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Novel water-soluble tetrasulfonatomethylcalix[4]resorcinarenes

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Abstract

Here we present a simple, high-yielding method of preparation of the novel water-soluble tetrasulfonatomethylcalix[4]resorcinarenes. Preliminary results of complex formation between the host **1** and several aminoacids are reported.

Keywords: water-soluble calixarenes; sulfonatomethylcalix[4]resorcinarenes; host–guest complexes.

The selective binding of a substrate by a molecular receptor is the basis of such biological processes as molecular transport, gene translation and protein assembly. The unique selectivity and variety of these processes stimulated the study of the rules and restrictions of the recognition and binding processes. Also, the design and synthesis of artificial receptors, based on the same principles as their natural prototypes, has become an important and rapidly growing field in chemistry.[1] The design of receptors focused on the construction of hydrophobic binding sites (molecular cavities, clefts, etc.) because aqueous media hydrophobic interactions and π-stacking are crucial elements for molecular recognition. While these forces have a relatively non-directed nature, the host–guest complexation in aqueous media is the result of contact over a large surface rather than at discrete points.[1,2] Water-soluble calixarenes with their relatively large hydrophobic cavity and bowl-shaped structure have excellent architecture for substrate binding in polar aqueous medium.[3] Shinkai et al. have reported the success in the regioselective cleavage of ribonucleoside 2′,3′-cyclic phosphates by using some water-soluble sodium hydroxycalix[*n*]arene-*p*-sulfonates.[3a] Williams et al. have shown that water-soluble calix[8]arenes may be used for extraction of fullerene-C_{60} into the aqueous phase.[3b] The X-ray investigations[3c,d] clearly demonstrated the ability of *p*-sulfonatocalix[5]arene to bind lanthanides and transition metal

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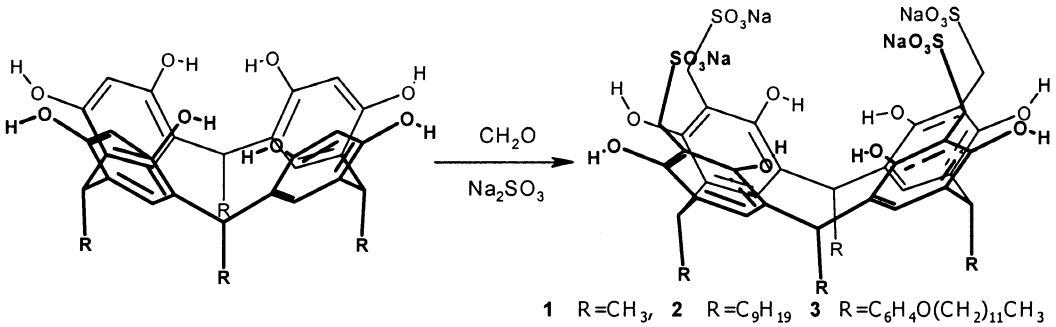
ions in aqueous solution and to form clay-like bilayer structures in the solid state. Previous work[3e] demonstrated that the reduction of Brilliant Cresyl Blue fluorescence in the presence of sulfonatocalix[4]arene is a static process resulting from the host–guest inclusion rather than excited-state reaction. The sulfonatocalixarene used in reference 3f is a component of mobile phase, providing successful separation of nitrophenols. Here we report a simple, high-yielding method of preparation of novel water-soluble calix[4]resorcinarenes (Scheme 1).

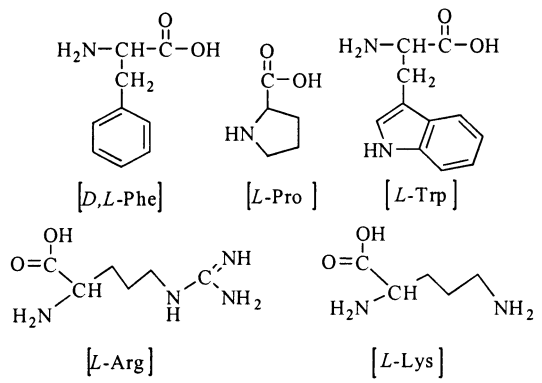


Scheme 1.

Tetrasulfonatomethylcalix[4]resorcinarenes **1**–**3** were produced by the reaction of corresponding calix[4]resorcinarenes with formaldehyde solution and sodium sulfite.[4] Isolated solid substances are soluble in polar solvents such as water, DMSO and glycerin. The structures of products **1**–**3** were assigned on the basis of the ^{1}H and ^{13}C NMR spectra and elemental analysis data.

In contrast to the initial unsubstituted calix[4]resorcinarene, which are soluble in water only at pH>9, all the obtained sulfonato-derivatives are very soluble in water. The hydrophilicity of the modified upper rim is so high that, even for **3**, containing four highly hydrophobic $C_6H_4O(CH_2)_{11}CH_3$ side chains, perfect solubility in water was observed. Acidic–basic properties of **1** are characterized with the following pK_a values: pK_1 9.0±0.08; pK_2 9.3±0.1; pK_3 10.82±0.3; pK_4 10.6±0.1.

The complexation of the host molecule **1** with several α-aminoacids (Scheme 2) was studied with the help of ^{1}H NMR in D_2O. The ^{1}H NMR titration experiment was performed at pD 7.3 with the fixed concentration of guest of 1.2×10^{-2} M, while the concentration of **1** was varied from 0 to 3.6×10^{-2} M.



Scheme 2.

The ^{1}H NMR spectrum of *L*-Trp in the presence and absence of **1** is shown in Fig. 1. The observed chemical shifts resulted from the fast exchange between free and complexed guest. For *D*,*L*-Phe, *L*-Pro, *L*-Trp, *L*-Arg and *L*-Lys in the presence of **1** we observed relatively large upfield shifts of the proton signals. This fact indicates formation of the host–guest complex of these aminoacids and host molecule **1**.

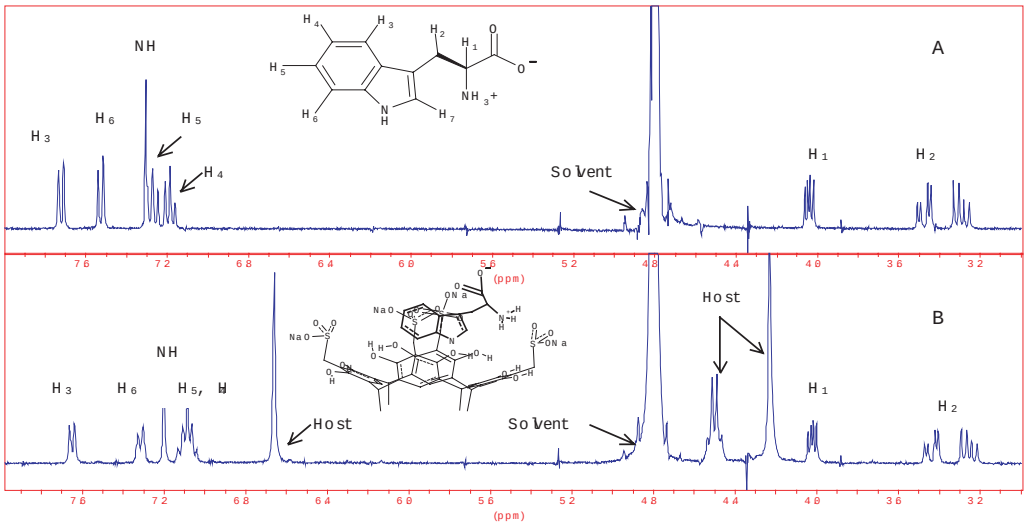


Figure 1. A fragment of the ^{1}H NMR spectrum of 1.2×10^{-2} M *L*-Trp in D_2O (at 25°C, pD 7.3, 0.1 M phosphate buffer, 200 MHz): (A) no host, (B) in the presence of 1.24×10^{-2} M of **1**

The analysis of ^{1}H NMR titration curves (Fig. 2) assumes 1:1 complex stoichiometry. They also demonstrate that the shielding effect for protons H_4 and H_3 is stronger than for the proton H_1. Thus it was suggested that the hydrophobic ring of *L*-Pro is included into the cavity of **1**, while the hydrophilic amino and carboxylic groups face the hydrophilic upper rim of the cavity. The same kind of driving forces can be assumed for *D*,*L*-Phe and *L*-Trp which also possess large aromatic substituents. On the other hand, it is well known that the aromatic cavity of calixarenes is able to bind quaternary ammonium ions; therefore, in the case of *L*-Arg and *L*-Lys, this kind of interaction is responsible for the host–guest complex formation.

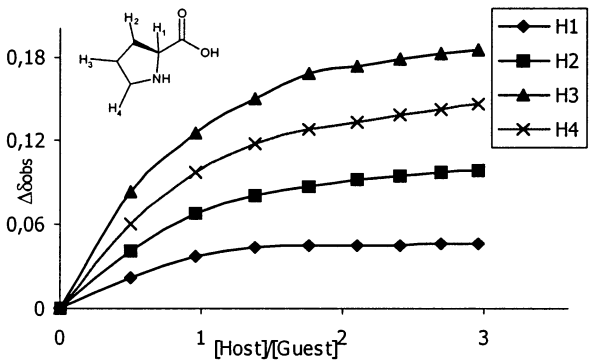
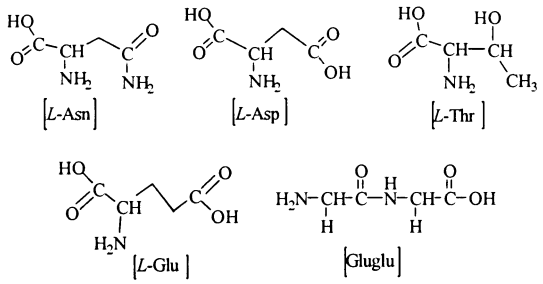
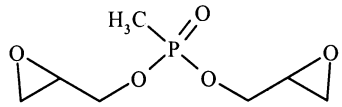


Figure 2. Plot of complexation-induced shifts $\Delta\delta_{obs}$ for the protons of *L*-Pro (1,2 e-2 M) as functions of [Host]–[Guest].

The analogous ^{1}H NMR experiments performed with the less hydrophobic α-aminoacids (*L*-Asp, *L*-Asn, *L*-Glu, *L*-Thr, Gly–Gly, Scheme 3) did not demonstrate significant changes in their proton signals in the presence of **1**. The shift $\Delta\delta_{obs}$ did not change considerably during the titration experiment; moreover, a negative value of $\Delta\delta_{obs}$ was observed. This supports the hypothesis that because these aminoacids possess neither large hydrophobic nor quaternary ammonium groups they are only able to take part in weak and not highly organized interactions with the polar groups on the upper rim of the cavity which are not strong enough for complex formation.



Scheme 3.



4

Recently we reported[5] the formation of strong molecular complexes between calix-[4]resorcinarene and the water-soluble polyfunctional organophosphorus compound—diglycidyl-methyl phosphonate **4**—in organic media. For the sulfonatocalix[4]resorcinarene **1** a stable complex with **4** was also obtained. Complex **5** is the product of interaction of **1** and **4** (1:1) in aqueous solution. The experimental evidence for complex formation was the disappearance of the spot for compound **4** on TLC. Complex **5** was isolated as a solid powder. The ^{1}H NMR spectrum of **5** displayed small upfield shifts of the signals of **1** and **4**. Proton signal doubling of the CH_2–O–P groups and the distinct appearance of the signal for OH groups of **1** are the most remarkable changes in the ^{1}H NMR spectrum of **5**. The results will be submitted for publication in the near future.

Acknowledgements

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4. Compound **1**: 5.44 g (0.01 mol) of calix[4]resorcinarene, a solution of 4.1 g (0.05 mol) of 37% formaldehyde and 6.3 g (0.05 mol) of sodium sulfite in H_2O (30 ml) was stirred and heated at 90–95°C for 4 h. Dilute hydrochloric acid was added after cooling until pH 7, then acetone (50 ml) was added to precipitate the product **1**. The solid was filtered, washed with acetone (20 ml) and dried for 20 h (700, 0.05 Torr). Compound **1** is a light yellow powder with mp>360°C. Yield 5.27 g (52.5%). Compounds **2** and **3** were obtained in 77 and 50% yield, respectively. ^{13}C NMR (D_2O) for **1**: 150.6, 110.1, 125.0, 127.6, 46.9, 29.8, 18.9; for **2**: 155.7, 125.3, 121.8, 108.1, 48.9, 36.1, 33.8, 32.3, 30.6, 30.1, 29.6, 28.9, 22.9, 14.17.
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