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New bifunctional compounds obtained by selective hydrolysis of tetrathiacalix[4]arene tetraethyl esters with Cs_2CO_3

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ABSTRACT

A new strategy for the synthesis of bifunctional compounds, based on *1,3-alternate* tetrathiacalix[4]arene precursors functionalized by pairs of carboxylic acid and ester groups located on opposite sides of the macrocycle platform is described. These building blocks were prepared by the Cs_2CO_3 induced selective hydrolysis of tetrathiacalix[4]arene tetraester derivatives. A mechanism for the selective hydrolysis is suggested. The structures of the compounds are elucidated by NMR spectroscopic analysis and X-ray single crystal diffraction.

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The rational design of artificial receptors is very important in the current chemistry.[1] In this context, the synthesis of heteroditopic receptors having unequal binding centres is of primary concern.[2] The possibility of coordinating at least two types of substrates simultaneously extends substantially the application area of these compounds. Heterometallic complexes that were obtained based on these receptors have numerous applications in catalysis,[3] reveal unique magnetic[4] and luminescent[5] properties and are commonly used as keystones for the creation of redox-responsive switches.[6]

Calix[n]arenes, in many respects, are very promising platforms for the design of bifunctional compounds.[7] Although the *cone*-isomers usually possess a high binding efficiency towards different ions in comparison with *1,3-alternate* isomers, the latter are interesting due to their enhanced binding selectivity.[8] This fact is vitally important for receptor design. Moreover, *1,3-alternate* stereoisomers can be considered as very suitable tectons for the construction of solid-state assemblies in crystal engineering,[9] and for the design of supramolecular allosteric receptors.[10] However, the synthesis of such compounds is associated with some difficulties.

The preparation of heteroditopic compounds based on a *1,3-alternate* platform usually proceeds in two stages.[11] The first step is the synthesis of 1,3-disubstituted calix[4]arenes, which is carried out using controlled amounts of base and alkylating agent. At the same time, along with the target product, compounds with different extents of substitution and side products can be formed.[7a,12] The next step involves functionalization of the two remaining hydroxy groups of the macrocycle in the presence of Cs_2CO_3.[12a,13] However, the template effect of the metal cation, shifting the equilibrium to the *1,3-alternate* isomer, depends considerably on the coordinating properties of the substituents present. Thus, instead of the desired product an intractable mixture of isomers is often formed. As a result, rigorous column chromatography for the purification of products is needed, that leads often to a serious hurdle in their large-scale synthesis.[12]

Taking these facts into account, an alternative strategy for the synthesis of bifunctional compounds based on *1,3-alternate* thiacalix[4]arenes can be proposed (Scheme 1). In the first stage, the synthesis of the *1,3-alternate* tetraester calix[4]arene derivatives 2 is carried out. The procedure for the preparation of thia- and *tert*-butylthiacalix[4]arene derivatives has been optimised and does not require additional chromatographic purification of the products.[14] The next stage is selective hydrolysis of the ester groups, which leads to the calix[4]arenes 3 bearing ester and carboxylic acid groups on opposite sides of the macrocycle. These compounds are promising precursors for further synthesis of a variety of bifunctional derivatives due to the different reactivity of ester and carboxylic acid functional groups.[15] Since the key step of this procedure is obtaining the calix[4]arenes **3a** and **3b**, the synthesis and structural characterization of these compounds was the main aim of our work.

It is known that along with fully substituted tetracarboxylic acid derivatives of calix[4]arene[16] and thiacalix[4]arene,[17] the monocarboxylic triester derivatives[18] and dicarboxylic diesters of

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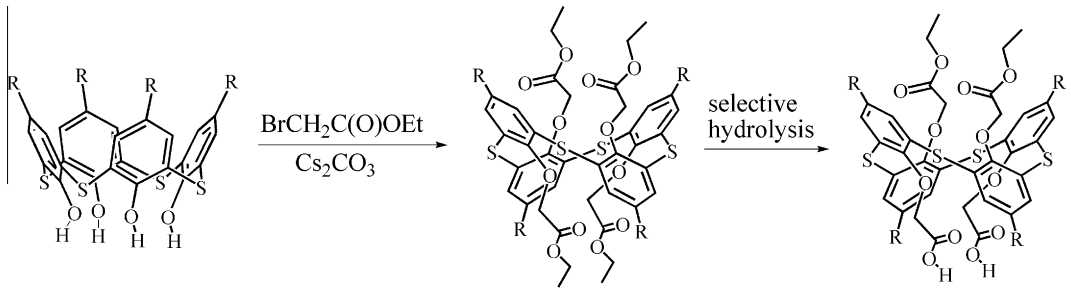

1a, R = *t-Bu*
1b, R = H

2a, R = *t-Bu*
2b, R = H

3a, R = *t-Bu*
3b, R = H

Scheme 1. The strategy for the synthesis of bifunctional tetrathiacalix[4]arene precursors.

calix[4]arene[16] can be obtained by the hydrolysis of tetraesters. However, the last two compounds were synthesized starting from the *cone* isomer of the 'classical' calix[4]arene only. The synthesis of calix[4]arenes similar to 3 has not yet been described in the literature.

The partial hydrolysis of tetraester calix[4]arene derivatives usually proceeds in the presence of acid. Treatment of the *cone*-isomer of calix[4]arene tetraethyl ester with ~0.5 and 2 equiv of trifluoroacetic acid in chloroform leads to the formation of mono- and dicarboxylic acid esters, respectively.[18a,19] To assess the general applicability of these reaction conditions we tried to hydrolyse the thiacalix[4]arene **2a**,**b** with two equivalents of TFA. However, even after seven days, we found only starting tetraester **2a**,**b** in the reaction mixture.

Another pathway for the synthesis of carboxylic acid derivatives of calix[n]arenes is the alkaline hydrolysis of tetraesters. In the presence of a large excess of hydroxide, full conversion of ester substituents into carboxylic acid groups is usually realized. A decrease in base content leads to the uncontrolled formation of a mixture of partially hydrolysed products.

The use of mild bases, such as alkali metal carbonates, also results in complete hydrolysis of calix[4]arene tetraesters.[20] However, these bases act more selectively than the corresponding hydroxides. For example, hydrolysis carried out in a mixture MeOH–H_2O (5:1) at reflux in the presence of excess K_2CO_3 does not affect the amide groups of the calix[4]arene.[18b] The nature of the alkali metal can also influence the hydrolysis rate because of the ability of the alkali metal ions to form complexes with ester derivatives of calix[4]arenes.[14a,17a,21] Thus, *1,3-alternate* tetrathiacalix[4]arene binds Cs^+ ions only on 'one side' of the macrocycle. This selectivity is obviously caused by the allosteric effect.[10,22] In addition, an example of Ba^{2+} assisted highly selective monodeacetylation of partial-cone calix[4]arene-crown-5 diacetate has been reported.[23] Taking these facts into account, we have developed an effective protocol for the synthesis of dicarboxylic acid calix[4]arene derivatives **3a** and **3b**.

It was found that heating compounds **2a**[24] and **2b**[14b] at reflux in THF solution containing 5 vol% of water and 12 equiv of Cs_2CO_3 resulted in formation of a precipitate. After treatment of the precipitate with HCl, the calix[4]arenes **3a** and **3b** were obtained in yields of 68% and 72%, respectively.[25–27] The filtrate separated from the water layer was composed of a mixture of initial tetraester **2a**(**b**) and a small amount of dicarboxylic acid diester **3a**(**b**). After removing the solvent this resulting residue could be used again during repeated synthesis. It should be noted that additional time was required to obtain calix[4]arene **3a** compared to **3b** (7 and 5 days, respectively). This fact is explained by the lower reaction rate for **3a** due to the steric effects of the *tert*-butyl groups.

On going from Cs_2CO_3 to Na_2CO_3, no efficient hydrolysis of tetraester **2a** was observed. In the case of **2b**, the relative content of the target product **3b** in the reaction mixture was not above 20%. This dramatic decrease in the yields of the desired products **3a** and **3b** can be explained by the poor stability of the inner sphere complexes of tetraesters **2a** and **2b** with the Na^+ ion.

The ^1H NMR spectra of **3a** and **3b** in $CDCl_3$ at 303 K show that these compounds possess symmetrical structures. The spectra contain only single signals for each proton group. The formation of the *1,3-alternate* isomer and pair-wise disposition of the same substituents in molecules **3a** and **3b** were proved by NOE experiments. In the spectra of these compounds, only the cross-peaks between protons of the $OCH_2C(O)$ and aromatic groups in **3b** or the *tert*-butyl groups in **3a** were observed, which testifies to the interaction between the upper and lower rims. The absence of cross-peaks between the protons of the $OCH_2C(O)$ groups adjacent to the carboxylic acid and ester fragments supports the pair-wise disposition of these substituents and the structures proposed for these compounds.

The presence of polar carboxylic acid groups in calix[4]arene molecules can lead to their dimerization in $CDCl_3$. The structure of the compound **3b**, as shown by X-ray data (see below) appeared to be the most suitable for the formation of such dimers. To check this assumption, we used pulsed-field gradient NMR (PFG-NMR), a technique that provides self-diffusion coefficients (Ds),[28] to confirm the dimeric structure of **3b**. The percentage of molecules of **3b** adopting the dimer form in this experiment was determined to be nearly 25%. The calculated equilibrium constant of dimerization (K_D) in this case was ~15 M^{-1} (see Supplementary data, Section S4 for details). This value is substantially lower than the constant determined for the dimerization of acetic acid in $CHCl_3$ (K_D = 300 ± 50).[29]

Final evidence for the structures of **3a** and **3b** was obtained by single crystal X-ray diffraction analysis[30–32] (suitable monocrystals were obtained by slow evaporation of EtOH/CH_2Cl_2 solutions). The calix[4]arene cores in both cases adopt the expected *1,3-alternate* isomer forms. The zig-zag packing of calix[4]arene molecules in the crystal of **3a** is apparent (Fig. 1). The presence of bulky *tert*-butyl groups in **3a** prevents the formation of a dimeric structure which is observed for compound **3b**.

Recrystallization of the precipitate formed by the hydrolysis of **2a** from MeOH yielded crystals of **3a**·2Cs^+·2MeOH.[30,33] In this crystal, one of the two independent Cs^+ cations coordinates with two carboxylate groups and is incorporated into the cavity of the calix[4]arene molecule (Fig. 2). Preliminary X-ray data obtained for **3b**·2Cs^+ showed the same mode of coordination of one Cs^+ ion as in the case of **3a**·2Cs^+·2MeOH. These results will be published in due course. The structures revealed for these complexes support the mechanism of hydrolysis proposed for tetraesters **2a** and **2b**.

The hydrolysis mechanism is very similar to the 'classical' route (Scheme 2).[34] The unusually selective saponification of *1,3-alternate* calix[4]arene 2a,b can be explained by its receptor properties towards Cs^+. An inner sphere complex forming at the first stage of hydrolysis undergoes nucleophilic attack on the carbonyl carbons.

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