Synthesis of per-*O*-(carboxymethyl)calix[4]pyrogallols and their complexation with some alkaline metal and lanthanide ions ✾

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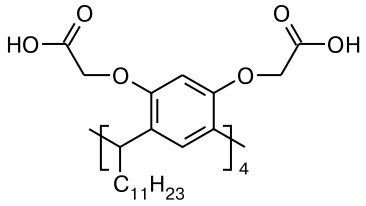
Complexones of a new class, *viz.*, carboxy-functionalized calix[4]pyrrogallols, were synthesized. The per-*O*-(carboxymethyl)calix[4]pyrogallols obtained were established to exist in the (*rel, cis, trans, trans*)-configuration by 2D NMR spectroscopic data. According to the pH-potentiometric data, the interaction of these compounds with alkaline metal ions (Li^+, Na^+, K^+, Cs^+) and lanthanide ions (La^{3+}, Gd^{3+}, Lu^{3+}) in a water—DMSO system produces 1 : 1 complexes. The specific features of complexation of per-*O*-(carboxymethyl)calix[4]pyrogallols, as compared to their acyclic analogs, with alkaline metal and lanthanide ions are due to the cooperative effect of donor groups preorganized on the calixarene matrix.

Key words: cyclophanes, calix[4]arenes, calix[4]pyrogallols, complexation, alkaline metals, lanthanides, stability constants, pH-potentiometry.

A key factor for solving the problem of directed synthesis of artificial ionophores is establishing a correlation between the structure of the compound and its properties. Carboxylate anions are known as efficient donor groups for coordination of hard (according to Pearson) acids, such as ions of alkaline metals and lanthanides.[1] Therefore, polycarboxylic acids allow one to create complexones for these metal ions. The introduction of four carboxylic groups into calix[4]arenes gave complexones, which are more selective in the series of lanthanide ions than complexones based on polycarboxylic acids.[2—4] Calix[4]resorcinolarenes[5] are convenient matrices for introducing different polyfunctional groups. *rccc*-Isomers[6] (*rel, cis, cis, cis*) of these macrocycles are characterized by predomination of the "cone" conformation caused by the formation of intramolecular hydrogen bonds between the hydroxyl groups of adjacent aromatic fragments.[7] The substitution of protons of the hydroxyl groups in calix[4]pyrogallols affords more conformationally labile compounds than the starting calix[4]arenes.[6]

A rising interest in complexation of lanthanide ions with carboxylate derivatives of calix[4]arenes is due to a possibility of creation of pH-controlled complexones and extracting agents of lanthanide ions.[2—4,6] For instance, using alkaline metal ions as an example, the authors[8] have shown a change in selectivity with the pH increase for compound **1**.



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The purpose of this work is to synthesize new carboxy-functionalized calix[4]pyrogallols, *viz.*, 2,8,14,20-tetraaryl-per-*O*-(carboxymethyl)calix[4]pyrogallols,* and to study their configurations in solutions and acid-base and complexing properties. To evaluate the influence of preorganization of carboxylate groups on the efficiency and complexation with alkaline metal ions (Li^+, Na^+, K^+, Cs^+) and lanthanide ions (La^{3+}, Gd^{3+}, Lu^{3+}), we also studied the complexing properties of model com-

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* Locants for aryl groups are given according to the IUPAC nomenclature for carbocycles.

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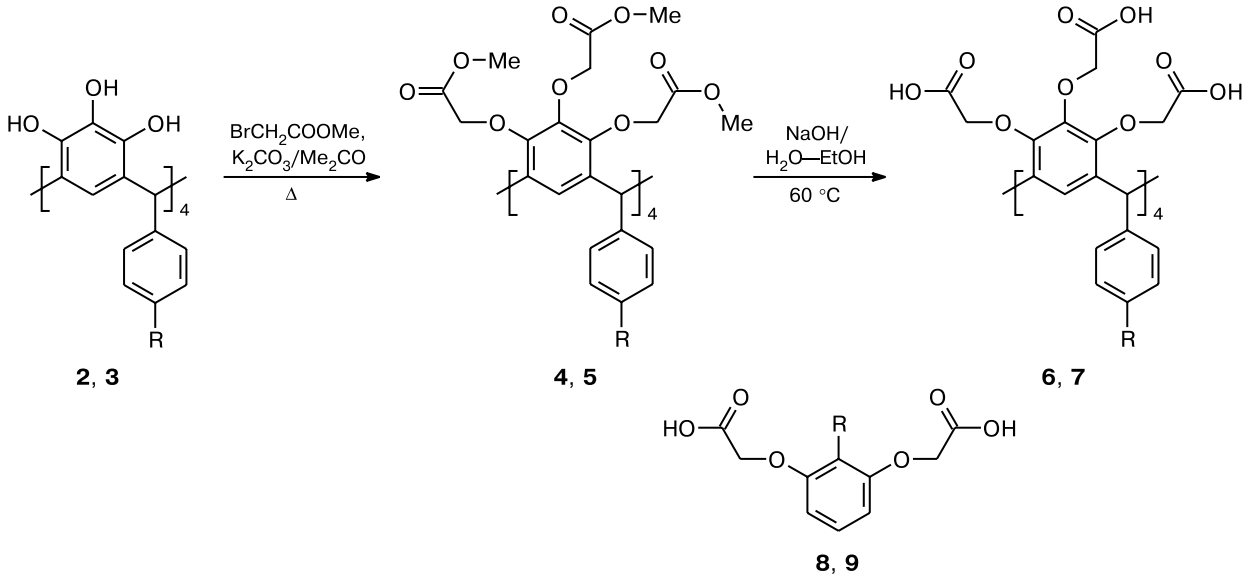
Scheme 1



R = OMe (**2**, **4**, **6**), OH (**3**), OCH_2COOMe (**5**), OCH_2COOH (**7**, **9**), H (**8**)

pounds, which are structural fragments of per-*O*-(carboxymethyl)calix[4]resorcinols and similar derivatives of calix[4]pyrogallols.

The general scheme of syntheses and structural formulas of the macrocyclic ligands under study are presented in Scheme 1.

Experimental

Model 1,3-bis(carboxymethoxy)- and 1,2,3-tris(carboxymethoxy)benzenes **8** and **9** were synthesized according to described procedures.[9,10]

Alkaline metal and lanthanide chlorides and hydroxides (analytical purity grade) and bidistilled water were used. Dimethylsulfoxide (reagent grade) was additionally purified according to a standard procedure.[11] Starting organic reagents (resorcinol, pyrogallol, methyl bromoacetate, 4-methoxybenzaldehyde, and 4-hydroxybenzaldehyde (Merck or Aldrich) were used as received.

^{1}H NMR spectra were recorded on Bruker DRX-300 and Bruker DRX-500 instruments with working frequencies of 300 and 500.13 MHz, respectively. Chemical shifts in the δ scale were measured using Me_4Si as an internal standard. Mass spectra (matrix-activated laser desorption and ionization with a MALDI-TOF time-of-flight mass ionizer) were detected on a Finnigan MALDI-TOF Dynamo mass spectrometer. 1,8,9-Trihydroxyanthracene or 4-nitroaniline were used as matrices. Melting points of substances were determined on a Boetius heating stage. Purity of compounds was monitored by TLC.

pH-Metric titration. Titration was carried out using a solution of $Bu^n{}_4NOH$ (Merck) with a concentration of $8.5 \cdot 10^{-2}$ mol L^{-1} in an H_2O—DMSO (70 vol.%) mixture on an I-130 instrument with the measurement accuracy to 0.05 pH units. To determine the acidity in an H_2O—DMSO (70 vol.%) mixture, a known procedure[12,13] was used, according to which the ionometer was calibrated by standard buffer solutions in water and then the electrode was preliminarily kept in an H_2O—DMSO (70 vol.%) mixture for 1 day to measure the pH of aqueous-organic solutions. The pH values of aqueous-organic solutions were determined from the equation

$$pH = pH_{exp} - \Delta pH,$$

where pH_{exp} is the measured value in a mixed solvent, and ΔpH reflects the difference in proton activities in aqueous and aqueous-organic solutions.

The ΔpH values were determined by measuring the pH of solutions with different HCl concentrations in a mixed solvent (pH_{w+s}) and water (pH_w) from the following equation:

$$\Delta pH = pH_{w+s} - pH_w.$$

Solutions were titrated in an interval of pH 6—12 with a constant concentration of the ligand-host of $2.2 \cdot 10^{-3}$ mol L^{-1} and the molar ratio of the "host" to "guest" (alkaline metal or lanthanide) from 1 : 1 to 1 : 4. These composition of the mixed solvent, concentrations used, and host to guest ratios were chosen, because it was necessary to provide a satisfactory solubility of the starting components and reaction products.

Experimental data were processed by the CPESSP program.[14] Equations of the following types were composed for the chosen basis species (H_wX are ligands **6**—**9**, and M^{q+} is the metal ion):

$$H_wX \rightleftharpoons H_{w-k}X^{k-} + kH^+, \quad (1)$$

$$mH_wX + nM^{q+} \rightleftharpoons \rightleftharpoons \{([H_{w-k}X]^{k-})_m(M^{q+})_n\}^{n-km} + kH^+, \quad (2)$$

These equations are characterized by inherent equilibrium constants.

According to Eq. (2), stoichiometry of any complex formed was designated through m, n, and k, where m is the number of anions of the ligand $[H_{w-k}X]^{k-}$ entering into the reaction, n is the number of cations, k is the charge of the $[H_{w-k}X]^{k-}$ anion-host, and w is the number of carboxy groups in the ligand. The mathematical model represented the set of Eqs. (1) and (2). The dissociation and complexation constants ($\beta_{i...q}$) corresponding to the minimum of the Fischer functional were found by the iteration procedure using the CPESSP program.

2,8,14,20-Tetra(4-methoxyphenyl)-4,5,6,10,11,12,16,17,18,22,23,24-dodecahydroxypentacyclo[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 (2). 4-Methoxybenzaldehyde (15 g, 0.11 mol) was added slowly dropwise with stirring at 5 °C to a solution of pyrogallol (14.32 g, 0.11 mol) in a mixture of EtOH (200 mL), water (200 mL), and concentrated HCl (100 mL). The reaction mixture was left to stir until room temperature (~20 °C) was reached, and then it was heated slowly to 50 °C and stirred for 2 days under argon. A precipitate that formed was separated, washed with water several times, and recrystallized from an EtOH—DMF (50 vol.%) mixture. Compound **2** was obtained as a beige powder in 75% yield (20 g), temperature of decomposition being ~225 °C. Found (%): C, 68.86; H, 5.13. $C_{56}H_{48}O_{16}$. Calculated (%): C, 68.85; H, 4.95. ^{1}H NMR (DMSO-d_6), δ: 3.60 (m, 12 H, OMe); 5.20 (s, 2 H, Ar); 5.60 (s, 4 H, CH); 5.90 (s, 2 H, Ar); 6.40 (d, 8 H, Ar, J = 8.4 Hz); 6.50 (d, 8 H, Ar, J = 8.4 Hz); 7.40 (s, 4 H, OH); 7.10 (s, 4 H, OH); 7.60 (s, 2 H, OH); 7.80 (s, 2 H, OH). MS, m/z: 998 $[M + Na]^+$.

2,8,14,20-Tetra(4-hydroxyphenyl)-4,5,6,10,11,12,16,17,18,22,23,24-dodecahydroxypentacyclo[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 (3). 4-Hydroxybenzaldehyde (20.7 g, 0.17 mol) was added slowly dropwise with stirring at 5 °C to a solution of pyrogallol (22 g, 0.17 mol) in a mixture of 95% EtOH (230 mL), water (110 mL), and concentrated HCl (110 mL). The reaction mixture was stirred until a temperature of ~20 °C was reached, and then it was heated slowly to 50 °C and stirred for 2 days under argon. A precipitate that formed was separated, washed with water several times, and recrystallized from an EtOH—DMF (50 vol.%) mixture. Solvate **3**·DMF was obtained as a beige powder in 43% yield (18 g), temperature of decomposition >300 °C. Found (%): C, 65.42; H, 5.03; N, 1.92. $C_{55}H_{47}NO_{17}$. Calculated (%): C, 66.46; H, 4.77; N, 1,41. ^{1}H NMR (DMSO-d_6), δ: 5.50 (s, 4 H, CH); 5.68 (s, 2 H, Ar); 5.89 (s, 2 H, Ar); 6.32 (d, 8 H, Ar, J = 8.8 Hz); 6.40 (d, 8 H, Ar, J = 8.8 Hz); 7.31 (s, 4 H, OH); 7.45 (s, 4 H, OH); 7.72 (s, 2 H, OH); 7.78 (s, 2 H, OH); 8.7 (s, 4 H, OH). MS, m/z: 995 $[M + DFM]^+$.

2,8,14,20-Tetra(4-methoxyphenyl)-4,5,6,10,11,12,16,17,18,22,23,24-dodeca(methoxycarbonylmethyloxy)pentacyclo[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 (4). Methyl bromoacetate (9.8 g, 0.06 mol) was added with stirring at ~20 °C to a mixture of calix[4]pyrogallol **2** (3 g, 3.1 mol) and K_2CO_3 (8.5 g, 0.06 mol) in anhydrous Me_2CO (50 mL). The reaction mixture was stirred for 3 days under argon at 70 °C and filtered. Then Me_2CO was distilled off from the filtrate. An oily residue was treated with EtOH and recrystallized from an EtOH—DMF (50 vol.%) mixture. Ester **4** as a yellow powder was obtained in 83% yield (4.6 g), m.p. 148 °C. Found (%): C, 59.02; H, 5.17. $C_{92}H_{96}O_{40}$. Calculated (%): C, 60.0; H, 5.25. ^{1}H NMR (DMSO-d_6—$CDCl_3$), δ: 3.65 (m, 16 H, OMe); 4.40 (m, 24 H, CH_2); 5.51 (s, 4 H, CH); 5.85 (s, 8 H, Ar); 5.95 (s, 8 H, Ar); 6.51 (s, 4 H, Ar). MS, m/z: 1863 $[M + Na]^+$.

2,8,14,20-Tetra(4-methoxycarbonylmethyloxyphenyl)-4,5,6,10,11,12,16,17,18,22,23,24-dodeca(methoxycarbonylmethyloxy)pentacyclo[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) was synthesized similarly to compound **4** from calix[4]pyrogallol **3** (3 g, 3 mmol), K_2CO_3 (8.5 g, 0.06 mol), methyl bromoacetate (9.8 g, 0.06 mol), and Me_2CO (50 mL). Compound **5** was obtained as a white powder in 72% yield (4.5 g), m.p. 170 °C. Found (%): C, 58.02; H, 5.27. $C_{100}H_{104}O_{48}$. Calculated (%): C, 57.92; H, 5.05. ^{1}H NMR ($CDCl_3$), δ: 3.65 (m, 48 H, Me); 4.10—4.80 (m, 32 H, CH_2); 5.45 (s, 8 H, Ar); 5.85 (s, 8 H, Ar); 6.06 (s, 4 H, CH); 6.6 (s, 4 H, Ar). MS, m/z: 2091 $[M + Na]^+$.

2,8,14,20-Tetra(4-methoxyphenyl)-4,5,6,10,11,12,16,17,18,22,23,24-dodeca(carboxymethyloxy)pentacyclo[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 (6). A mixture of ester **4** (0.8 g, 0.43 mmol) and NaOH (0.28 g, 7 mmol) in a water—EtOH (50%) mixture (15 mL) was stirred for 3 days under argon at 50 °C. Then 20% H_2SO_4 (15 mL) was added dropwise with stirring to the reaction mixture, and light flakes precipitated during addition. The flakes were filtered off and washed with water and EtOH. Compound **6** was obtained as a white powder in 70% yield (0.5 g), temperature of decomposition >250 °C. Found (%): C, 57.69; H, 4.5. $C_{80}H_{72}O_{40}$. Calculated (%): C, 57.42; H, 4.34. ^{1}H NMR (DMSO-d_6—$CDCl_3$), δ: 3.65 (s, 12 H, OMe); 4.00 (m, 12 H, CH_2); 4.40 (m, 12 H, CH_2); 4.65 (d, 8 H, Ar, J = 15.8); 5.69 (s, 4 H, Ar); 5.90 (d, 8 H, Ar, J = 18.8 Hz); 6.55 (s, 12 H, OH). MS, m/z: 1696 $[M + Na]^+$.

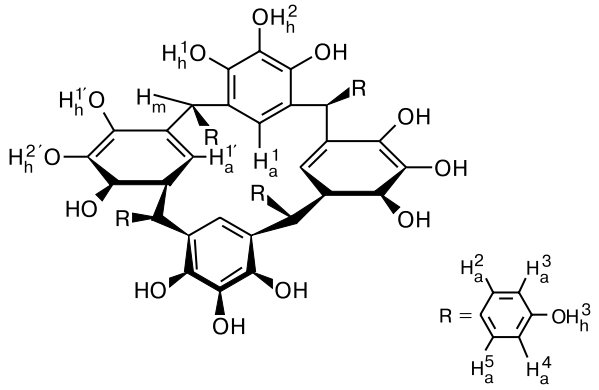
2,8,14,20-Tetra[4-(carboxymethyloxy)phenyl]-4,5,6,10,11,12,16,17,18,22,23,24-dodeca(carboxymethyloxy)pentacyclo[19,3,1,1^{3,7},1^{9,13},1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene (7) was synthesized similarly to acid **6** from calix[4]pyrogallol **5** (1.4 g, 0.6 mmol), NaOH (0.5 g, 125 mmol), and a water—EtOH (50%) mixture (25 mL). Compound **7** was obtained as a light gray powder in 72% yield (0.8 g), temperature of decomposition being ~200 °C. Found (%): C, 54.51; H, 3.90. $C_{84}H_{72}O_{48}$. Calculated (%): C, 54.55; H, 3.92. ^{1}H NMR (DMSO-d_6—$CDCl_3$), δ: 4.10 (d, 24 H, CH_2, J = 6.9 Hz); 4.40 (m, 8 H, CH_2); 4.70 (s, 4 H, CH); 5.50 (s, 4 H, Ar); 5.86 (s, 8 H, Ar); 5.95 (d, 8 H, Ar, J = 11.1 Hz); 6.50, 7.90 (both s, 16 H, OH). MS, m/z: 1868 $[M + Na]^+$.

Results and Discussion

The compositions and structures of the macrocyclic compounds synthesized were confirmed by the data of elemental analysis, MALDI-TOF mass spectrometry, and ^{1}H NMR and 2D NMR spectroscopies.

Configurations of per-*O*-(carboxymethyl)calix[4]pyrogallols in solutions according to NMR data. According to the ^{1}H NMR spectroscopic data, newly synthesized calix[4]pyrogallols **2** and **3**, as well as related esters **4** and **5** and acids **6** and **7**, were isolated as only one *rctt*-isomer (*rel*, *cis*, *trans*, *trans*). In particular, it follows from the above-presented data for compound **3** that one characteristic singlet signal δ(H_m) 5.5 corresponds to the

methine proton. The presence of two signals $\delta(H_a^1)$ 5.68 and $\delta(H_a^{1'})$ 5.89 from the protons of the benzene rings and from the hydroxyl protons $\delta(H_h^1)$ 7.3, $\delta(H_h^{1'})$ 7.45 and $\delta(H_h^2)$ 7.72 and $\delta(H_h^{2'})$ 7.78 indicates that the pyrogallol fragments are nonequivalent, which is caused by the *rctt*-configuration of calix[4]pyrogallol **3**.



In addition, the *rctt*-configuration was confirmed for calixarenes **2** and **3** by 2D NMR spectroscopy (H,H-COSY, HETCOR, ROESY). Analysis of the ROESY NMR spectra of compounds **3** (Fig. 1) shows a relatively strong interaction (in the space of the H_m methine protons) of the H_a^2 and H_a^5 protons of the R radical with the aryl protons of the pyrogallol fragments ($H_a^{1'}$), indicating their tight contact. At the same time, a weak interaction is observed with the H_a^1 protons of other pyrogallol fragments, which indicates their remoteness. The H_a^1 protons exhibit a weak spatial interaction with the H_a^5 protons and a strong interaction with the $H_a^{1'}$ and H_a^2 protons. Similarly to the H_a^1 protons, the $H_a^{1'}$ protons interact weakly with the H_a^5 protons of the hydroxy-

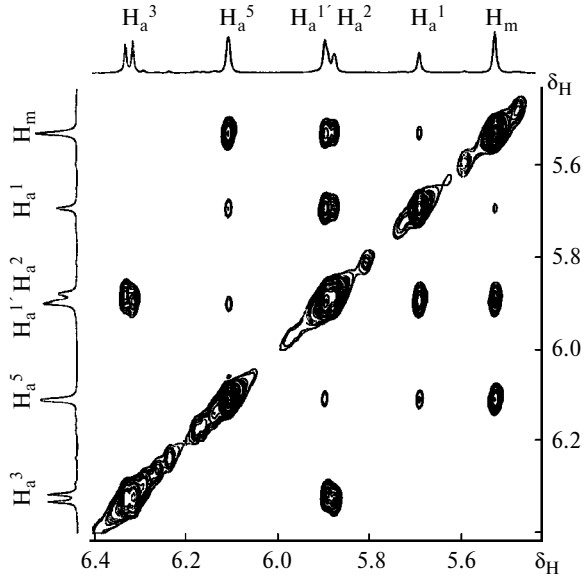


Fig. 1. 2D ROESY NMR spectrum of compound **3**.

aromatic radical. The H_a^2 protons of the R substituent interact strongly with the adjacent H_a^3 protons. The NMR spectra for compound **2** are similar.

Acid-base properties of compounds 6—9 in aqueous-dimethylsulfoxide solutions. The difference in stepwise dissociation constants pK of polycarboxylic acids is known to characterize the mutual influence of the carboxy groups.

For instance, the intramolecular hydrogen bond between the carboxy and carboxylate groups decreases pK_1 and increases pK_2 during dissociation of dicarboxylic acids.[15] It was shown for the tetracarboxy derivative of calix[4]arene in the "cone" conformation that the increased acidity of its first proton is also caused by the strong intramolecular hydrogen bond between the carboxy and carboxylate groups.[16] The lower pK_1 value and the higher difference $\Delta pK = pK_2 - pK_1$ for compound **8** compared to **9** (Table 1) indicate that the presence of the third carboxy group leads to a weaker (lower in energy) intramolecular hydrogen bond between the carboxy and carboxylate groups of monoanion **9** compared to **8**. The third carboxy group in **9** does not dissociate in the pH interval studied, indicating the presence of a strong intramolecular hydrogen bond in the dianion that formed. This bond prevents the elimination of the third proton. On going from acid **8** to its cyclic analog **1**, pK_1 increased to 5.78,[8] while pK_1 decreased, as has already been mentioned,[16] on going from phenylacetic acid to tetracarboxylated calix[4]arene in the "cone" and "partial cone" conformations. The acidity decrease indicates a more efficient stabilization of the molecular form of compound **1** by intramolecular hydrogen bonds compared to its monoanion, which is also characteristic of the phosphonomethyl derivatives of calix[6]arenes.[17] On going from compound **9** to **6**, dissociation by the first and second steps becomes much easier to occur. The pK_1 and pK_2 values of compound **6** are lower than pK_1 and pK_2 for **9** by almost unity (see Table 1). It seems natural to assume that the stabilization of the dianion of compound **6** that formed is caused by the intramolecular hydrogen bond between the adjacent carboxymethylated pyrogallol fragments.

The further dissociation of acid **6** by the third (with elimination of the third and fourth protons) and fourth (with elimination of the fifth and sixth protons) steps (see Table 1) occurs much more easily than that for compound **1** ($pK_{3,4}$ = 15.6 and $pK_{5,6}$ = 16.9).[8] Under the conditions of pH-metric experiments, compound **1** exhibited the formation of species to the hexaanion only,[8] while compound **6** dissociated to the decaanion. This can be explained by the fact that the carboxylate groups of compound **6** experience a much lower influence of the negative electrostatic charge, which is formed upon the dissociation of the molecule and prevents its further deprotonation compared to the anion of molecule **1**. This is likely caused by different structures of these compounds, because the functional groups in the *rctt*-isomer, unlike

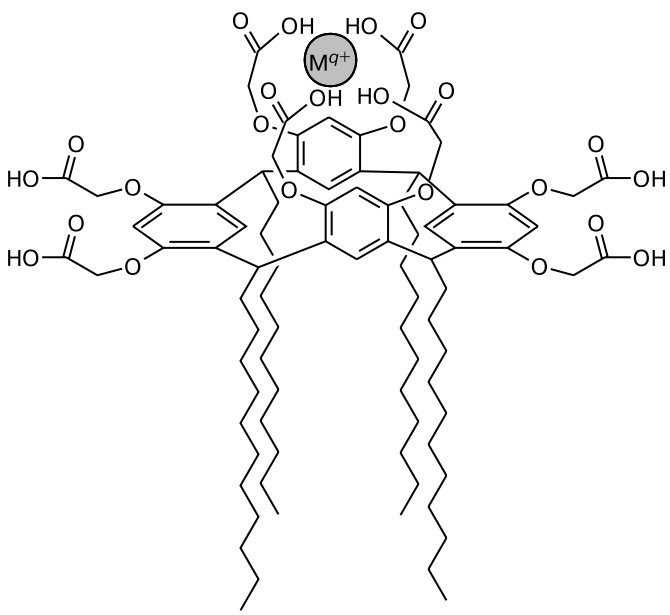
Table 1. Stepwise dissociation constants (*p*K) of compounds **6**—**9** in aqueous-dimethylsulfoxide solutions

Equilibrium	p*K*			
	6	**7**	**8**	**9**
$H_wX = H_{(w-1)}X^- + H^+$	5.05±0.02	5.11±0.02	5.19±0.05	6.06±0.1
$H_{(w-1)}X^- = H_{(w-2)}X^{2-} + H^+$	4.98±0.02	5.94±0.06	6.04±0.10	6.20±0.1
$H_{(w-2)}X^- = H_{(w-3)}X^{3-} + H^+$	—	6.09±0.06	—	—
$H_{(w-2)}X^- = H_{(w-4)}X^- + 2\ H^+$	12.19±0.03	12.53±0.06	—	—
$H_{(w-4)}X^- = H_{(w-6)}X^{6-} + 2\ H^+$	13.97±0.07	13.83±0.06	—	—
$H_{(w-6)}X^- = H_{(w-8)}X^{8-} + 2\ H^+$	15.59±0.08	14.96±0.07	—	—
$H_{(w-8)}X^- = H_{(w-10)}X^{10-} + 2\ H^+$	18.15±0.17	16.33±0.10	—	—

those in the *rccc*-isomer, are arranged at different sides of the plane passing through the methine fragments (Fig. 2).

Despite additional four carboxy groups in **7** over those in **6**, acid **7** also eliminates only ten protons in the pH region studied. The pK_1 values for acid **7** is close to pK_1 for **6**. However, unlike acid **6**, the deprotonation constant of **7** by the second step is almost an order of magnitude lower than that by the first step, and dissociation is accompanied by trianion formation (see Table 1). This indicates that the introduction of additional carboxy groups on going from **6** and **7** results in a noticeable stabilization of the mono- and trianions due to a change in the energy of intermolecular hydrogen bonds between the carboxy and carboxylate groups. It is of interest that the dissociation of the seventh and eighth, as well as ninth and tenth, protons of compound **7** occurs much more easily than that for **6**. Therefore, the octa- and decaanions of compounds **7** are weaker bases than similar anions of compound **6**. Thus, the replacement of the substituent R = OMe by R = OCH_2COOH in calix[4]pyrogallols **6** and **7** leads to slight changes in the dissociation constants to the hexaanion but facilitates substantially further dissociation to the decaanion. It is known that the lanthanide complexes with carboxylic acids exhibit a linear correlation between the logarithm of the stability constant of the complex and the p*K* of the acid.[1] As a result, one can expect a lower complexing ability toward hard Lewis acids of the octa- and decaanions of compound **7** compared to **6**.

Complexation of aryloxyacetic acids 6—9 with alkaline metal and lanthanide ions. The complexing ability of aryloxyacetic acids **6**—**9** toward the series of alkaline metal and lanthanide ions was estimated in a wide pH interval by pH-metric titration. The complexation of ionophore **1** with alkaline metal ions has previously been studied[8] by



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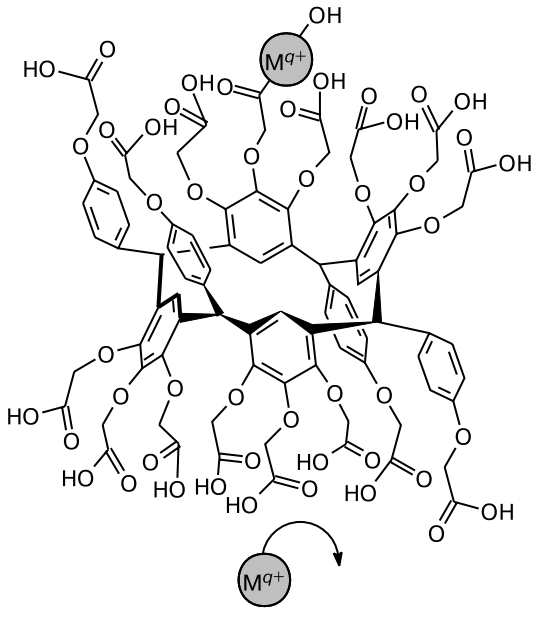

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Fig. 2. Model of complexation of H_wX (**1**, **7**) with metal ions M^{q+}.

^{1}H NMR spectroscopy and pH-potentiometry. These results suggested that the conformational mobility of the carboxymethyleneoxyresorcinol fragments in **1** was a prerequisite for the formation of a ionophore, which preferentially binds potassium ions in the neutral region and lithium ions in the weakly alkaline region. In turn, the pH-dependent selectivity of compound **1** is a consequence of the pH-dependent preorganization of the carboxymethyleneoxy groups at the rim of the ionophore.

The complexing properties of model compound **8**, which is a structural fragment of compound **1**, were studied to estimate the influence of preorganization of carboxylate groups on the efficiency and selectivity of complexation of alkaline metal ions (Li^+, Na^+, K^+, Cs^+) and lanthanide ions (La^{3+}, Gd^{3+}, Lu^{3+}). However, alkaline metal ions taken in an equimolar ratio have no effect on the acidity of carboxymethyl groups of acid **8**, which indicates that no noticeable (higher than 10%) accumulation of the corresponding complexes is observed under these conditions. Thus, the fixation of carboxymethyl groups on the calix[4]resorcinol matrix (*rccc*-isomer) (compound **1**) leads to the creation of the much more efficient (compared to its noncyclic analog, compound **8**) and selective pH-controlled ionophore **1**.

In the presence of tricharged lanthanide ions, the acidity of compound **8** increases noticeably already at an equimolar ratio, which makes it possible to estimate the stoichiometry and stability of the complexes formed. Compound **8** with lanthanide ions forms complexes with $m = 1$, $n = 1$, and $k = 1$—3 (Table 2). The complex with $m = 1$, $n = 1$, and $k = 1$ (at most 15%) is accumulated not for all systems studied.

The complex with $m = 1$, $n = 1$, and $k = 2$ is deprotonated to the complex with $m = 1$, $n = 1$, and $k = 3$ due to the deprotonation of the water molecule in the first coordination sphere. This process can be described by the following equation:

$$[Ln^{3+}H_{w-2}X^{2-}H_2O]^+ = [Ln^{3+}H_{w-2}X^{2-}(OH^-)] + H^+. \qquad (3)$$

Lanthanide ions are bound by compound **1** in a weakly acidic region (pH < 3), resulting in the precipitation of the complexes, which makes it difficult to estimate their composition and stability in aqueous-dimethylsulfoxide solutions.

To estimate the effect of preorganization of carboxymethyl groups on the calix[4]pyrogallol matrix, we synthesized the carboxymethyl derivative: tri-*O*-(carboxymethyl)pyrogallol (triacid **9**). The complexing ability of triacid **9** toward alkaline metal ions is similar to that for diacid **8**. However, lanthanide ions are bound by triacid **9** much more efficiently to form complexes with $m = 1$, $n = 1$, and $k = 1$—3 (see Table 2). The deprotonation constants of the complex with $m = 1$, $n = 1$, and $k = 2$ to the complex with $m = 1$, $n = 1$, and $k = 3$ are close for both ligands. This suggests that the complex is deprotonated, in both cases, due to the deprotonation of the water molecule in the first coordination sphere according to Eq. (3). It should also be noted that the appearance of the third carboxy group on going from diacid **8** to **9** changes the ratio between the binding constants of the La^{3+}, Gd^{3+}, and Lu^{3+} ions. In particular, the stability constants of the complexes with $m = 1$, $n = 1$, and $k = 2$ of the lanthanide ions with diacid **8** increase in the series La < Gd < Lu, while for triacid **9**, the stability constants increase in the series Gd < Lu ≈ La.

When going from the noncyclic analogs to calix[4]pyrogallols, one can introduce 12 and 16 carboxymethyl groups into the ionophore (compounds **6** and **7**, respectively). As follows from the data of pH-metric titration (see Table 2), calixarenyl acid **6** binds alkaline metal ions more efficiently than triacid **9** but much less selectively than calix[4]resorcinol **1** does.[8] The ionophoric ability decreases on going from the anions of calixarenyl acid **6** to similar anions of calixarenyl acid **7**. The Li^+, Na^+, K^+, and Cs^+ ions exert a much lower effect on the deprotonation of compound **7** than that in the case of **6** due to a decrease in the stability of the complexes formed (see Table 2). The order of changing the stability constants of the complexes of anion **7** in the series of alkaline metal ions ($Li^+ < Cs^+ \approx K^+$) differs from that for **6** ($Cs^+ \approx K^+ < Li^+$). Note that calixarenyl acid **7** exhibits a decrease in the stability constants with an increase in the degree of deprotonation k (see Table 2).

The *rctt*-configuration of calixarenyl acids **6** and **7** assumes a possible formation of two donor centers arranged symmetrically at the upper and lower rims (see Fig. 2). However, all ions studied are bound in a ratio of 1 : 1. Thus, the change in the configuration of the cyclophanic matrix from the *rccc*-isomer for calixresorcinyl acid **1** to the *rctt*-isomer for calixarenyl acids **6** and **7** and the corresponding change in the preorganization of the carboxy groups decrease the selectivity of binding of alkaline metal ions.

Calixarenyl acids **6** and **7** also bind lanthanide ions in a molar ratio of 1 : 1, affording precipitates of neutral complexes with La^{3+} and Gd^{3+} ions with $m = 1$, $n = 1$, and $k = 3$, while the for Lu^{3+}, the complex with $m = 1$, $n = 1$, and $k = 3$ is not prevailing and transforms easily into the complex with $m = 1$, $n = 1$, and $k > 3$, which prevents precipitation. The stability constants of the complexes with lanthanide ions are much higher than those with alkaline metal ions. Compound **6** is also a more efficient ionophore toward lanthanide ions than compound **7** (see Table 2). Unlike alkaline metal ions, the stability constants of the complexes with lanthanide ions increase with an increase in the degree of deprotonation of calixarenyl acid **7**, although this increase is much lower than that for calixarenyl acid **6**. The higher the number of lanthanide, the more efficient the binding of the lan-

Table 2. Stability constants (logβ) of the complexes formed in the $H_wX—M^{q+}$ system and deprotonation constants (pK) of the complexes with $m = 1$, $n = 1$, and $k = 2$

M^{q+}	$\{([H_{w-k}X]^{k-})_m(M^{q+})_n\}^{n-km}$			logβ(pK)			
	m	n	k	**6**	**7**	**8**	**9**
Li^+	1	1	2	4.05±0.02	2.70±0.08	—	—
	1	1	4	5.46±0.06	2.9±0.1	—	—
	1	1	6	6.90±0.10	2.80±0.25	—	—
	1	1	8	8.6±0.2	2.5±0.5	—	—
Na^+	1	1	2	3.94±0.03	*	—	—
	1	1	4	5.10±0.07	*	—	—
	1	1	6	6.40±0.10	*	—	—
	1	1	8	7.81±0.20	*	—	—
K^+	1	1	2	3.70±0.03	3.35±0.08	—	—
	1	1	4	4.86±0.06	3.7±0.1	—	—
	1	1	6	6.0±0.1	3.60±0.25	—	—
	1	1	8	7.2±0.2	—	—	—
Cs^+	1	1	2	3.67±0.02	3.4±0.1	—	—
	1	1	4	4.82±0.04	3.6±0.2	—	—
	1	1	6	5.90±0.06	3.4±0.5	—	—
	1	1	8	7.10±0.10	3.1±0.7	—	—
La^{3+}	1	1	1	—	—	3.16±0.06	—
	1	1	2	—	5.45±0.04	4.55±0.07	6.84±0.06
				—	—	(7.7±0.2)	(7.8±0.6)
	1	1	3	7.73±0.02	7.03±0.06	—	—
	1	1	4	8.1±0.3	8.16±0.09	—	—
	1	1	6	—	—	—	—
	1	1	8	—	—	—	—
	1	1	10	—	—	—	—
Gd^{3+}	1	1	1	—	—	3.01±0.08	—
	1	1	2	6.2±0.2	5.64±0.06	4.67±0.03	6.35±0.05
				—	—	(7.4±0.6)	(7.8±0.3)
	1	1	3	8.9±0.2	7.75±0.05	—	—
	1	1	4	11.6±0.1	9.28±0.08	—	—
	1	1	6	15.9±0.1	—	—	—
	1	1	8	—	—	—	—
	1	1	10	26.2±0.2	—	—	—
Lu^{3+}	1	1	1	—	—	3.24±0.08	4.73±0.09
	1	1	2	6.46±0.05	6.27±0.05	5.14±0.06	6.79±0.07
				—	—	(7.3±0.5)	(7.9±0.5)
	1	1	3	—	8.56±0.05	—	—
	1	1	4	11.80±0.04	9.87±0.1	—	—
	1	1	6	16.0±0.1	11.6±0.1	—	—
	1	1	8	—	12.1±0.1	—	—
	1	1	10	26.3±0.2	11.2±0.1	—	—

* No data.

thanide ion by both ionophores. However, for calixarenyl acid **6**, the stability constants change with an increase in the number of lanthanide ion in the order La < Gd < Lu, while for **7**, La < Gd ≈ Lu (see Table 2).

Thus, an increase in the number of carboxymethyleneoxyl substituents on going from acid **8** to acid **9** results in the more efficient binding of lanthanide ions. At the same time, an increase in their number on going from ionophore **6** to ionophore **7** decreases the affinity to both lanthanide metal ions and lanthanide ions. Although calix[4]pyrogallols under study contain two possible centers of coordination of metal ions, coordination to only one metal ion is observed. This indicates the negative cooperative effect in binding of metal ions due to the distortion of the spatial preorganization of carboxy groups caused by coordination to the metal ion (see Fig. 2).

The results obtained demonstrate the effect of preorganization of donor groups on the calixarene matrix on the ionophoric molecules and the influence of different types of noncovalent interactions, in particular, forma-

tion of intramolecular hydrogen bonds and electrostatic interactions, on the preorganization of donor groups.

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