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Anion receptors based on intramolecularly bridged calix[4]arenes bearing ureido functions

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ABSTRACT

A novel type of anion receptor, based on the intramolecularly bridged calix[4]arene immobilized in the cone conformation, is described. The reductive coupling of a distal dialdoxime using $Zn/TiCl_4$ led to calix[4]arene with a *meso*-1,2-diaminoethane-1,2-diyl bridge that was transformed into the corresponding receptors by reaction with aryl isocyanates. ^{1}H NMR titration experiments revealed that the combination of a unique structural feature (bridge) with arylureido functional groups led to the formation of very potent anion receptors. Contrary to model non-bridged compounds, these well-preorganized receptors can efficiently bind selected anions ($H_2PO_4^-$, AcO^-, BzO^-) via hydrogen bonding interactions even in highly competitive solvent (DMSO-d_6).

1. Introduction

Calix[n]arenes[1] are macrocyclic compounds consisting of [n] phenolic subunits mutually connected via methylene bridges in the 2,6-positions of aromatic rings. In the last decades the chemistry of these compounds has been well established allowing synthetically easy derivatization with minimal limitations. Moreover, one can not only select the size of the cavity (from calix[4]- to calix[8]arene), but in the case of calix[4]arene derivatives, the three-dimensional shape of the basic skeleton can be tuned using any of the four possible conformations (atropoisomers) resulting from the hindered rotation of the phenolic subunits through the macrocyclic cavity. All of these features make calixarenes very popular molecules frequently used in supramolecular chemistry as molecular scaffolds in the design of various receptors.[2]

The essential function of some anions in various biological systems and living organisms is well recognized. Hence, designing methods for anion recognition has become an important part of supramolecular chemistry as demonstrated by the increasing number of papers, review articles[3] and books[4] recently published on this topic. The ongoing efforts to design and develop new synthetic receptors and sensors for the recognition of anions can be easily noticed in calixarene chemistry where the macrocyclic skeleton is able to serve as a platform for the deliberate arrangement of functional groups in a well-defined and highly preorganized manner.[5] Thus, the combination of unique tuneable shapes of the parent macrocycle with moieties capable of highly directional hydrogen bonds (amides, sulfonamides,[6] ureas and/or thioureas[7]) can lead to efficient binding of anions.

As proven in our previous work,[8] a typical design (see Fig. 1a) of calix[4]arene-based anion receptor starts from a macrocycle being immobilized in a suitable conformation (the most common example is the cone conformer) which is provided by ureido (amido) scaffolding either on the upper rim (aromatic subunits) or on the lower rim (phenolic oxygens) of the basic skeleton.[9] Very recently we reported the unprecedented formation of calixarene derivatives bearing a unique 1,2-diaminoethane bridge possessing *meso* stereochemistry.[10] In this context, we have realised that such a compound could be perfectly suitable as a starting point for the design of receptors exhibiting very high rigidity (see Fig. 1b).

Consequently, in this paper we report on our attempts to use the

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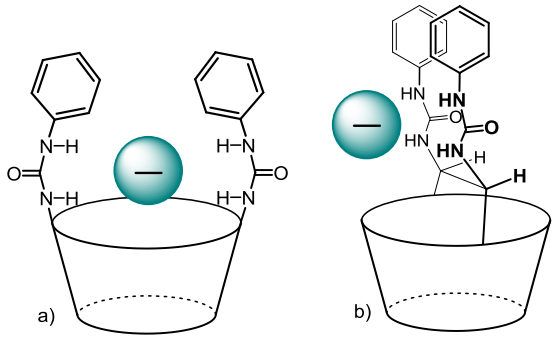

Fig. 1. Comparison of the classical (a) and novel (b) design of calixarene-based anion receptors.

above mentioned unique compound for the construction of novel types of anion receptors. The role of preorganization was demonstrated by the complexation ability of these receptors in comparison to similar compounds lacking this unusual structural feature (bridging moiety).

2. Results and discussion

The synthesis of diamino substituted bridged calix[4]arene derivative **4** was carried out as reported previously[10] (Scheme 1). Briefly, the starting dialdehyde **1** was obtained in high yield (95%) from the parent dipropoxy calixarene derivative by employing formylation with dichloromethyl methyl ether.[11] Subsequent alkylation of **1** using PrI/Na_2CO_3/MeCN led to the cone conformer **2**[12] in good yield (65%), which was then transformed ($NH_2OH{\cdot}HCl$/TEA in CH_2Cl_2 at room temp.) into the corresponding oxime **3** in quantitative yield. The reaction of **3** with a preformed low-valent titanium agent (generated from activated Zn and $TiCl_4$ in THF) provided the product of intramolecular reductive coupling **4**[10] which was isolated after column chromatography on alumina in 26% yield. Finally, the corresponding receptors **5a**-**5c** were prepared by stirring with aryl isocyanates in CH_2Cl_2 at room temperature for several days.

To evaluate the role of the rigidification and the overall complexation ability of the receptors, the same reactions were carried out with diamino derivative **7**[13] which lacks the additional ethylene bridge moiety. In fact, the resulting receptors **8a**-**8c** are structurally almost identical to compounds **5a**-**5c**, the only difference is one missing single bond between the carbon atoms bearing the ureido functionality (Scheme 1). To provide greater insight into the complexation properties of the receptors, both diamino derivatives **4** and **7** were also transformed into the corresponding amides **6** and **9**, respectively, by reaction with *p*-methylbenzoyl chloride in the presence of NEt_3.

The structures of the novel bridged receptors were confirmed using a combination of NMR and MS techniques. Thus, the ^{1}H NMR spectrum of compound **5c** ($CDCl_3$, 400 MHz) showed two doublets (3.03 and 3.12 ppm) originating from the equatorial C–H bonds of the methylene bridges, and two doublets (4.35 and 4.38 ppm) from the axial bonds. All doublets possessed typical geminal coupling constants (J ≈ 14 Hz) indicating the expected *cone* conformation with C_s symmetry (due to the *meso*-configuration of the ureido units). The TOF HRMS ESI+ analysis of the same compound confirmed the presence of the most intense peak at *m*/*z* = 969.47675 which is in good agreement with the calculated value for the $[M+Na]^+$ ion (969.47729). On the other hand, the ^{1}H NMR spectrum of non-bridged analogue **8c** exhibited only two doublets for the bridging CH_2 units (3.14 ppm from the equatorial and 4.12 ppm from the axial CH bonds) as a consequence of the C_{2v} symmetry of this molecule.

Moreover, the structure of derivative **8c** was unequivocally assigned using single crystal X-ray analysis. The compound crystalized in the orthorombic system, space group *Pbca*. The calixarene adopted a noticeable pinched cone conformation (Fig. 2a and b) with two aromatic rings pointing outside the cavity (the corresponding interplanar angles *Φ* between the main plane of the macrocycle defined by the four C atoms of the CH_2 bridges and the phenolic moieties were 139.02° and 140.10°). The other two phenolic moieties bearing the ureido functions were almost perpendicular to the main plane, but displayed a very slight bend into the cavity, (*Φ*. = 85.35° and 83.85°). The urea moieties are interconnected with each other using cooperative binding via N–H···O=C hydrogen bonding interactions. As shown in Fig. 2c, every carbonyl group is bonded to both NH groups of neighbouring ureido moiety, finally leading to the formation of an infinite belt of urea moieties. The corresponding NH···O=C distances (2.037, 2.095, 2.119 and 2.182 Å) indicated quite a strong binding in the solid state.

While we were unable to grow suitable monocrystals of the corresponding bridged receptors **5a**-**5c**, the amide derivative **6** allowed us to study the basic geometry parameters of such unusual compounds. Amide **6** crystallized in the orthorombic system, space group $P2_12_12_1$ as a 1:2 complex with methanol. The presence of the bridge on the upper rim ordered the calixarene into the pinched cone conformation (Fig. 3a and b) possessing much more extreme values of interplanar angles than encountered in **8c**. It can be documented on the corresponding angles *Φ* = 144.61° and 149.57° (much more flattened compared to **8c**) for the aromatic subunits pointing outside from the cavity, and *Φ* = 65.51° and 64.71° for the phenols oriented inside the cavity.

The complexation abilities of bridged ureas **5a-c** and amide **6**, and the non-bridged analogues **8a-c** and **9** towards selected anions were then studied using standard ^{1}H NMR titration technique. All anions employed in the titration experiments were used as tetrabutylammonium (TBA) salts to avoid/minimize potential complexation of bulky cations within the calixarene cavity. The selected anions represented various possible geometries, like spherical (Cl^-, Br^-), trigonal (NO_3^-), Y-shaped (BzO^-, AcO^-) or tetrahedral ($H_2PO_4^-$) shapes. Aliquots of anions were gradually added into the solution of ligands in an NMR tube (DMSO-d_6) to obtain calixarene/anion ratios of up to 1:10–15 depending on the specific anion.

The addition of anions to the ureido derivatives resulted in reasonable downfield complexation induced shifts (CIS) of the NH signals indicating the complexation phenomenon under fast exchange conditions. Despite the fact, that DMSO-d_6 is a highly competitive solvent towards hydrogen bonding interactions, the CIS values for **5a**/benzoate and **8a**/benzoate systems (after addition of ca 10 equivs. of BzO^-) were 1.09 ppm and 3.09 ppm, respectively. These values indicated a fundamental role of hydrogen bonding interactions in the overall complexation phenomenon. The Job plot[14] analyses (Fig. 4a) revealed the formation of complexes with 1:1 stoichiometry for all anions measured (the only exception was found in the **8b**:$H_2PO_4^-$ system where a 1:2 stoichiometry (calixarene:anion) was encountered). The complexation constants were determined by analysis of the binding isotherms (Fig. 4b) obtained from the CIS values of the NH protons of ureido moieties using the original curve-fitting program (ESTAC).[15] The corresponding values of the complexation constants for the 1:1 complexes are collected in Table 1.

As follows from Table 1, the trigonal NO_3^- ion was not bound by the novel receptors, while the spherical ions possessed some complexation with the K values smaller than 100 for Cl^-, or even