

Aramidocalix[4]arenes as new anion receptors

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Abstract—Calix[4]arenes bearing aromatic amide (*aramid*) moieties at the upper rim display interesting recognition properties toward anions and in particular versus planar trigonal nitrate and Y-shaped benzoate. Molecular modeling and DFT calculations indicate that the high affinity displayed by aramidocalix[4]arenes **3** and **4** for nitrate anion is likely due to the planar arrangement of the NH groups, which form an unusual six-hydrogen-bond scheme with nitrate anion.

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The development of synthetic molecules designed to bind anionic guests is an intensively active area of research in supramolecular chemistry,¹ since anions play important roles in a wide range of natural processes.^{2,3}

Calixarenes⁴ have become one of the leading host systems, currently most studied in the context of anion receptor development, as shown recently by a few reviews.⁵ The main reason for this success, besides their ready availability, is their easy chemical modification, which allows the introduction of appropriate functional groups able to create complementarity with anionic guests. Thus, calixarenes featuring cobaltocenium⁶ or ferrocene⁷ groups have been used for electrochemical sensing of anions in polar solvents.

However, more recently an increasing attention has also been devoted to the synthesis of electroneutral calixarene hosts bearing hydrogen-bond-donor units such as amide^{1c,8} and urea groups,^{1c,9} which often display remarkable host properties. The majority of the investigated amide derivatives have the amide carbonyl groups linked to the lower rim or to amino groups at the para position of the aromatic rings (C-linked amides).^{5,8} Unexpectedly, only a very limited number of the corresponding N-linked derivatives (with the NH amide groups linked to *p*-carboxycalixarene aromatic

rings) have been reported and considered for anion recognition.¹⁰

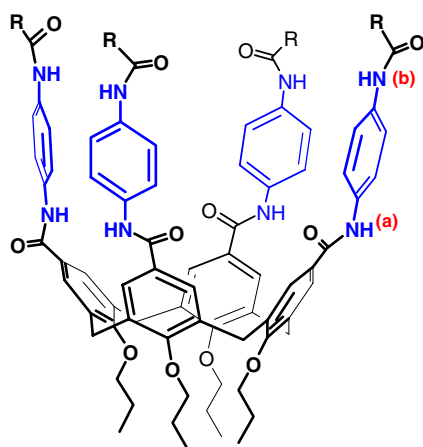
This observation prompted us to investigate the introduction of aromatic amide (*aramid*)¹¹ moieties at the upper rim of a tetracarboxylated calix[4]arene macrocycle.

In this Letter, we wish to report the synthesis of N-linked aramidocalix[4]arene derivatives **1–5** (Fig. 1), and their recognition properties versus anionic guests. *N*-Acetyl-*p*-aramidocalix[4]arene **1** was readily obtained in 30% yield by coupling the known calix[4]arenetetracarboxylic acid **6**,¹² with 12 equiv of *p*-acetamidoaniline **7**,¹³ in the presence of DCC as the coupling reagent and DMAP, in a mixture of dry CH₂Cl₂/DMF as the solvent (Scheme 1).¹⁴

The structure of **1** was assigned by means of spectral analysis. In particular, the presence of a pseudomolecular ion peak at *m/z* 1297 in the ESI(+) mass spectrum confirmed the molecular formula. The C_{4v} symmetrical structure was confirmed by pertinent signals in the ¹H and ¹³C NMR spectra in DMSO-*d*₆. In fact, two singlets were present at low field (9.83 and 9.73 ppm, 4H each) in the ¹H NMR spectrum, due to the NH protons, while the ArCH₂Ar groups give rise to an AX system at 3.43/4.49 ppm (*J* = 13.6 Hz, 8H), and the terminal Me groups originate a singlet at 2.01 ppm (12H). The ¹³C NMR spectrum displayed two characteristic resonances at 167.9 and 164.7 ppm relative to the two –CONH– groups.

Keywords: Calixarenes; Aromatic amides; Anion recognition; Hydrogen bonds.

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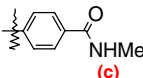
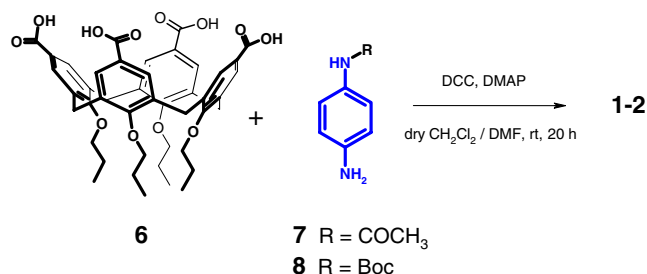
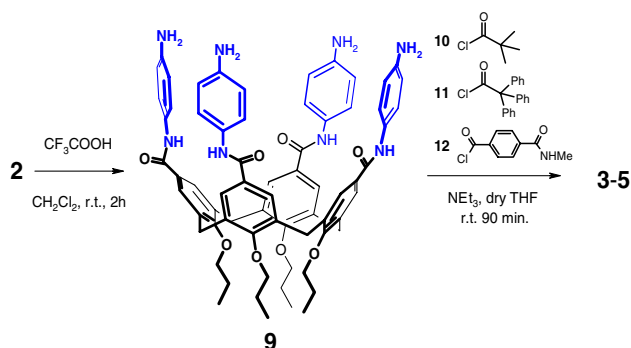
- 1 R = Me
- 2 R = O-*t*-Bu
- 3 R = *t*-Bu
- 4 R = C(Ph)₃ (Trityl)
- 5 R =  (c)

Figure 1. Aramidocalix[4]arene derivatives 1–5.



Scheme 1. Synthesis of aramidocalix[4]arenes 1 and 2.

In a similar way, the corresponding Boc-protected derivative **2** was obtained by coupling tetracarboxylic acid **6** with Boc-protected *p*-phenylenediamine **8**¹³ (Scheme 1). Compound **2** proved to be very useful because its *N*-Boc deprotection with TFA in dry CH₂Cl₂ afforded the key intermediate **9** which was used for the synthesis of additional aramidocalix[4]arenes (Scheme 2).¹⁴



Scheme 2. Synthesis of aramidocalix[4]arenes 3–5.

In fact, *p*-aramidocalix[4]arene derivatives **3–5** were obtained from compound **9** by coupling with the corresponding acyl chloride **10**, **11**, or **12**,¹³ in the presence of NEt₃ in dry THF (Scheme 2).¹⁴ The structure of *p*-aramidocalix[4]arene derivatives **3–5** was readily assigned by spectral analysis.¹⁴

The binding ability of *p*-aramidocalix[4]arene derivatives **1** and **3–5** toward anionic guests was studied by standard ¹H NMR titrations, in which the host concentration was kept constant while the guest concentration was varied (Table 1). The addition of anions, in the form of tetrabutylammonium salts, to the solution of each receptor caused significant downfield shifts of the signals relative to both amide hydrogen atoms in the ¹H NMR spectrum. This indicated that these groups were engaged in hydrogen bonding interactions with the anionic guest with a fast complexation equilibrium.

In each binding experiment, a 1:1 stoichiometry of the *p*-aramidocalix[4]arene/anion complex was determined by means of mole ratio or Job plots.^{15–17} The titration data were analyzed by nonlinear least-squares fitting procedures and in all cases, a good fit of the experimental data with the theoretical model confirmed the 1:1 stoichiometry of the complexes.

The binding properties of **3** and **4** were studied in CDCl₃, whereas, due to solubility problems, **1** and **5** were investigated in a mixture of CDCl₃/DMSO-*d*₆ (9/1, v/v) instead. For each compound addition of aliquots of the anion solution led to a downfield shift of both NH^a and NH^b (Fig. 2) signals, which were assigned by means of a 2D-NOESY spectrum. Usually, NH^a exhibited higher shifts indicating a preference for this recognition site.

Receptor **3** exhibited a lower affinity for spherical Cl[−] and tetrahedral H₂PO₄[−] anions (Table 1) and interestingly displayed a good selectivity for trigonal planar NO₃[−] (*K*_a = 14,000 M^{−1}) and Y-shaped PhCOO[−] (*K*_a = 13,500 M^{−1}).

This selectivity for nitrate anion was unexpected because of the different symmetry between guest and host (C₃ vs C₄)¹⁸ and is likely due to the planar arrangement of the four NH groups.¹⁹ A possible structure of the complex between *N*-pivaloyl-*p*-aramidocalix[4]arene **3** and nitrate

Table 1. Complexation constants (*K*_{ass}) of receptors **1** and **3–5** toward selected anions determined by ¹H NMR titrations at 298 K (400 MHz)

	<i>K</i> _{ass} (M ^{−1})			
	1 ^a	3 ^b	4 ^b	5 ^a
Cl [−]	70	3100	1200	30
CH ₃ COO [−]	80	850	—	40
H ₂ PO ₄ [−]	330	1700	570	^c
NO ₃ [−]	90	14,000	2000	40
PhCOO [−]	160	13,500	5700	50

^a ¹H NMR titrations were carried out in CDCl₃/DMSO-*d*₆, 9/1, v/v.

^b ¹H NMR titrations were carried out in CDCl₃.

^c No changes in NMR spectra were observed. (*K*_{ass}, error < 15%).

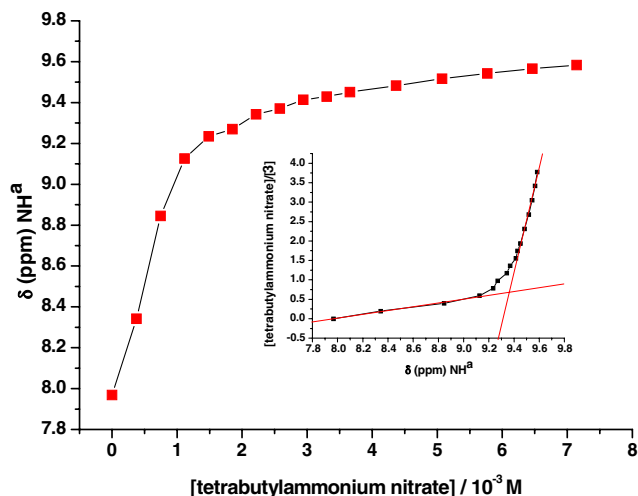


Figure 2. ^1H NMR titration curve of *p*-aramidocalix[4]arenes **3** with tetrabutylammonium nitrate (400 MHz, CDCl_3). Inset: corresponding mole ratio plot.

anion was obtained by molecular modeling,²⁰ and its geometry was refined by means of DFT calculations²¹ (Fig. 3) to obtain a more accurate positioning of the nitrate ion. A careful analysis of the structure shows that the NO_3^- anion is almost coplanar with the amide hydrogen atoms NH^a of **3**, forming an unusual six-hydrogen-bond arrangement.²² In particular, all the oxygen atoms of the nitrate anion exhibit a similar hydrogen bond pattern, forming one strong ($\text{NH}\cdots\text{O}$ distance, 1.78–2.12 Å) and one weak ($\text{NH}\cdots\text{O}$ distance, 2.42–2.54 Å) H-bond with two amide hydrogen atoms (Fig. 3). Interestingly, the terminal amide NH^b groups are engaged in two rigidifying interchain H-bonds.

In a similar way, DFT calculations indicated that the high affinity of **3** for benzoate anion could be ascribed to favorable H-bonds conjugated to $\text{CH}-\pi$ or $\pi-\pi$ interactions between aromatic rings of both guest and host.

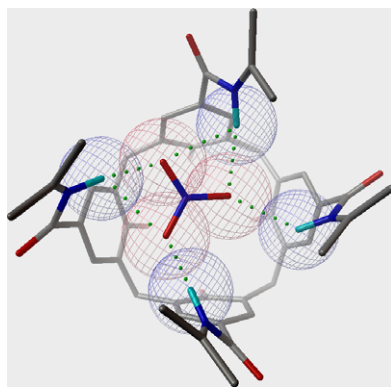


Figure 3. Top view of the geometry of the energy-minimized structure of the complex formed between *N*-pivaloyl-*p*-aramidocalix[4]arene **3** and nitrate anion NO_3^- (ONIOM DFT calculation using the MPW1PW91 functional). For clarity, nonpolar hydrogen atoms, aramid and *O*-propyl chains have been omitted. Red and blue meshed spheres represent the van der Waals surface of nitrate O and amide H atoms, respectively.

For *N*-triphenylacetyl-*p*-aramidocalix[4]arene **4** a reduction in binding constant values was observed in comparison to **3** (Table 1), likely because of the steric crowding of trityl groups that should hamper the access to the binding site. The complexation properties of *N*-acetyl-*p*-aramidocalix[4]arene **1** and elongated bis-aramidocalix[4]arene **5**, bearing additional hydrogen bond-donating sites (NH^c , Fig. 1), were studied in $\text{CDCl}_3/\text{DMSO}-d_6$ (9/1, v/v). Compared to **3** and **4**, both derivatives **1** and **5** showed an expected lower anion-binding ability (Table 1) due to the H-bond-acceptor competing the solvent. In addition, a lower selectivity was observed probably because of a poorer preorganization of the binding site due to the lack of the rigidifying NH^b interchain H-bonds, which would be destroyed by solvent interactions.

In conclusion, we have demonstrated that N-linked amidocalix[4]arene derivatives are effective receptors for anion recognition, which may show different properties with respect to the C-linked counterparts.²³ In particular, pivaloyl and triphenylacetyl aramidocalix[4]arene derivatives, **3** and **4**, reported here, show a good selectivity for trigonal planar nitrate and Y-shaped benzoate anions. The high affinity for nitrate anion is probably due to the planar disposition of the amide hydrogen atoms and an unusual six-hydrogen-bond arrangement. Further studies are in progress in our laboratory with the aim to extend the investigation on the properties of other N-linked amidocalix[4]arene derivatives and to exploit *p*-aramidocalix[4]arene receptors for anion sensing.²⁴

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Supplementary data

Synthetic details, $^1\text{H}/^{13}\text{C}$ and 2D NMR data, binding isotherms, details of molecular modeling and DFT calculations. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.09.046.

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