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SHORT COMMUNICATIONS

New Salt Structures Based on Aminomethylated Calix[4]-resorcinarenes and (1-Hydroxyethane-1,1-diyl)bisphosphonic Acid

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Abstract—Aminomethylation of calix[4]resorcinarenes with (1-hydroxyethane-1,1-diyl)bisphosphonic acid afforded a series of new water soluble onium salts.

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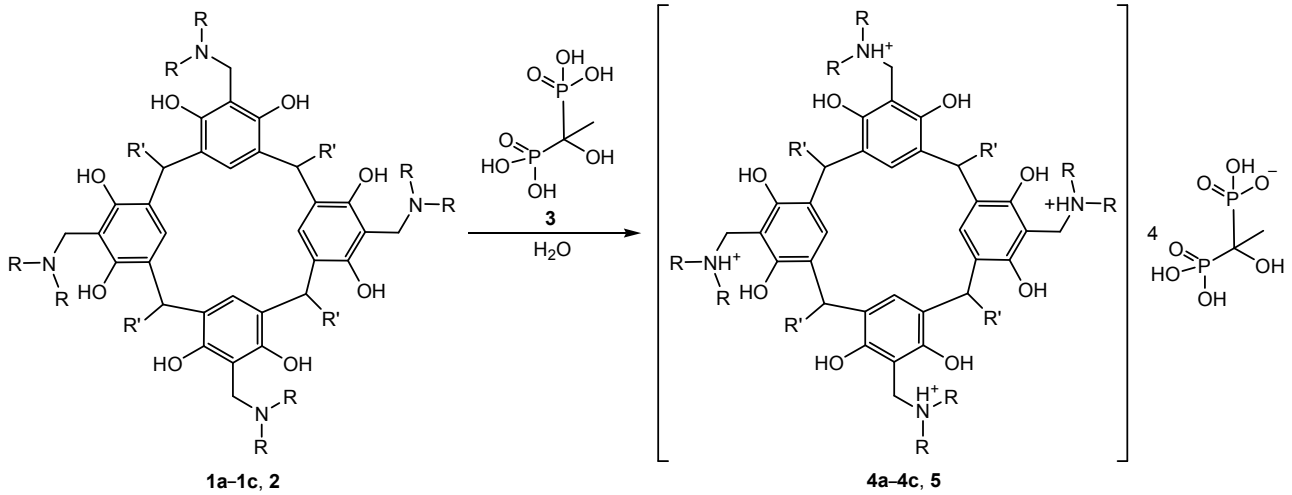
Bisphosphonates are nowadays applied to designing new materials for biology and medicine more and more often [1–3]. The ability of bisphosphonic acids to form gels and stable complexes with metals as well as their low toxicity makes it possible to use them as components of supramolecular gels for medical applications [1, 2] and ligands for preparation of coordination polymers [3].

Now an interest grows to the preparation of organic molecules salts based on bisphosphonic acids [4–6]. Recently from 1-(aminoethylidene)-1,1-bisphosphonic acid and benzotriazole, 1,2,4-triazole, and urea supramolecular aggregates were obtained possessing adsorption [4], bactericidal [5], and absorption [6] properties.

Other interesting objects for designing supramolecular structures involving bisphosphonic acids are aminomethylated calix[4]resorcinarenes [7]. The presence in these macrocycles of a hydrophobic cavity along with four strongly basic dialkylaminomethyl



1, **4**, R = Et, R' = Me (**a**), Et (**b**), C_5H_{11} (**c**); **2**, **5**, R = R' = Me.

groups makes it possible to construct new supramolecules possessing a catalytic activity in hydrolysis reactions of some phosphonates [8], and also opens an opportunity to involve them in the synthesis of new salt structures with additional coordination sites [9, 10].

In this study aiming at the preparation of new water soluble macrocyclic ligands we investigated the reaction of aminomethylated calix[4]resorcinarenes **1a–1c** and **2** with (1-hydroxyethane-1,1-diyl)bisphosphonic acid **3**. The reaction was performed at various reagents ratios (from 1 : 1 to 1 : 4). The macrocycles reacted with acid **3** giving tetraonium salts of calix[4] resorcinarenes **4a–4c** and **5** regardless of the reagents ratio and the order of their mixing.

The structure of synthesized compounds **4a–4c** and **5** was confirmed by ^{1}H, ^{13}C, and ^{31}P NMR spectra, and the composition was proved by the data of elemental analysis.

^{1}H NMR spectra of compounds **4a–4c** and **5** contain the signals of the protons of methylene and methyl groups linked to a nitrogen atom in the region 3.01–3.11 and 2.79 ppm, in the spectra of initial compounds the signals of analogous protons appear at 2.70–2.80 (**1a–1c**) and 2.3 ppm (**2**). The downfield shift of the signals of the protons of methylene and methyl groups linked to the nitrogen atom as well as the presence in the IR spectrum of compounds **4a–4c** and **5** of a wide absorption band in the region 2362–2530 (NH^+) indicate the formation of onium salts **4a–4c** and **5**.

The study of antimicrobial (bacteriostatic and fungistatic) activity *in vitro* showed that compounds **4a** and **4b** in the concentration range 500–0.97 μg/mL exhibit no action.

Compounds 4a–4c and 5. General procedure. To 1.5 mmol of aminomethylated calix[4]resorcinarenes **1a–1c** and **2** was added dropwise at constant stirring 6 mmol of acid **3** in 200 mL of water. 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.

{4,6,10,12,16,18,22,24-Octahydroxy-2,8,14,20-tetramethylpentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-5,11,17,23-tetrayl}tetrakis(*N,N*-diethylmethylammonium)tetra[(1-hydroxy-1-phosphonoethyl)hydrophosphonate] (4a). Yield 2.5 g (97%), mp 157–158°C. IR spectrum, ν, cm^{-1}: 3381 (OH), 3200 br, 2510–2362 br (NH^+), 1600 (C=C$_{arom}$), 1230 (P=O), 1168 s, 1050 m (POH). ^{1}H NMR spectrum (D_2O), δ, ppm: 1.22 t (24H, $NCH_2C\underline{H}_3$, $^{3}J_{HH}$ 6.9 Hz), 1.32 d (12H, CH_3, $^{3}J_{HH}$ 6.7 Hz), 1.49 d (6H, CCH_3, $^{3}J_{PH}$ 15.9 Hz), 1.53 d (6H, CCH_3, $^{3}J_{PH}$ 15.6 Hz), 3.07–3.11 m (16H, $NC\underline{H}_2CH_3$), 4.18 s (8H, CH_{2arom}), 4.40–4.42 m (4H, CH), 6.64 s (1H$_{arom}$). ^{13}C NMR spectrum (D_2O), δ, ppm: 8.15 (CH_3), 19.32 (CH_3), 19.87 (CH_3), 31.42 (CH), 46.07 (CH_{2arom}), 47.64 (CH_2N), 70.48 t ($P\underline{C}CH_3$), 109.44 (CH_{arom}), 126.53 (CH_{arom}), 126.95 (CH_{arom}), 150.94 (COH). ^{31}P NMR spectrum (D_2O), δ, ppm: 19.70. Found, %: C 41.75; H 6.47; N 3.24; P 14.31. $C_{52}H_{76}N_4O_8\cdot4C_2H_8NO_7P_2$. Calculated, %: C 42.16; H 6.37; N 3.28; P 14.50.

{4,6,10,12,16,18,22,24-Octahydroxy-2,8,14,20-tetraethylpentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-5,11,17,23-tetrayl}tetrakis(*N,N*-diethylmethylammonium)tetra[(1-hydroxy-1-phosphonoethyl)hydrophosphonate] (4b). Yield 2.60 g (96%), mp > 250°C (decomp.). IR spectrum, ν, cm^{-1}: 3381 (OH), 3200 br, 2510–2362 br (NH^+), 1600 (C=C$_{arom}$), 1232 (P=O), 1168 s, 1052 m (POH). ^{1}H NMR spectrum (D_2O), δ, ppm: 0.81 t (12H, CH_3, $^{3}J_{HH}$ 6.4 Hz), 1.15 (24H, $NCH_2C\underline{H}_3$, $^{3}J_{HH}$ 6.5 Hz), 1.50 d (6H, CCH_3, $^{3}J_{PH}$ 15.6 Hz), 1.54 d (6H, CCH_3, $^{3}J_{PH}$ 15.7 Hz), 1.96–1.99 m (8H, $CHC\underline{H}_2$), 3.04 br.s (16H, $NC\underline{H}_2CH_3$), 4.23–4.25 m (12H, CH_{2arom}, CH), 7.02 s (1H$_{arom}$). ^{13}C NMR spectrum (D_2O), δ, ppm: 8.19 (CH_3), 11.61 (CH_3), 19.41 (CH_3), 27.46 (CH_2), 36.97 (CH), 46.60 (CH_{2arom}), 47.85 (CH_2N), 70.66 t ($P\underline{C}CH_3$), 109.08 (CH_{arom}), 126.46 (CH_{arom}), 150.94 (COH). ^{31}P NMR spectrum (D_2O), δ, ppm: 19.55. Found, %: C 43.35; H 6.77; N 3.24; P 13.91. $C_{56}H_{84}N_4O_8\cdot4C_2H_8NO_7P_2$. Calculated, %: C 43.54; H 6.62; N 3.17; P 14.04.

{4,6,10,12,16,18,22,24-Octahydroxy-2,8,14,20-tetrapentylpentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-5,11,17,23-tetrayl}tetrakis(*N,N*-diethylmethylammonium)tetra[(1-hydroxy-1-phosphonoethyl)hydrophosphonate] (4c). Yield 2.80 g (97%), mp > 250°C (decomp.). IR spectrum, ν, cm^{-1}: 3382 (OH), 3200 br, 2530–2368 (NH^+), 1598 (C=C$_{arom}$), 1230 (P=O), 1167 s, 1052 m (POH). ^{1}H NMR spectrum (D_2O), δ, ppm: 0.71 br.s (12H, CH_3), 1.10 br.s [48H, CH_2CH_3, $(CH_2)_3$], 1.52 d (6H, CCH_3, $^{3}J_{PH}$ 15.5 Hz), 1.56 d (6H, CCH_3, $^{3}J_{PH}$ 15.6 Hz), 1.80 (8H, $CHC\underline{H}_2$),

3.01 br.s (24H, $NC\underline{H}_2CH_3$), 4.19 br.s (8H, CH_{2arom}), 4.42 br.s (4H, CH), 6.87 br.s ($1H_{arom}$). ^{31}P NMR spectrum (D_2O), δ, ppm: 19.93. Found, %: C 47.05; H 7.47; N 2.84; P 12.61. $C_{68}H_{108}N_4O_8 \cdot 4C_2H_8NO_7P_2$. Calculated, %: C 47.21; H 7.30; N 2.90; P 12.81.

{4,6,10,12,16,18,22,24-Octahydroxy-2,8,14,20-tetramethylpentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-5,11,17,23-tetrayl}tetrakis(*N*,*N*-dimethylmethylammonium)tetra[(1-hydroxy-1-phosphonoethyl)hydrophosphonate] (5). Yield 2.30 g (96%), mp 132–134°C. IR spectrum, ν, cm^{-1}: 3382 (OH), 3200 br, 2530–2368 br (NH^+), 1598 ($C{=}C_{arom}$), 1232 (P=O), 1165 s, 1052 m (POH). ^1H NMR spectrum (D_2O), δ, ppm: 1.43 d (12H, CH_3, $^3J_{HH}$ 6.4 Hz), 1.55 d (6H, CCH_3, $^3J_{PH}$ 15.6 Hz), 1.58 d (6H, CCH_3, $^3J_{PH}$ 15.7 Hz), 2.79 br.s (24H, NCH_3), 4.27 br.s (8H, CH_{2arom}), 4.45–4.48 m (4H, CH), 6.77 br.s ($1H_{arom}$). ^{31}P NMR spectrum (D_2O), δ, ppm: 19.88. Found, %: C 38.95; H 5.97; N 3.44; P 15.41. $C_{44}H_{60}N_4O_8 \cdot 4C_2H_8NO_7P_2$. Calculated, %: C 39.11; H 5.81; N 3.51; P 15.52.

^1H NMR spectra were registered on a spectrometer Bruker Avance 400 (400 MHz) with respect to the signals of the residual protons of the deuterated solvent (D_2O). ^{13}C NMR spectra were registered on a spectrometer Bruker Avance 600 (150 MHz) with respect to the signals of the residual protons of the deuterated solvent (D_2O). ^{31}P NMR spectra were registered on a spectrometer Bruker Avance II-400 (161 MHz), external reference 85% H_3PO_4.

IR spectra were recorded on a spectrophotometer UR-20 from pellets with KBr. Melting points were determined in glass capillaries on an instrument Stuart SMP 10.

Bacteriostatic and fungistatic activity was determined by the method of serial dilution in a liquid nutritive medium along procedures [11, 12]. As test objects the following cultures were used: gram-positive bacteria *S. aureus ATCC 209p*, *B. ereus ATCC 8035*, gram-negative bacteria *E. coli CDC F-50*, *P. aeruginosa ATCC 9027*, and fungi *A. niger BKMF-1119*, *T. mentagrophytes 1773, C. albicans 855-653*.

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