of NaOH in refluxing MeOH (Scheme 2) to give *p*-carboxylatocalix[4]arene **2** in 78% yield. Details on the conformation adopted by **2** were obtained by spectral analysis. In particular, in the ^{1}H NMR spectrum of 2(CD$_3$OD), the chemical shifts of OCH$_2$ hydrogens are about 0.3 ppm apart in accord with a C_{2v} pinched-cone conformation.[22] In addition, the position of ArH signals of substituted and unsubstituted aromatic rings [respectively, at 7.74 (4H) and 6.14 (6H) ppm] indicates that the two carboxylato-bearing rings are pointing outwards from the calixarene cavity probably to minimize the electrostatic repulsion between the anionic groups. This conclusion was fully confirmed by the lowest energy conformation found by OPLS-calculations (Fig. 2a). Addition of paraquat **3** to a solution of host **2** in CD$_3$OD resulted in a dramatic inversion of the relative position of OCH$_2$ signals (Fig. 3a). In particular, those belonging to carboxylato-bearing rings are shifted about 0.3 ppm upfield, whereas those of unsubstituted aromatic rings are shifted more than 0.5 ppm downfield (Fig. 3a). In addition, an upfield shift of the resonances of unsubstituted aromatic protons, with a con-

Figure 1. The two possible partial-cone conformations for derivatives **1** and **7**.

Scheme 2. Synthesis of *p*-carboxylatocalix[4]arene derivatives **1** and **2**.
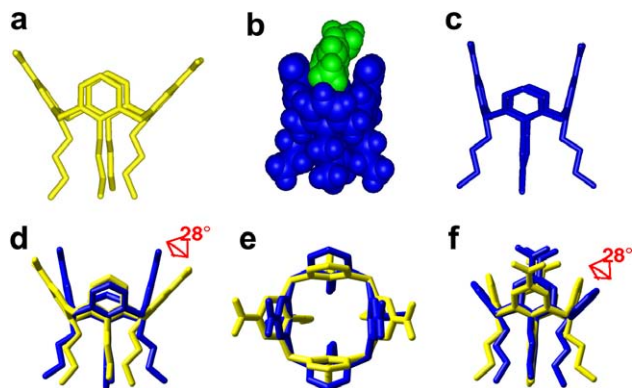

Figure 2. Lowest OPLS-energy structures of free **2** (a) and **3·2** complex (b).
(c) Structure of the complexed form of **2** obtained from (b) by omitting the guest.
(d–f) Different views of the superimposition of free [(a), yellow] and complexed
[(c), blue] forms of **2**.

comitant downfield shift of the signal of ArH in ortho to carboxy-
lato group (Fig. 3b) was also observed. These data indicate that
upon complexation *p*-carboxylatocalix[4]arene **2** switches from
the previous C_{2v} structure to an opposite C_{2v} pinched-cone confor-
mation with the two carboxylato-bearing rings pointing inwards
the calixarene cavity to maximize electrostatic and van der Waals
interactions with cationic guest **3**. These adaptive conformational
changes were fully confirmed by molecular modeling (Fig. 2). In
conclusion, the presence of **3** induces the fitting of host **2**, which
undergoes a C_{2v}-to-C_{2v} transition to 'grab' the guest.

This induced-fit process can be quantified through the measure
of the angles spanned by aromatic rings in the lowest OPLS-energy
structures. In free *p*-carboxylatocalix[4]arene **2** the canting angle
of the unfunctionalized aromatic rings was 77° (Fig. 2a), which be-
came 49° (Fig. 2b, c, f) upon complexation with paraquat **3**. On
the opposite, the canting angle of ArCOOH rings changes from

51° to 79° upon complexation (Fig. 2d). Thus, both types of aro-
matic rings of host **2** spanned an angle of 28° during the in-
duced-fit process, but in opposite directions (Fig. 2d–f). The
association constant between *p*-carboxylatocalix[4]arene **2** and
paraquat **3** was estimated by means of standard NMR titration.[23]
Thus, a Kass of 150,000 ± 30,000 M^{-1} was calculated, while a 1:1
stoichiometry for complex **2·3** was estimated by means of Job plot.
When paraquat dichloride **3** was added into a solution of conform-
ationally mobile tetramethoxy-*p*-carboxylatocalix[4]arene **1** in
CDCl$_3$/CD$_3$OD (45/1, v/v), new ^{1}H NMR peaks appeared that were
assignable to **1·3** complex (Fig. 4). In particular, a new ArCH$_2$Ar
AX system at 4.40/3.30 ppm emerged, which was indicative of a
cone conformation of **1** in the complex (Fig. 4b). Therefore, the
presence of **3** induces the oxygen-through-the-annulus rotation
of the inverted ArCOOH ring (spanned angle = 160°) of the preva-
lent partial-cone conformer **1a** to 'wrap' the guest. Concomitantly,
the less concentrated cone conformer undergoes a C_{2v}-to-C_{2v} tran-
sition, similar to that observed for **2**, to 'grab' the guest. Both types
of induced-fit processes can be visualized by inspecting the corre-
sponding lowest OPLS-energy structures (Scheme 3).

Diffusion-Ordered SpectroscopY (DOSY) NMR has been parti-
cularly used in the characterization of host–guest systems in
solution.[24]

Thus, we decided to perform DOSY NMR measurements to
investigate complex formation between *p*-carboxylatoca-
lix[4]arene **1** and paraquat **3**. In particular, at 298 K, we obtained
a diffusion coefficient of 8.01 × 10^{-10} m^2/s for *p*-carboxylatoca-
lix[4]arene **1** in CDCl$_3$/CD$_3$OD (45/1, v/v), while in a 1:1 mixture
with paraquat **3**, it showed a significant decrease in the diffusion
rate (5.27 × 10^{-10} m^2/s).[17] This indicates that paraquat **3** and *p*-
carboxylatocalix[4]arene **1** form a stable complex, which diffuses
slower than free **1**. The DOSY technique, in addition, provides infor-
mation about the stoichiometry of the complex in solution. In fact,
by means of the difference of the diffusion coefficients between
free host **1** and complex **1·3** in DOSY experiments, we deduced a
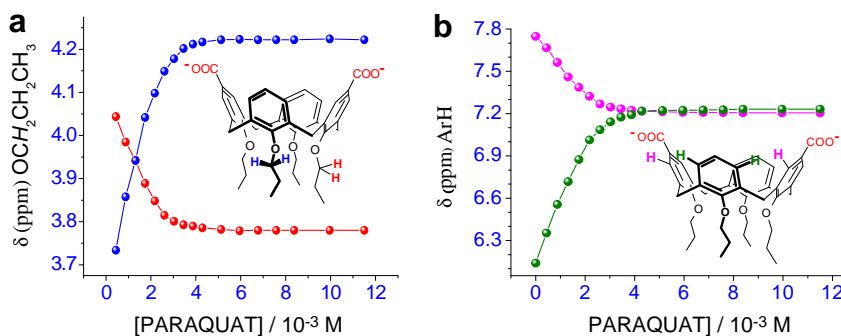molecular weight of 706 for complex **1·3**,[25] which matched the

Figure 3. Plots of chemical shift δ as a function of the concentration of paraquat dichloride **3** (CD$_3$OD, 25 °C, 400 MHz): (a) OCH$_2$ protons of **2**; (b) ArH protons of **2**.
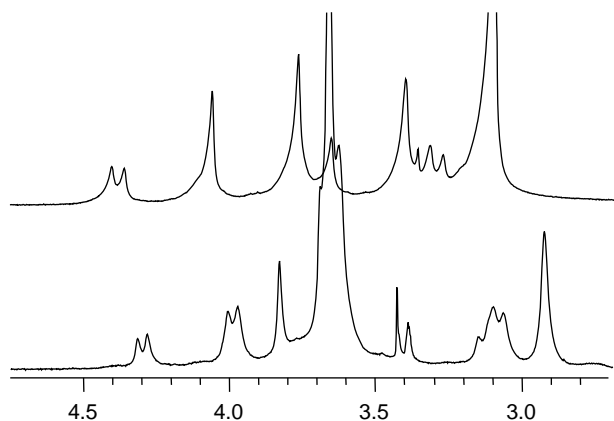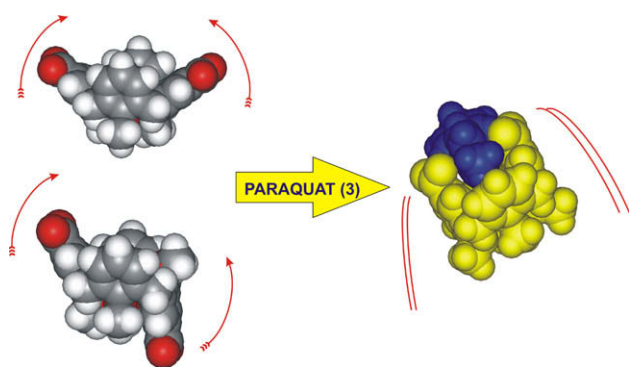
Figure 4. ArCH$_2$Ar region of the ^{1}H NMR spectra (400 MHz, CDCl$_3$/CD$_3$OD (45/1, v/v), 298 K) of free tetramethoxy-*p*-carboxylatocalix[4]arene **1** (bottom) and after the addition of 1 equiv of paraquat dichloride **3** (top).

Scheme 3.

theoretical molecular weight of the 1:1 complex (752 g/mol). Therefore, the result of DOSY experiments indicates a 1:1 stoichiometry of the complex **1·3**. The association constant between *p*-carboxylatocalix[4]arene **1** and paraquat **3** was estimated by means of standard NMR titration,[23] and a Kass of 100,000 ± 30,000 M^{-1} was calculated.

In conclusion, we have shown that *p*-carboxylatocalix[4]arene derivatives **1** and **2** are able to 'grab' a dicationic guest such as paraquat dichloride **3** through an induced-fit mechanism, which originates from the conformational flexibility of calixarene macrocycle.

Preliminary studies revealed that the recognition ability of **1** and **2** were sensitive to the pH of the medium, making them very attractive as switching systems. These aspects and further applications of carboxylatocalixarenes are currently under study in our laboratory.

Supplementary data

Synthetic details, ^{1}H/^{13}C and 2D NMR spectra, NMR titrations data, OPLS-energy minimized structures. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.11.016.

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