Complexation of Gd^{III} with tetra-*p*-*tert*-butylthiacalix[4]arenoic acid in micellar media

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The conditions for the formation of gadolinium(III) complexes possessing high relaxivity with various tetraacid stereoisomers based on *p-tert*-butylthiacalix[4]arene in micellar solutions of nonionic surfactants were established. The acid-base properties of individual isomers of the ligand were studied by pH-metric titration and UV spectroscopy. The composition and stability constants of the solubilized gadolinium(III) complexes with the obtained thiacalixarenes were determined using computer simulation of the NMR relaxation data.

Key words: *p-tert*-butylthiacalix[4]arene, gadolinium(III), NMR relaxation, complex formation, stability constants, micelles, nonionic surfactants.

Search for high-relaxivity metal complexes is one of the most urgent problems in the development of new contrast agents (CAs) for magnetic resonance imaging (MRI), which is a non-invasive method for NMR-based clinical diagnostics of diseases.[1] At present stable gadolinium(III) complexes with linear and cyclic polyaminopolycarboxylates are used as CAs.[2] A substantial drawback of these CAs is their low relaxivity factor (3000—5000 L mol^{-1} s^{-1}), which requires the administration of large doses of the drug to the body. Since natural biochemical cycles involving Gd^{3+} ions are absent, the decrease in the amount of the gadolinium compounds introduced into the body is an important task. This requires the design of contrast agents with high spin-lattice relaxivity values (relaxivity is the paramagnetic contribution to the relaxation rate of protons of the solvent, R_1).[2,3] It is known that one of the methods for increasing the relaxivity of solutions containing gadolinium ions is the retardation of their rotation due to the formation of high-molecular-weight particles (aggregation, complexes) in their composition.[4] It was shown[5,6] than an increase in the relaxivity in solutions of long-chain alkyl sulfates in the presence of Gd^{3+} ions is caused by the adsorption of the latter on the surface of anionic micelles. The increase in the relaxivity of the gadolinium(III) complex with the diethylenetriaminepentaacetic acid derivative containing the cholesterol moiety as the substituent is due to its self-aggregation in water with an increase in the concentration or the incorporation of the complex in mixed aggregates with the nonionic surfactant.[7] Thus, the choice of amphiphilic compounds capable of self-aggregation or incorporation in the composition of mixed aggregates seems to be one of the promising approaches to the design of contrast preparations.

From this point of view, metacyclophanes, in particular, calixarenes, whose ability to complexation and hydrophilic—lipophilic balance can be varied in a wide range,[8—11] are very promising ligands for chelating rare-earth metal ions, including gadolinium(III).[12,13] Meanwhile, in a few known works,[14,15] calixarenes with insufficient lipophilicity were used to design potential contrast agents. However, the influence of the ligand conformation on the stability and relaxation parameters of their complexes with Gd^{III} was not examined. The purpose of the present study is to reveal the influence of the spatial arrangement of the functional groups in the *p-tert*-butylthiacalix[4]arene stereoisomers substituted by carboxy groups at the lower rim on the ability of such ligands to bind the Gd^{3+} ions to form water-soluble complexes possessing high relaxivity. In addition, we attempted to evaluate the influence of the type and concentration of the nonionic surfactant in solution on the degree of binding of the paramagnetic probe and relaxivity of gadolinium solutions containing calixarene—surfactant mixed aggregates.

For this purpose, we synthesized tetraesters based on thiacalix[4]arene in the conformations *cone* (**1a**), *partial cone* (**1b**), and *1,3-alternate* (**1c**), from which the corresponding stereoisomers of tetra-*p*-*tert*-butylthiacalix[4]-arenoic acid **2a**—**c** were prepared.

It is known that the mutual conformational transformations of calix[4]arene (*cone*, *partial cone*, *1,2-alternate*, *1,3-alternate*) become impossible if the lower rim contains substituents larger than or equal to the *n*-propyl fragment.[16,17] When synthesizing the thiacalix[4]arene stereo-

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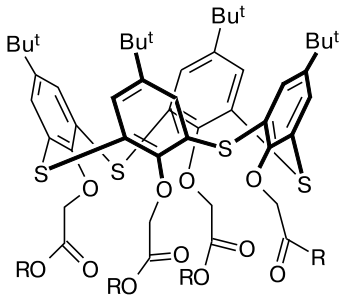
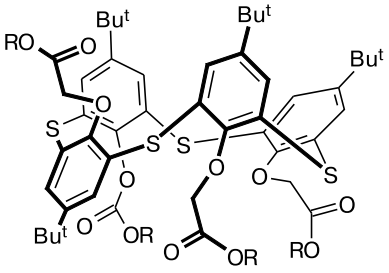
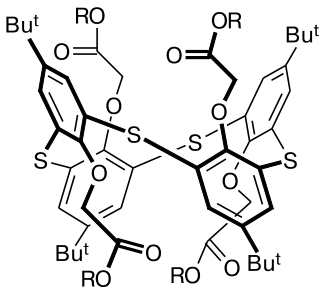


1a, **2a**



1b, **2b**

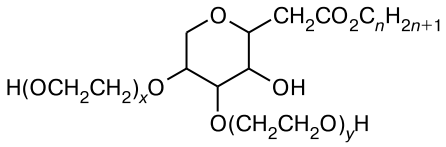


1c, **2c**

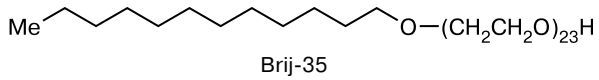
R = Et (**1**), H (**2**)

isomers substituted at the lower rim, both the nature of the substituent and the reaction conditions (solvent, temperature) were taken into account.

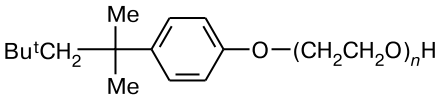
The following nonionic surfactants were used for the preparation of calixarene—surfactant mixed aggregates: oxyethylated alkyl sorbates Tween-20, -40, and -60, oxyethylated dodecanol Brij-35, and oxyethylated isooctylphenols Triton X-100 and X-405.



$x + y = 20$; $n = 11$ (Tween-20), 15 (Tween-40), 17 (Tween-60)



Brij-35



$n = 10$ (Triton X-100), 40 (Triton X-405)

Experimental

Commercial $Gd(NO_3)_3 \cdot 6H_2O$ (reagent grade, Reakhim) was used in the work. The concentration of Gd^{3+} ions in solution was determined by complexonometric titration.

Commercial nonionic surfactants Tween-20, -40, and -60 (Ferak), Brij-35 (MP Biomedicals), Triton X-100, and X-405 (MP Biomedicals) were used.

The starting *p-tert*-butylthiacalix[4]arene was synthesized according to the previously described[18] procedure by the condensation of *p-tert*-butylphenol and elementary sulfur at 260 °C in the presence of sodium hydroxide.

Tetra-*p-tert*-butylcalix[4]arenoic acid tetraesters (*cone* (1a), *partial cone* (1b), and *1,3-alternate* (1c)) and 5,11,17,23-tetra-*tert*-butyl-25,26,27,28-tetrakis[(hydroxycarbonyl)methoxy]-thiacalix[4]arene (*cone* (2a), *partial cone* (2b), and *1,3-alternate* (2c)) (general procedure). Compounds **1a**—**c** were synthesized[19] by the exhaustive alkylation of *p-tert*-butylthiacalix[4]arene with ethyl bromoacetate in boiling acetone in the presence of the corresponding alkaline metal carbonate.

Tetraesters **1a**—**c** were subjected to quantitative hydrolysis to the corresponding tetraacids **2a**—**c** by lithium hydroxide in aqueous THF.[20]

Preparation of calixarene—surfactant aggregates and study of complexation. Since thiacalixarene samples were not completely dissolved even in a large excess of nonionic surfactant, a weighed sample of the ligand was dissolved in water containing 4 equiv. NaOH, and then the necessary amount of a surfactant and 4 equiv. HCl were added. When studying complexation, the pH of the medium was changed by the addition of an aqueous solution of NaOH, and the pH value was measured with a Thermo Electron ThermoOrion 420A pH-meter with an accuracy of ±0.01 pH units.

The pH-metric titration was carried out using a Thermo Electron microliter dispenser in such a way that at the end of the experiment the increase in the solution volume due to the addition of an aqueous carbonate-free solution of NaOH did not exceed 12%.

Electronic absorption spectra of solutions were recorded on a Perkin—Elmer Lambda EZ-210 instrument using an aqueous solution of the surfactant at the same concentration as a reference.

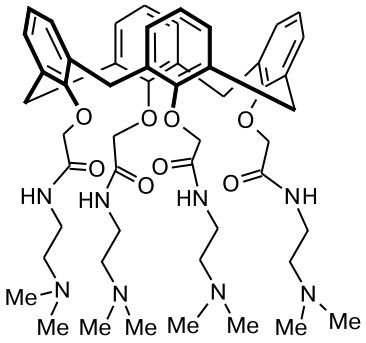
The spin-lattice relaxation times (T_1) of water protons were measured on a Bruker Minispec MQ20 pulse NMR relaxometer (19.75 MHz). The error of measurement of relaxation times did not exceed 1%. The temperature was maintained at 298 K using a Thermo Electron Haake DC10 thermostat.

The spin-lattice relaxation rate of protons ($1/T_1$) in aqueous solutions containing paramagnetic ions Gd^{3+} includes the diamagnetic ($1/T_{2A} \approx 0.4$ s^{-1}, in the absence of a paramagnetic impurity) and paramagnetic ($1/T_{1p}$) contributions: $1/T_1 = 1/T_{1A} + 1/T_{1p}$. The experimental results are presented using the relaxivity values (R_1/L mol^{-1} s^{-1})[2] of solutions, namely, the paramagnetic contribution ($1/T_{1p}$) reduced to the gadolinium ion concentration unit (C_{Gd}): $R_1 = 1/(C_{Gd}T_{1p})$. The spin-lattice relaxivity factor (RF_1)[3] of gadolinium(III) equal to the relaxivity of the solution of its aqua ions was 14 000 L mol^{-1} s^{-1}. The possibilities of the NMR relaxation method for studying complexation and aggregation processes in solutions using paramagnetic probes have been described previously.[3,4]

The experimental data were mathematically processed using the CPESSP program.[21]

Results and Discussion

The literature data on the relaxivity and stability of the gadolinium(III) complexes with metacyclophanes are given only for two derivatives of classical calixarene **3** and **4** in the *cone* conformation substituted by functional groups at the lower rim.[14,15] Tetraamide **3** forms a rather lowly stable complex with gadolinium(III) ($\beta = 2 \cdot 10^5$, where β is the stability constant) for which $RF_1 < 5000$ L mol^{-1} s^{-1} (see Ref. 14). The stability of the Gd^{III} complex with ligand **4** determined from the NMR relaxation data by competitive complexation is substantially higher ($\beta \approx 1 \cdot 10^{13}$).[15] The relaxivity of a solution of the Gd^{III} complex with ligand **4** in the pH range 4—9 is 9600 L mol^{-1} s^{-1}, which is approximately twice as large as the RF_1 values for commercial CAs based on gadolinium polyaminocarboxylates.



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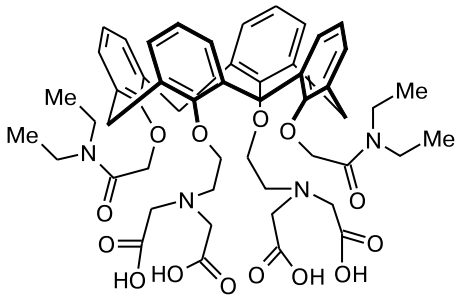

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As already mentioned, one of the methods for increasing the relaxivity of solutions of the metal complexes is the use of ligands containing lipophilic substituents.[4] Similar complexes are capable of self-aggregating in water or incorporating in the existing ensembles of amphiphilic compounds (surfactants, micelles, liposomes, *etc.*). This approach has previously been applied[7,22] to increase the relaxivity (up to 25 000—40 000 L mol^{-1} s^{-1}) in solutions of gadolinium complexes in which the lipophilic derivatives of diethylenetriaminepentaacetic acid, being a component of the known contrast agents, are used as ligands.

The higher R_1 values (about 35 000—60 000 L mol^{-1} s^{-1}) were observed for gadolinium(III) solutions in the presence of a series of tetrasulfonatometacyclophanes.[23—25] It was shown that the relaxivity of aqueous solutions containing Gd^{3+} ions and sulfonatocalix[*n*]arene[23] or sulfonatocalix[4]resorcinarenes[24,25] increases considerably with an increase in the lipophilicity of their molecules. As in the case of anionic surfactants, this is due to the binding of Gd^{3+} ions with aggregates of amphiphilic metacyclophanes formed in water. The relaxivity also increased upon the addition of nonionic surfactants to solutions of the listed metacyclophanes due to the formation of mixed micelles. The results obtained indicate that the gadolinium complexes with very high R_1 values can exist in water.

The latter, as compounds **3** and **4**, have the *cone* configuration. Meanwhile, the change in the configuration of the calixarene platform (*partial cone*, *1,2-* and *1,3-alternates*) makes it possible to vary the composition and stability of the corresponding metal complexes.[8—11] The thiacalix[4]arene platform in which the phenol fragments are sulfur-bridged is more appropriate for these purposes. The efficient methods for the template synthesis of thiacalix[4]arene stereoisomers were developed.[17,26,27]

Complexation in solution is the competition of the cation and proton for binding with the donor atom of the ligand and, hence, according to the commonly accepted point of view, more basic functional groups form a more stable bond with the complexing cation.[28] Therefore, the complexes with rare-earth metal cations with the involvement of the O atoms of the carboxyl groups possessing higher electron-donating ability than the O atoms of the sulfur groups should be more stable. In this connection, we intended to study the composition and stability of the gadolinium(III) complexes with various stereoisomers of *p-tert*-butylthiacalixarene containing functional substituents with carboxyl groups at the lower rim and to determine their relaxivity. In the present work, we studied three stereoisomers of 5,11,17,23-tetra-*tert*-butyl-25,26,27,28-tetrakis[(hydroxycarbonyl)methoxy]thiacalix[4]arene: *cone* (**2a**), *partial cone* (**2b**), and *1,3-alternate* (**2c**).

Thiacalixarenes **2a**—**c** are dissolved in water only upon alkalization to form opalescent solutions. When gadolinium(III) is added to these solutions, its hydroxide is formed rapidly and then is slowly and partially dissolved to give, most likely, mixed hydroxo complexes. Micelle-forming nonionic surfactants were used to transform thiacalixarenes and their metal complexes into the water-soluble state in neutral and acidic media. It was found that among nonionic surfactants with various structures (Tween-20, -40, and -60, Brij-35, Triton X-100 and X-405) polyoxyethylated dodecanol Brij-35 has the best solubilizing properties with respect to isomers of the carboxylate derivative of *p-tert*-butylthiacalixarene. An analogous result was obtained for the gadolinium(III) complexes and, therefore, the results using the nonionic surfactant Brij-35 will be presented further.

The acid-base properties of compounds **2a**—**c** in micellar solutions of Brij-35 were studied by UV spectroscopy in a region of 250—350 nm (Fig. 1, *a*—*c*).

The electronic absorption spectra (EAS) of three isomers differ noticeably in positions of the maxima. The shape of these spectra changes differently with the change in the pH of the medium. Interestingly, in the case of *1,3-alternate* **2c** (see Fig. 1, *c*), the molar absorption coefficient (ε) was almost twice as large as the ε values for two other isomers (see Fig. 1, *a*, *b*), and the spectrum remains almost unchanged upon the deprotonation of the carboxyl groups.

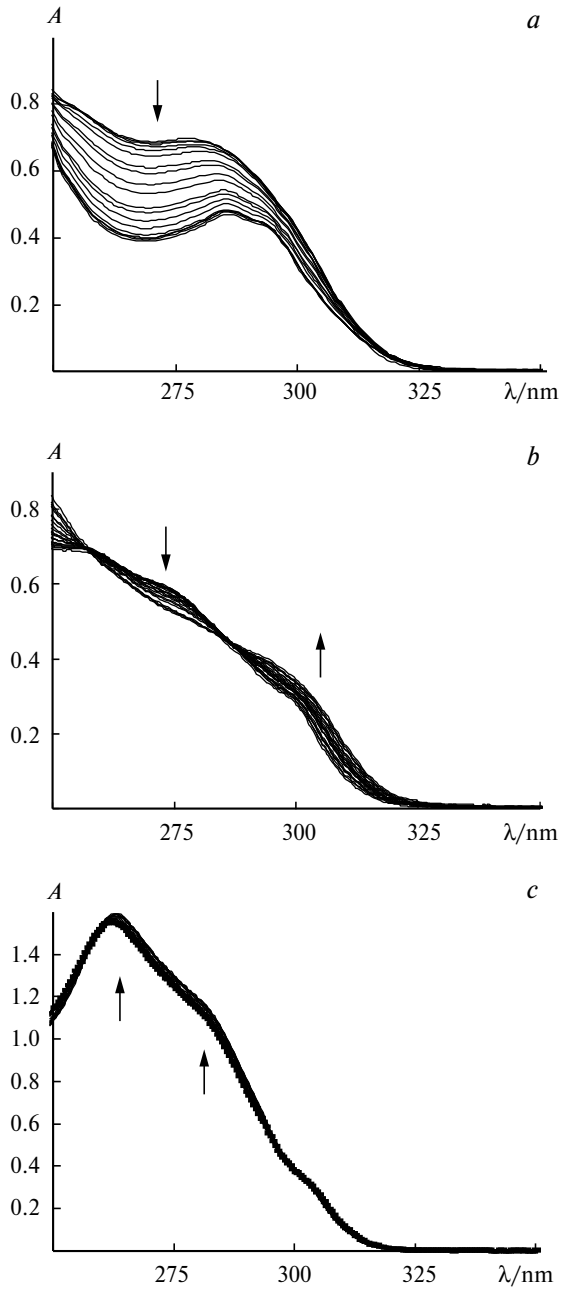

Fig. 1. Electronic absorption spectra of micellar solutions of thiacalixarenes **2a** (*a*), **2b** (*b*), and **2c** (*c*) at various pH (C_2 = = 0.05 mmol L^{-1}, $C_{Brij\text{-}35}$ = 2 mmol L^{-1}; arrows show the direction of changing the spectra with an increase in pH).

Thus, the EAS in the UV region make it possible to identify isomers **2a**—**c**. In particular, the EAS can be used for the estimation of the purity of samples of all the synthesized compounds in order to reveal impurities of other isomers in the samples. However, insignificant changes in the ε values depending on the acidity of the medium (especially in the case of conformer **2c**) do not allow one to determine quantitatively the dissociation constants of individual isomers of thiacalixarenoic tetraacid. Therefore, the apparent dissociation constants (pK_n) for all tetraacids were evaluated by the mathematical processing of the pH-metric titration data.

The titration curves of micellar solutions of thiacalixarenes **2a**—**c** are shown in Fig. 2. The shape of the initial region of the titration curve suggests that of three isomers the studied compound **2b** has the lowest pK_1 value. This was confirmed by the computer simulation of the experimental data (Table 1). Evidently, the acid-base properties of three isomers of thiacalixarenes are rather similar. Meanwhile, a different spatial arrangement of the carboxyl substituents should result in a noticeable difference in the ability of compounds **2a**—**c** solubilized by nonionic micelles to interact with Gd^{3+} ions, which is confirmed by the analysis of the NMR relaxation data.

The pH dependence of the relaxivity of the Gd^{III}—**2a**—Brij-35 system is shown in Fig. 3 (curve *1*).

The relaxivity of the system remains almost unchanged at pH ≤ 4 and corresponds to the RF_1 value of the free gadolinium(III) aqua ion. In acidic solutions all carboxyl groups are protonated, which prevents their binding to Gd^{3+} ions. At pH 4—5 the deprotonation of the carboxyl groups of compound **2a** begins and the relaxivity increases sharply up to R_1 = 60 000 L mol^{-1} s^{-1}. The high R_1 values are retained up to pH 8, after which the

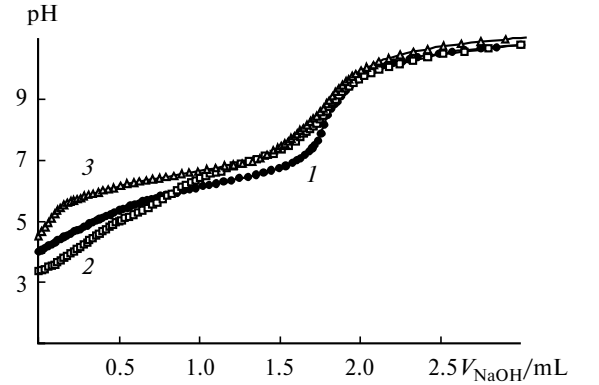

Fig. 2. Titration curves of micellar solutions of compounds **2a** (*1*), **2b** (*2*), and **2c** (*3*) with a NaOH solution (C_2 = 1 mmol L^{-1}, $C_{Brij\text{-}35}$ = 10 mmol L^{-1}, C_{NaOH} = 48 mmol L^{-1}).

Table 1. Apparent stepwise dissociation constants of the dimers of *p-tert*-butylthiacalix[4]arenoic acid in 10 m*M* solutions of Brij-35

Equilibrium	pK_a		
	2a	**2b**	**2c**
$H_4L \leftrightarrows H_3L^- + H^+$	4.74±0.01	4.03±0.02	5.80±0.02
$H_3L^- \leftrightarrows H_2L^{2-} + H^+$	5.76±0.02	5.50±0.02	6.10±0.10
$H_2L^{2-} \leftrightarrows HL^{3-} + H^+$	6.40±0.04	6.77±0.04	6.88±0.06
$HL^{3-} \leftrightarrows L^{4-} + H^+$	6.55±0.04	7.08±0.05	7.70±0.10

relaxivity decreases sharply, which is due, most likely, to hydrolysis.

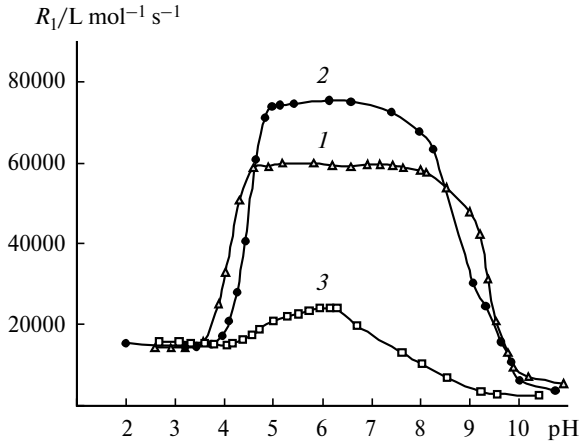

Fig. 3. Dependences of the relaxivity (R_1) on the pH of micellar solutions of compounds **2a** (*1*), **2b** (*2*), **2c** (*3*) ($C_{Gd^{III}}$ = = 0.1 mmol L^{-1}, C_2 = 0.25 mmol L^{-1}, $C_{Brij\text{-}35}$ = 10 mmol L^{-1}).

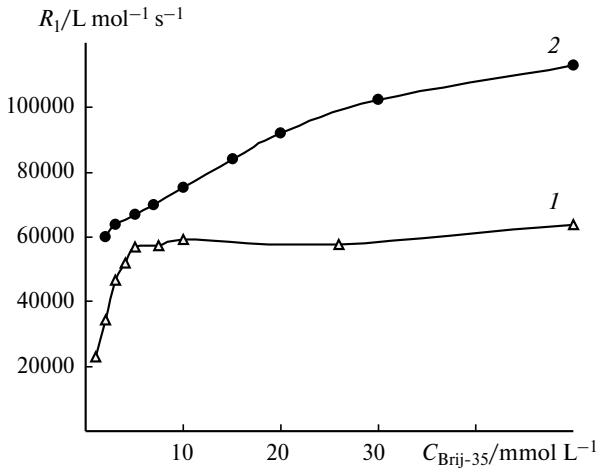

Fig. 4. Dependences of the relaxivity (R_1) of aqueous solutions of thiacalixarenes **2a** (*1*) and **2b** (*2*) on the nonionic surfactant Brij-35 concentration ($C_{Gd^{III}}$ = 0.1 mmol L^{-1}, C_2 = = 0.25 mmol L^{-1}, pH 6.5).

When choosing the nonionic surfactant concentration necessary for the solubilization of the complex, it was found that even small additives of Brij-35 increase the relaxivity of the system (Fig. 4, curve *1*).

To obtain transparent stable solutions of the gadolinium complexes with thiacalixarene **2a**, it is enough that the Brij-35 concentration would be equal to 10 mmol L^{-1}. The further addition of the nonionic surfactant does not reflect the relaxation parameters of the complexes, indicating that the nearest environment of the Gd^{3+} ion is retained. This influence of the nonionic surfactant differs from that observed in the case of mixed ionic and nonionic micelles,[29] where an excess of the nonionic component results in the displacement of ions of the paramagnetic probe from the surface of the micellar aggregate into water and, hence, in a decrease in the relaxivity to the values characteristic of the aqua ion.

The study of the dependence of the relaxivity on the concentration of ligand **2a** at pH 6 (Fig. 5) showed that the addition of even small amounts of the ligand (curve *1*) to a micellar aqueous solution of Brij-35 containing Gd^{3+} ions results in a sharp increase in the R_1 values.

The addition of ligand **2a** in an amount exceeding the equimolar thiacalixarene to metal ion ratio exerts almost no effect on the measured times of proton spin-lattice relaxation. Earlier, when studying the complexation of paramagnetic cations with low-molecular-weight ligands, the relaxivity of solutions usually decreased due to a decrease in the number of water molecules, which are replaced by the electron-donating atoms in the ligand, in the first coordination sphere of the probing ion.[3]

We observed the increase in the relaxivity for both individual anionic surfactants[6] and their mixtures with nonionic surfactants,[29] tetraalkyl derivatives of sulfonate calix[*n*]arenes,[23] and calix[4]resorcinarenes[25] capable of binding paramagnetic probes by their own aggregates

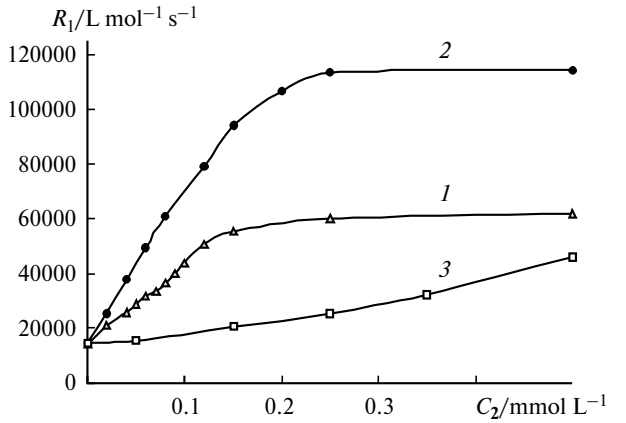

Fig. 5. Dependences of the relaxivity (R_1) of micellar solutions of Brij-35 on the concentration of thiacalixarenes **2a** (*1*), **2b** (*2*), and **2c** (*3*) ($C_{Gd^{III}}$ = 0.1 mmol L^{-1}, $C_{Brij\text{-}35}$ = 10 (*1*, *3*) and 50 mmol L^{-1} (*2*), pH 6.5).

formed in an aqueous solution. Therefore, a reason for the fourfold increase in the relaxivity in the studied system compared to the aqua ion can also be the binding of Gd^{3+} ions to the aggregate of thiacalixarene with the nonionic surfactant. The relaxivity growth upon binding with the solubilized ligands[3] is due to the fact that the relaxation rate of protons in a solution of the gadolinium(III) complex is controlled by its rotation. A similar effect achieved upon the binding of the gadolinium complex to a protein globule (in particular, albumin) is used in magnetic resonance imaging.[2,4]

The pH dependence of the relaxivity for micellar solutions of gadolinium(III) ions containing thiacalixarene **2b** is shown in Fig. 3 (curve *2*). The general shape of the relaxation curves is similar for compounds **2b** and **2a**. However, in the latter case, the formation of high-relaxivity complexes begins somewhat earlier. Although the pK_1 value for ligand **2b** is lower than that for **2a**, the result obtained indicates the lower ability of thiacalixarene **2b** to complexation with gadolinium. The complexes with ligand **2b** manifest high relaxivity and exist in a wide pH range of 5—8. However, the precipitation was prevented only by the reaction of a considerable excess of surfactant. Note that the increase in the surfactant concentration makes it possible to achieve higher relaxivities (up to 110 000 L mol^{-1} s^{-1}; see Fig. 4, curve *2*). The latter value is close to the theoretical maximum value R_1 = 110 000—120 000 L mol^{-1} s^{-1} obtained from the Solomon—Bloembergen—Morgan theory[2]). Meanwhile, in the case of ligand **2a**, the maximum relaxivity of the gadolinium(III) complex is independent of the nonionic surfactant concentration (see Fig. 4, curve *1*). An analysis of the influence of the ligand concentration on the proton relaxation times showed (see Fig. 5) that the distinct inflection in the saturation curve is observed at the equimolar Gd^{3+} to ligand ratio only for isomer **2a**. The less steeper curves for stereoisomers **2b** and **2c** possibly indicate a lower stability of their complexes with the gadolinium(III) ion compared to the complexes formed by ligand **2a**.

The relaxivity values exceeding that of the aqua ion were also detected in micellar solutions of other nonionic surfactants: oxyethylated isooctylphenol (Triton) and alkyl sorbate (Tween). However, no such high R_1 values as for Brij-35 were observed (Fig. 6). The solutions became turbid at neutral pH followed by precipitation. Nevertheless, the character of the rise was the same for all the three relaxation curves in acidic solutions, which

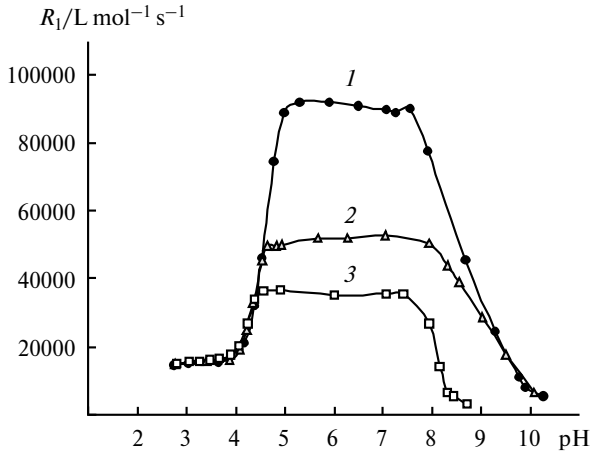

Fig. 6. Influence of the type of the nonionic surfactant on the dependence of the relaxivity on the pH of solutions of the Gd complexes and ligand **2a**: nonionic surfactant (NSurf) is Brij-35 (*1*), Triton X-405 (*2*), and Tween-20 (*3*) ($C_{Gd^{III}}$ = 0.1 mmol L^{-1}, C_{NSurf} = 20 mmol L^{-1}, $C_{\mathbf{2a}}$ = 0.25 mmol L^{-1}).

suggests that the stability of the complex of the Gd^{III} ion with ligand **2a** is independent of the type of the nonionic surfactant.

The gadolinium(III) complexes with the *1,3-alternate* stereoisomer exist in a narrower pH range (see Fig. 3, curve *3*). In this case, high relaxivity values are achieved at considerably higher concentrations of ligand **2c** in solution compared to the other isomers (see Fig. 5, curve *3*). In addition, solutions of the complexes of compound **2c** manifested rather low relaxivity and opalescence even in a nonionic surfactant excess. This suggests that isomer **2c** is of little promise for the formation of high-relaxivity complexes with Gd^{3+} ions.

It was initially assumed that stereoisomer **2c**, whose molecule contains two carboxyl substituents directed to the opposite sides from the calixarene platform, can act as a bridging ligand linking the metal cations to form an infinite chain (Scheme 1).

This interaction should favor an increase in the concentrations of the components in the solution. It could be expected that high R_1 values would be achieved in the case of the Gd^{3+} ion (with allowance for the aggregation of the monomeric complexes). We studied the dependences of the relaxivity on the concentrations of ligand **2c** and Gd^{3+}; however, no increase in the relaxivity was observed.

Scheme 1

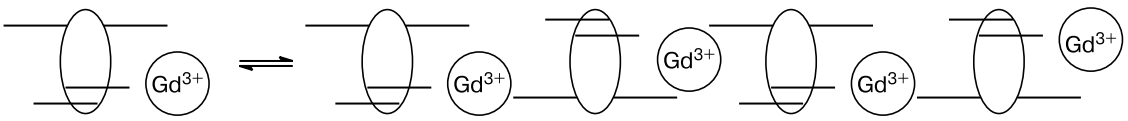

Table 2. Logarithms of the apparent equilibrium constants for the formation of the gadolinium(III) complexes with ligands **2a** and **2b** in 10 m*M* solutions of Brij-35

Equilibrium	log*K*	
	2a	**2b**
$Gd^{3+} + H_4L \leftrightarrows [GdHL]^0 + 3\ H^+$	−8.4±0.1	−9.52±0.04
$Gd^{3+} + H_4L \leftrightarrows [GdL]^- + 4\ H^+$	−13.34±0.1	−15.63±0.1

Table 3. Logarithms of the apparent stability constants and the RF_1 values of the Gd^{III} complexes with ligands **2a** and **2b**

Equilibrium	logβ		RF_1 /L mol^{-1} s^{-1}	
	2a	**2b**	**2a**	**2b**
$Gd^{3+} + HL^{3-} \leftrightarrows [GdHL]^0$	8.5±0.1	6.8±0.1	60000	110000
$Gd^{3+} + L^{4-} \leftrightarrows [GdL]^-$	10.1±0.1	7.8±0.1	60000	110000

The stability of the complexes formed in micellar solutions of the surfactant was estimated by the computer simulation of the pH dependences of the relaxivity. The complex analysis of the data showed that in acidic and neutral media the Gd^{3+} ions form successively two high-relaxivity equimolar complexes with the tri- and tetraanions of the ligands. The equilibria constants of complex formation are given in Table 2.

The stability constants calculated using the acid-base properties of the studied thiacalixarenes (see Table 1) and the relaxivity factors of the gadolinium complexes are listed in Table 3. As can be seen, the *cone* isomer (**2a**) forms somewhat more stable complexes with gadolinium(III) than the *partial cone* (**2b**) does.

Thus, to form high-relaxivity complexes with gadolinium(III) ions, it is necessary that the molecule of the *tert*-butylthiacalix[4]arene ligand contains at least three carboxyl substituent at the lower rim. The results obtained showed that the *cone* and *partial cone* isomers are of most interest as ligands for the design of potential contrast agents in magnetic resonance imaging.

All studied complexes of thiacalixarene **2** possess high spin-lattice relaxivity R_1 (up to 60 000—110 000 L mol^{-1} s^{-1}) considerably exceeding the RF_1 values of the commercial contrast agents (3000—5000 L mol^{-1} s^{-1}). However, insufficient stability (logβ ≤ 10) of these complexes does not allow them so far to be proposed for practical use as contrast agents (for the stability constants of the latter the condition logβ ≥ 20 should be fulfilled).[2]

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