Synthesis and Aggregation Properties of Salts Based on Aminomethylated Calix[4]resorcinols and 1–Aminoethylidenediphosphonic Acid

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A series of new water-soluble onium salts was obtained by the interaction of aminomethylated calix[4]resorcinol with 1-aminoethylidenediphosphonic acid at reagent ratio of 1:4. To confirm the structure of the compounds, the data of elemental analysis, IR and NMR (1H, 13C, 31P) spectroscopy were used. For salt structure with pentyl substituents along the lower rim of the macrocycle the ability to form nanoscale aggregates in an aqueous solution has been shown. Values of the critical association concentration were determined by the methods of tensiometry (9·10⁻⁴ mol/L) and conductometry (CAC₁ = 9·10⁻⁴ mol/L, CAC₂ = 5·10⁻³ mol/L). Aggregate sizes were determined by means of dynamic light scattering (4 nm).

Keywords: Calix[4]resorcinol, bisphosphonic acid, synthesis, self-aggregation.

Синтез и агрегационные свойства солей на основе аминометилированных каликс[4]резорцинов и 1–аминоэтилидендифосфоновой кислоты

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Серия новых водорастворимых ониевых солей получена взаимодействием аминометилированных каликс[4]-резорцинов с 1-аминоэтилидендифосфоновой кислотой при соотношении реагентов 1:4. Для подтверждения структуры соединений использовали данные элементного анализа, ИК, ЯМР (1H, 13C, 31P) спектроскопии. Для солевой структуры с пентильными заместителями по нижнему ободу макроцикла показана возможность образовывать наноразмерные агрегаты в водном растворе. Определены агрегационные характеристики соли с пентильными заместителями: критическая концентрация ассоциации (ККА) по данным методов тензиометрии (9·10⁻⁴ M) и кондуктометрии (ККА₁ = 9·10⁻⁴ М, ККА₂ = 5·10⁻³ М), а также размер их ассоциатов по данным метода динамического рассеяния света (4 нм).

Ключевые слова: Каликс[4]резорцин, бисфосфоновая кислота, синтез, самоорганизация.
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Introduction

Supramolecular chemistry has originated from the study of the selective binding of alkali metal cations to macrocyclic ligands, crown ethers and cryptands.[1] Later, the range of objects of supramolecular chemistry was expanded to a wide class of systems connected in a single unit due to intermolecular bonds.[2-5] However, calix[4]resorcinols are widely used as building blocks for supramolecular structures due to the developed synthesis methods, the possibility of functionalization along the upper and lower rims, and also the presence of an internal cavity for guest recognition.[6-9] Modification of calix[4]resorcinol allows to obtain new spatially organized structures with practically useful properties.[10] In addition, the ability to form aggregates (micelles, vesicles) has been shown for amphiphilic calix[4]resorcinol in aqueous, aqueous-organic and organic solvents.[2]

Earlier, by Mannich reaction of calix[4]resorcinol with formaldehyde and amines, aminomethylated calix[4]resorcinols were obtained.[11,12] The formation of a hydrophobic cavity in these macrocycles along with four strongly basic dialkylaminomethyl groups allows us to construct new supermolecules that can provide, for example, a catalytic activity in reactions of phosphonates hydrolysis,[13] and also practically useful properties.[14] Modification of calix[4]resorcinol with 1-aminoethylidenediphosphonic acid.[6-9] Modification of calix[4]resorcinol

The interaction of aminomethylated calix[4]resorcinols with 1-aminoethylidenediphosphonic acid.

Currently, there is growing interest in obtaining salts of organic molecules based on bisphosphonic acids.[15,16] The ability of these low-toxicity acids to form gels, as well as stable complexes with metals[17-19] allows their using as components of supramolecular gels.[20] In addition, bisphosphonates are recognized as an important class of drugs for the treatment of various diseases associated with excessive bone resorption, including Paget’s disease,[21] bone metastases and osteoporosis.[22] For instance, in[23] it was performed a computer simulation of the correspondence of nine different calix[4]arenes and calix[4]resorcaneres cavity to the osteoporosis inhibitor zoledronic acid (a third generation of bisphosphonates) and it was found that in the gaseous states some of the complexes may be unstable, but in an aqueous medium almost all complexes can form spontaneously.

In the present work, in order to obtain new water-soluble macrocyclic “hosts” we have studied the interaction of aminomethylated calix[4]resorcinols 1a-c, 2, 3 with 1-aminoethylidenediphosphonic acid 4 (Figure 1). The reaction was carried out at different ratio of reagents (from 1:1 to 1:4). It was found that macrocycles react with acid 4 and form tetraonium salts of calix[4]resorcinol 5a-c, 6, 7 regardless of the ratio of the reactants and the order of their mixing.

Experimental

The general procedure for obtaining compounds 5a-c, 6, 7 was as follows: to 1.5 mmol of aminomethylated calix[4]resorcaneres 1a-c, 2 and 3 the acid 4 (6 mmol in 200 mL of water) was added dropwise at constant stirring. The reaction mixture was stirred till complete dissolution of initial reagents and afterwards for 12 h more, the solvent was distilled off in a vacuum on a rotary evaporator. The residue was washed with acetone and dried in a vacuum of an oil pump. The structure of the synthesized compounds 5a–c, 6 and 7 was confirmed by 1H, 13C, and 31P NMR spectra, and the composition was confirmed by elemental analysis. NMR spectra were recorded on a Bruker AVANCE 400 spectrometer at 303 K. IR spectra were recorded on a Vector 22 Fourier spectrometer (Bruker, Germany) in the range 400–4000 cm⁻¹. Crystalline samples were studied as suspensions in Nujol. Elemental analyzes were performed on a Carlo Erba elemental analyzer EA 1108.

4, 6, 10, 12, 16, 18, 22, 24-Octahydroxy-5, 11, 17, 23-tetraakis-[N-diethylaminomethyl]-2, 8, 14, 20-tetramethylpentacyclo-[19, 3, 1, 1.3, 1, 1.1, 1.1, 1.1]octacos-1(25), 3, 5, 7(28), 9, 11, 13(27), 15, 17, 19(26), 21, 23-dodecaene-N, N, N-tetraakis(1-amino-l-phosphonoethyl)phosphonate) (5a). Slightly pink powder, yield 92%, m.p. 234–236 °C decomp. Anal. Calcd for C₆₀H₇₆N₄O₁₆P₂ (H₂O): C, 56.8; H, 5.1; N, 5.3; P, 14.0. Found: C, 56.8; H, 5.1; N, 5.3; P, 14.0. IR (nujol) vs cm⁻¹: m 1056 (POH), s 1166, 1232 (P=O), 1605 (C=Ocar), br 2268–2538 (NH@Getter), 287-291

Figure 1. The interaction of aminomethylated calix[4]resorcinols with 1-aminoethylidenediphosphonic acid.

1a–c, 5a–c (R=R'=Et, R''=Me(a), Et(b), C₆H₁₁(c)); 2, 6 (R=R'=Me, R''=Me); 3, 7 (R=Me, R''=CH₃CH(OMe)₂, R''=Me)
4.6.10.12, 16, 18, 22, 24-Octahydroxy-5,11,17,23-tetraakis-\([N\text{-diethylaminomethyl}]-2,8,14,20\text{-tetramethylpentacyclo[19.3.1.1^5,9]26,31,7,13,17,19(26),21,23\text{-dodecaene-N,N,N,N-tetraakis(hydro(1-amino-1-}
\text{-phosphonoethyl)phosphonate})\) (5b).

Slightly pink powder, yield 92 %. M.p. >250 °C decomp. Anal. Calcd for C_{190}H_{318}N_{25}O_{25}P_5: C 47.14, H 7.48, N 5.77, P 13.22.

Found: C 40.58, H 6.34, N 5.82, P 13.22. IR (nujol) \(v_{\text{max}}\): 3135, 3384 (OH).

\[ \delta_{\text{H NMR}} (400 \text{ MHz}, \text{D}_2\text{O} \delta_{\text{H}}: 8.21 (\text{СH}=\text{C} \text{ar}), 6.71 (s, 4\text{H}, \text{Ar}-\text{СH}), 4.73 (s, 8\text{H}, \text{PCHC}) \]

On the surface tension isotherm of compound 5a (Figure 2a), a slight decrease in the surface tension up to 58 mN/m is observed without a pronounced exit to the plateau, which does not allow us to identify the value of CAC. This can be explained by a short (methyl) tail on the lower rim of aminomethylated calix[4]resorcinol. The concentration dependence of the specific conductivity (Figure 3a) shows a smooth increase associated with an increase in the number of charge carriers with break point at concentration of 5a equal to 0.01 mol/L.

The presence of a pentyl substituent on the lower rim of aminomethylated calixarene allowed us to suggest the possibility of the formation of aggregates in 5c solution. From the surface tension isotherm (Figure 2b) it can be seen that, compared to compound 5a for salt with pentyl substituents 5c the dependence goes to a plateau. The value of CAC for compound 5c is 9·10^{-4} mol/L. However, it is worth noting that for classical surfactants in aqueous solutions, it is possible to achieve a much larger decrease in surface tension up to 30–35 mN/m. The location of the plateau region for compound 5c at values of 45–47 mN/m is most likely due to the bulk structure of the onium salt molecule, which prevents its large accumulation in the surface layer.

On the dependence of the specific conductivity (Figure 3b) on the concentration of compound 5c, there are two inflections: CAC (9·10^{-4} mol/L) can be attributed to the beginning of the formation of aggregates in solution, and CAC (5·10^{-3} mol/L) can be attributed to structural rearrangements in the system. The hydrodynamic diameter of the aggregates, determined by dynamic light scattering,
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Figure 2. Surface tension isotherms of aqueous solutions of compounds 5a (a) and 5c (b), 25 °C.

Figure 3. The specific conductivity versus concentration of onium salts 5a (a) and 5c (b), aqueous solution, 25 °C.

Conclusions

The first representatives of new water-soluble onium salts based on aminomethylated calix[4]resorcinol having different hydrophobicity and 1-aminomethylendiphosphonic acid were obtained by varying the ratio of reagents (from 1:1 to 1:4). The structure of the compounds formed was confirmed by elemental analysis, IR, NMR (1H, 13C, 31P) spectroscopy. For a salt structure with pentyl substituents along the lower rim of the macrocycle, the possibility of the formation of nanoscale aggregates in an aqueous solution was shown. Values of the critical association concentration were determined by tensiometry ($9 \times 10^{-4}$ mol/L) and conductometry ($CAC_1 = 9 \times 10^{-4}$ mol/L, $CAC_2 = 5 \times 10^{-3}$ mol/L).

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