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p-*tert*-Butyl thiacalix[4]arenes functionalized at the lower rim by *o*-, *m*-, *p*-amido and *o*-, *m*-, *p*-(amidomethyl)pyridine fragments as receptors for α-hydroxy- and dicarboxylic acids

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ABSTRACT

A series of new *p*-*tert*-butyl thiacalix[4]arenes with *o*-, *m*-, *p*-amido and *o*-, *m*-, *p*-(amidomethyl)pyridine substituents at the lower rim in *cone*, *partial cone*, and 1,3-*alternate* conformations were synthesized. The ability of the obtained compounds to recognize the α-hydroxy (glycolic, tartaric) and dicarboxylic (oxalic, malonic, succinic, fumaric, and maleic) acids was investigated by UV–vis spectroscopy. Also, the efficiency and selectivity of binding, the association constants log K_a (10^2 to 10^7 M^{-1}) and the stoichiometry were determined for the complexes of *p*-*tert*-butyl thiacalix[4]arenes with the acids. The receptors based on *p*-*tert*-butyl thiacalix[4]arenes with (amidomethyl)pyridine substitutes are most efficient in complexation in many cases.

1. Introduction

The principles for constructing the receptor molecules are based on careful studies of biological systems.[1] The creation of biomimetic receptor structures offers new opportunities for modeling artificial living systems and physiological processes,[2] therapeutic agents,[3] and sensors for medicine technology.[4,5] Biologically active compounds, among them carboxylic acids, are one of the most attractive targets in this field[6] because of their central role in many enzyme activities, DNA regulation, hormone transporting, peptide synthesis, and intracellular communication.[7,8] In addition, carboxylic acid groups are typically presented in the structure of many natural biomacromolecules, e.g., proteins.

Intensive development in this area led to the creation of a number of 'host' molecules for carboxylic acids, which are functionalized with various groups, i.e., calixarenes, porphyrins, cyclodextrins, and metal based systems.[9–18] Despite these achievements, a general approach for the receptor design for carboxylic acids has not been specified.[19–21]

Presently, one of the basic directions for selective binding of a protein surface involves recognition of amino and carboxylic groups of amino acid residues that prevail on the protein surface by means of a synthetic molecular platform.[14,16,22,23] For this purpose, rather simple and synthetically available molecules able to reversibly change various functions of proteins are demanded to create medical drugs and diagnostic tools.

Effective binding of acid side chains by receptors is extremely important for molecular recognition of α-hydroxylic and dicarboxylic acids.[20] In addition, the binding area between the receptor and substrate should be maximal.[20] This occurs if the receptor provides multiple interactions with a guest.[21]

Among other currently used artificial molecules, *p*-*tert*-butyl thiacalixarenes seem promising for these requirements.[20,21] Their three-dimensional structures with various sizes of internal cavity, number and type of binding centers, and spatial arrangement of binding groups are very applicable for the design of large number of receptors for highly selective recognition of the required substrates.[24] The thiacalixarene scaffold because of its pre-organization, easy one-pot preparation, and simple derivatization can be used as a building block for creation of the receptor molecules with various groups and different conformations (*cone*, *partial cone*, 1,2-*alternate*, and 1,3-*alternate*).

Presently, *p*-*tert*-butyl thiacalix[4]arenes are widely used as molecular platforms for the efficient recognition of anions and cations.[24–26] The modification of macrocyclic platforms provides new synthetic receptors for various substrates. Previously, several

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approaches to the receptor design for α-amino, α-hydroxy-, and dicarboxylic acids based on calixarene molecules have been proposed.[27] We have shown that the addition of various functional groups at the lower rim of tetrasubstituted thiacalix[4]arenes led to molecular recognition of oxalic acid.[27]

Also, stereoisomers (*cone*, *partial cone*, and 1,3-*alternate*) of tetraacid based *p*-*tert*-butyl thiacalix[4]arenes **2a**–**c** as main 'blocks' for the creation of highly effective and selective hosts were described.[28–30] Previously, we have applied amidopyridine thiacalix[4]arenes for potentiometric determination of Ag^+ cations.[31,32] *o*-Amidopyridine groups with both proton donating and proton accepting properties were successively used for binding the carboxylic acid function.[10,16,17] For this reason, the thiacalix[4]arenes in *cone*, *partial cone*, and 1,3-*alternate* conformations with amidomethyl and amidopyridine fragments were suggested as hosts for the dicarboxylic and hydroxylic acids.

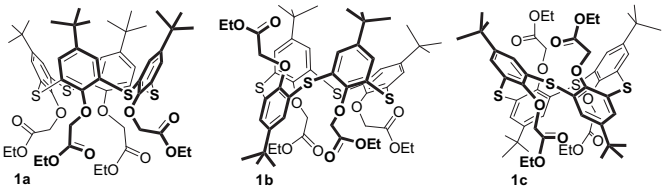
The use of functionalized thiacalix[4]arenes as receptors for α-hydroxylic and dicarboxylic acids makes it possible to investigate the relationship between the macrocycle conformation or degree of substitution and the receptor abilities of the obtained hosts toward studied guests.

2. Results and discussion

2.1. Synthesis of the *p*-*tert*-butyl thiacalix[4]arene derivatives containing amidopyridine fragments at the lower rim

Two approaches liable to the formation of amides from the tetraesters[33] **1a**–**c** on the basis of *p*-*tert*-butyl thiacalix[4]arene, i.e., direct aminolysis of tetraester by appropriate amine[28] and its hydrolysis to the tetraacid followed by conversion to acyl chloride and then to amide. The latter stage is performed in methylene chloride in the presence of a base, commonly triethylamine.[28,34,35]

The advantages of the first approach are obvious: reduction of the synthesis steps, simpler techniques for target compound isolation, and hence higher yield of the product. However, the conditions required for aminolysis as well as the final products are limited. First, only primary amines can be used. Then, easily oxidizable amines are inappropriate due to their high chemical activity. In addition, steric shielding of the nitrogen atom influences the reactivity of primary amines to a great extent.

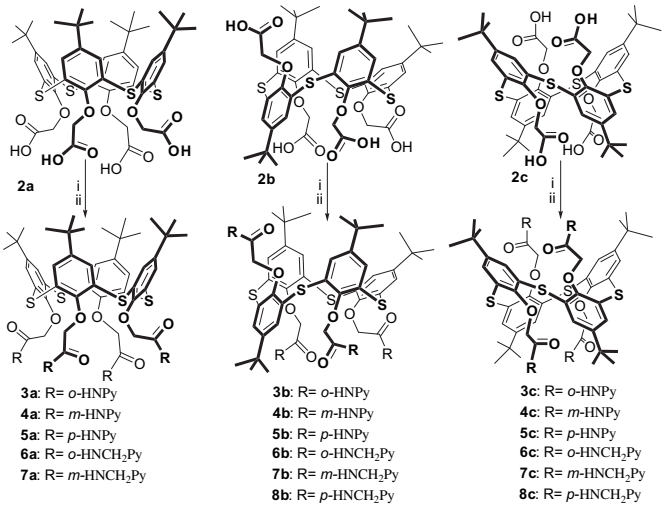


The second above mentioned way is more universal, a majority of primary and secondary amines react with acid chloride rather rapidly. However, the high chemical activity of acylating agent limits the approach because of initiation of the side reactions related to other functions like hydroxylic groups or heterocyclic fragments containing nucleophilic centers.

The possibility of the aminolysis of tetraesters **1a**–**c** in reaction with the aminopyridines was first investigated. Even after 10 h exposure of the reaction mixture at 160 °C no changes in the quantity of the initial tetraester were observed by TLC. The increase of the time and the temperature resulted in the resin formation and oxidation of initial amidopyridines. As was established, benzyl analogs, which differed from aminopyridines by one additional methylene group between the pyridine ring and the amino group were stable in aminolysis. For this reason, another approach based on in situ synthesis of acid chlorides was used. For that tetraacid derivatives of the thiacalix[4]arenes **2a**–**c** were obtained as described elsewhere.[36]

The tetraacids **2a**–**c** were boiled in thionyl chloride, which was removed in vacuum and the acid chlorides obtained were treated by the appropriate aminopyridine in methylene chloride containing triethylamine. However, the target compound was obtained with low yield of 10–30%. In some cases, e.g., for the reaction of tetraacid chloride in the *cone* conformation with *p*-amidopyridine, no target product was found. The use of catalysts, e.g., DMAP, the variation of the temperature from −5 to +40 °C, and changes of the solvent for the pyridine did not improve the yield of the target products. It was found that even in harsh conditions no target products were formed. Instead of that mixture of differently substituted derivatives and resin formation products were isolated. Probably, this was due to side reactions, e.g., acylation at the nitrogen atom of the pyridine ring and the aromatic electrophilic substitution.

Due to low yields and the complications in the isolation of the target compounds, the amidopyridine synthesis was modified to bind the released HCl using the initial aminopyridine (see Scheme 1). The two-fold excess of the initial aminopyridine against each carboxylic group should provide full binding of the releasing HCl. All the isomeric aminopyridines show basic properties, which are more pronounced than those of non-substituted pyridine. Thus, it was found that heterocyclic nitrogen atom is protonated in the crystalline salt. The delocalization of the positive charge is higher in *p*-amidopyridine (pK_a 9.1) than in the *o*-isomer (pK_a 7.2).[37] In the case of the *m*-isomer, the delocalization of the charge is impossible and *m*-amidopyridine given in strong acids two protonation steps with final formation of a dication (pK_a 6.6 and 1.5) (Fig. 1). The amidopyridine catalyzes the reaction with the acyl chloride yielding a cation, which itself is a strong acylating agent (Fig. 2), so that no other catalysts were required.



Scheme 1. Reagents and conditions: (i) $SOCl_2$, reflux; (ii) RH, CH_2Cl_2.

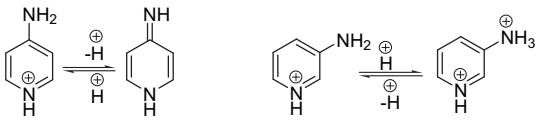


Figure 1. Protonation equilibria of *p*- and *m*-amidopyridines.

Carrying out the reaction of aminopyridines with the acyl chloride of the tetraacids in the absence of triethylamine made it possible to avoid the resin formation and provided a significant increase of the yield up to 60–80% as well as simplification of the target compound isolation. The highest yields (70–82%) were

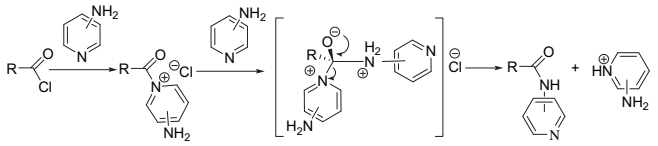


Figure 2. The mechanism of acylation of isomeric aminopyridines by acyl chloride.

observed in the case of the derivatives of *o*-amidopyridine **3a–c**. The synthesis of *p*-amidopyridine substituted **5a–c** was found to be most hampered due to the low solubility of *p*-amidopyridine in methylene chloride.

The structure and the composition of the derivatives of thiacalix[4]arenes synthesized were characterized by a number of physical–chemical methods, i.e., NMR spectroscopy, IR spectroscopy, MALDI-TOF or ESI mass-spectrometry, and elemental analysis. ^{1}H NMR spectra of all the obtained compounds clearly corresponded to the structures ascribed by the number of signals and their multiplicities.

In the case of the *cone* and 1,3-*alternate* stereoisomers, the protons of *tert*-butyl, oxymethylene, and the aromatic fragments appear in the shape of singlets, pyridine protons as a system of multiplets, those of the amide group both as a singlet (amidopyridine derivatives **3–5**) and as a triplet (macrocycles **6–8** containing amidomethylene substituents). However, for the stereoisomers *partial cone*, the spectrum is complicated due to the decrease of the structure symmetry. The protons of the *tert*-butyl and amide groups appear as three singlets with the intensity ratio 2:1:1, and oxymethylene and aromatic protons as two singlets and AB-system. The protons of the two distally located CH_2NH groups (A) of compound **6b** appear as an ABX system due to their diastereotopy and availability of the neighboring NH proton (Fig. 3). The protons of CH_2NH (B) and CH_2NH (C) groups give two doublets.

The chemical shifts of the NH protons in *cone* **3a–5a** and *partial cone* **3b–5b** are observed at weaker fields in comparison with those of the 1,3-*alternate* **3c–5c**. This can be related to the availability of the cyclic hydrogen bond between the neighboring amide groups. Simultaneously, chemical shifts of the corresponding (amidomethyl)pyridine derivatives were 1–2 ppm lower, and did not differ significantly between *cone–partial cone–*1,3-*alternate*.

Conformational comparison of *cone* **3a–8a** and 1,3-*alternate* **3c–8c** stereoisomers of the tetrasubstituted derivatives at the lower rim *p-tert*-butyl thiacalix[4]arenes can be done by comparing the chemical shifts of $OCH_2C(O)$ protons in NMR ^{1}H spectra. For all the compounds synthesized the signals of the oxymethylene protons of the *cone* stereoisomer appear at lower field as compared with the signals of similar protons of 1,3-*alternate* stereoisomer.

2.2. Study the complexation ability of amidopyridine thiacalix[4]arenes by UV-spectroscopy

The efficiency and selectivity of interaction between the *p-tert*-butyl thiacalix[4]arenes obtained and tartaric, oxalic, glycolic, malonic, succinic, fumaric, and maleic acids have been investigated by UV–vis spectroscopy.

Shifts in absorbance were found for the spectra of the complexes of thiacalix[4]arenes **3–8** containing amidomethyl and amidopyridine fragments with dicarboxylic and hydroxylic acids compared with the initial spectrum of *p-tert*-butyl thiacalixarenes in methylene chloride. The most significant changes were established for macrocycles **4c–6c** in the 1,3-*alternate* configuration (Figs. 4–6).

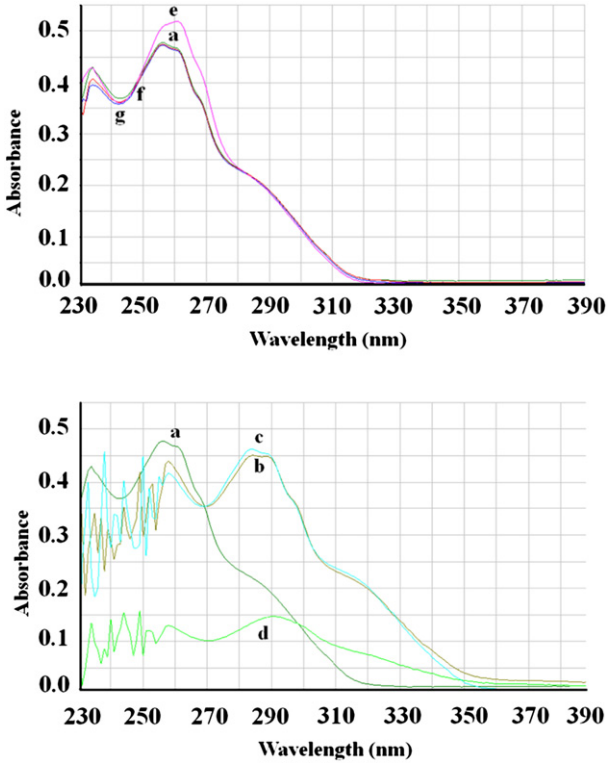


Figure 4. Changes in UV–vis spectra of *p-tert*-butyl thiacalix[4]arene **6c**, 1×10^{-5} M (a), upon addition of various acids in CH_2Cl_2: tartaric (b), glycolic (c), oxalic (d), malonic (e), succinic (f), and fumaric (g).

Probably, this is due to optimal orientation and accessibility of binding centers for the studied substrates. A hyperchromic effect

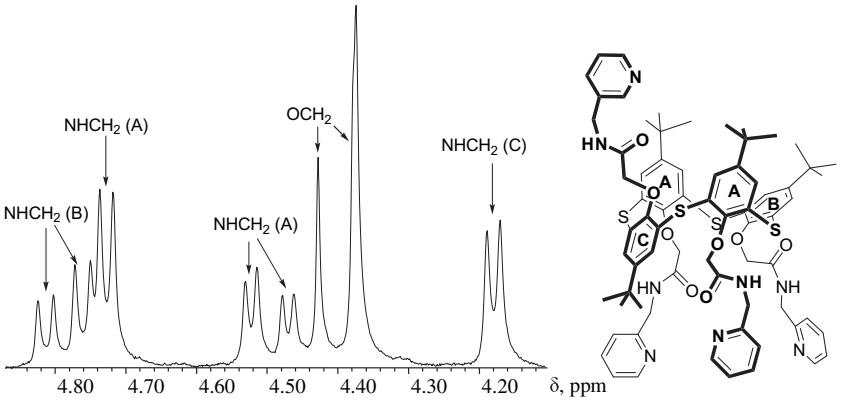


Figure 3. Fragment of NMR ^{1}H spectrum of compound **6b**.

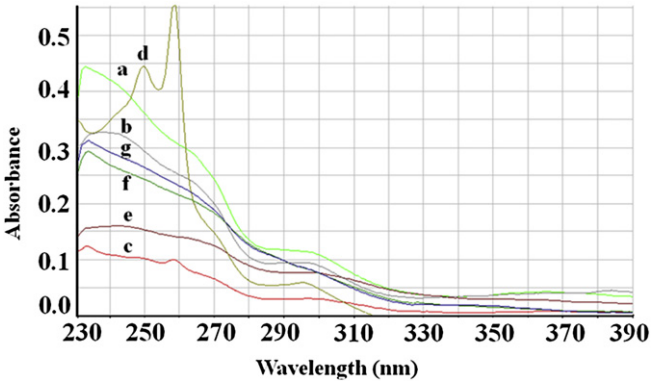


Figure 5. Changes in UV–vis spectra of *p-tert*-butyl thiacalix[4]arene **4c**, 1×10^{-5} M (a), upon addition of various acids in CH_2Cl_2: tartaric (b), glycolic (c), oxalic (d), malonic (e), succinic (f) and fumaric (g).

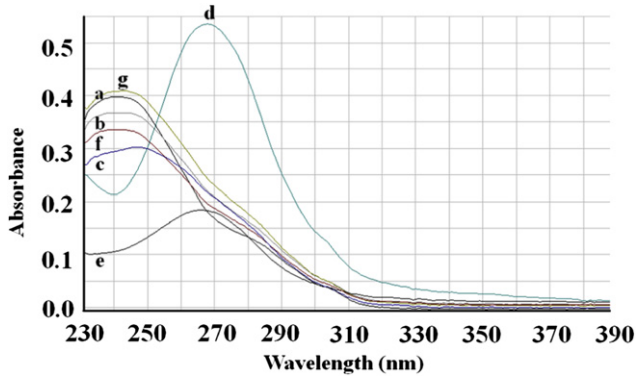


Figure 6. Changes in UV–vis spectra of *p-tert*-butyl thiacalix[4]arene **5c**, 1×10^{-5} M (a), upon addition of various acids in CH_2Cl_2: tartaric (b), glycolic (c), oxalic (d), malonic (e), succinic (f) and fumaric (g).

was found for the *p-tert*-butyl thiacalix[4]arene **6c** after the addition of tartaric and glycolic acids (Fig. 4). Also, a strong bathochromic shift for wide absorption zone with the maximum at 270 nm against the initial spectrum for the macrocycle **6c** was observed (Fig. 4).

Comparison of the spectra of stereoisomers of compounds **3** and **6** with *o*-amido and *o*-(amidomethyl)pyridine fragments shows weaker changes for compound **3**, which are generally similar for all the investigated acids. Probably, the introduction of a methyl group in *o*-substituted pyridines led to the increase of both the efficiency and the selectivity of hydroxylic acids binding.

In the case of thiacalix[4]arenes with *p*- and *m*-substituted pyridine fragments, another process took place. The introduction of a methyl group between the heterocycle and the amide group did not result in significant shifts in UV-spectra of the complexes of *p-tert*-butyl thiacalix[4]arenes with dicarboxylic and hydroxylic acids. Meanwhile, the interaction between the *m*-amidopyridine groups of compound **4c** and oxalic acid led to considerable changes in the spectrum shape, i.e., bathochromic shift and hyperchromic effect (Fig. 5).

Two clear peaks in the spectra of the complexes in the range 245–265 nm appeared as evidence of effective interaction between the *p-tert*-butyl thiacalix[4]arene **4c** and oxalic acid (Fig. 5).

In a series of thiacalix[4]arenes with *p*-substituted pyridine fragments, the most significant changes in UV-spectra of the complexes of *p-tert*-butyl thiacalix[4]arenes with the oxalic and malonic acids were found. For the peaks in the spectra of compound **5c** recorded after the addition of oxalic and malonic acids, the shift in long-wavelength range and hypochromic effect was observed (Fig. 6). The same tendency was established for *p*-(amidomethyl)pyridines, even though the changes in the spectra were not so evident because of an additional methylene bridging group between amide and pyridine fragments.

Thus, the study of complexation ability of *p-tert*-butyl thiacalix[4]arenes with amidomethyl- and amidopyridine fragments **3**–**8** toward dicarboxylic and hydroxylic acids in methylene chloride showed promising interactions between the obtained compounds and the mentioned guests. For this reason, quantitative evaluation of the binding ability of the hosts **3**–**8** toward a range of acids was performed.

The values of association constant K_a and stoichiometry for the complexes were determined in methylene chloride (Figs. 7–9). For all the studied systems, 1:1 complexes are formed (Figs. 7–9). The association constant logarithms for the investigated compounds are summarized in Table 1.

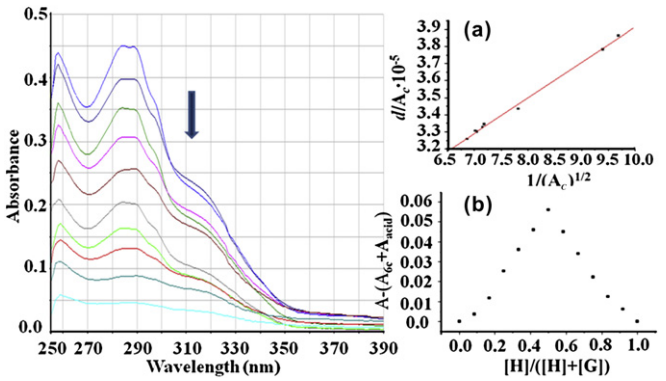


Figure 7. UV–vis absorption spectra obtained by titration of complexation system contained the receptor **6c** (1×10^{-5} M) and glycolic acid in CH_2Cl_2 (the volume ratio of the complex solution and solvent was 9:1, 8:2, 7:3, 6:4, 5:5, 4:6, 3:7, 2:8, 1:9); (a) linear fitting curve of absorption shifts (A) against concentration of solutions (*d*) in a series of dilutions and (b) the Job's plot.

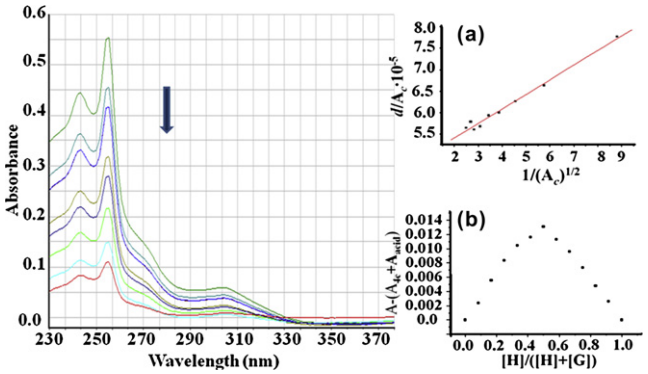


Figure 8. UV–vis absorption spectra obtained by titration of complexation system contained the receptor **4c** (1×10^{-5} M) and oxalic acid in CH_2Cl_2 (the volume ratio of the complex solution and solvent was 9:1, 8:2, 7:3, 6:4, 5:5, 4:6, 3:7, 2:8, 1:9); (a) linear fitting curve of absorption shifts (A) against concentration of solutions (*d*) in a series of dilutions and (b) the Job's plot.

According to the obtained constants (from 2.3 to 7.4), effective and to some extent selective binding of the guest molecules is reached. This might be mostly due to hydrogen bonding of carboxylic and hydroxylic acid groups with the pyridine fragments of the host substituents (Fig. 10). However, if complexation was controlled only by acid–base interactions, the strongest acids, i.e., malonic and oxalic (pK_a=1.25 and 1.38, respectively[38]), should be bound most effectively by all the studied macrocycles. This is not proved by the data from Table 1, which shows no relationship between the acid strength and complex stability for the studied

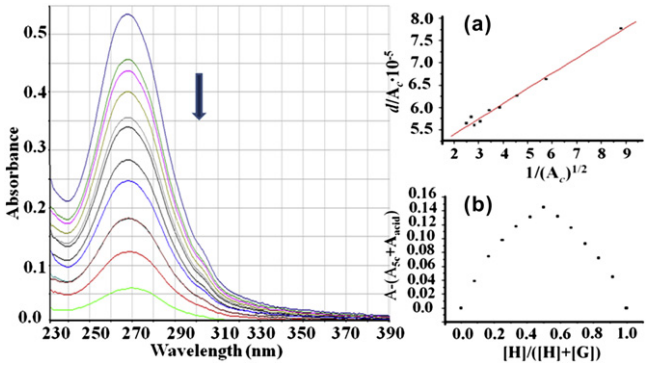


Figure 9. UV–vis absorption spectra obtained by titration of complexation system contained the receptor **5c** (1×10^{-5} M) and oxalic acid in CH_2Cl_2 (the volume ratio of the complex solution and solvent was 9:1, 8:2, 7:3, 6:4, 5:5, 4:6, 3:7, 2:8, 1:9); (a) linear fitting curve of absorption shifts (A) against concentration of solutions (d) in a series of dilutions and (b) the Job's plot.

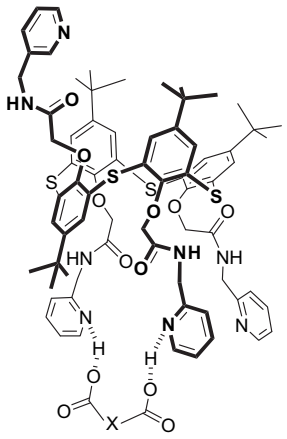


Figure 10. Possible structure of the complex of *p-tert*-butyl thiacalix[4]arene tetrasubstituted at the lower rim by *o*-(amidomethyl)pyridine groups with dicarboxylic acid.

p-tert-butyl thiacalix[4]arenes. 1:1 Stoichiometry of the complexes formed by the acids and receptors was determined by Job's plot method. Binding constants were determined as described elsewhere.[38]

The malonic and oxalic acids are bond more effectively in comparison with other substrates only for compounds **5a–c** and **8c** with *p*-substituted pyridine fragments. However, even for the most effective binding (*p-tert*-butyl thiacalix[4]arene **5c**, log K_a=6.1 and 7.1 for malonic and oxalic acids, respectively), the efficiency of complexation of tartaric and glycolic acid by the *p-tert*-butyl thiacalixarenes **6c** with *o*-amidopyridine fragments in the 1,3-*alternate* conformation was found to be higher (log K_a=7.0 and 7.4, respectively).

It should be noted that in the latter case both high efficiency and selectivity were observed for the interaction between *p-tert*-butyl thiacalix[4]arene and dicarboxylic acids. Such a selectivity of receptor molecules toward dicarboxylic and hydroxylic acids can be due to mutual steric pushing of methyl substituents. For this reason, the interaction of proton donating carboxylic and hydroxylic groups of hydroxylic acids with the proton accepting substituents of *p-tert*-butyl thiacalix[4]arene tetrasubstituted at the lower rim by the *o*-(amidomethyl)pyridine fragment in 1,3-*alternate* conformation is achieved.

It is interesting to follow the transition from *cone* to 1,3-*alternate* conformation. For example, for compounds **6a–c**, the hydroxylic acids are bond more effectively (log K_a=4.9–7.4) than the malonic and oxalic acids (log K_a=3.7–4.5). Probably, the efficiency of interactions of the acids and macrocycles results from the system of hydrogen bonds formed in complexation with participation of carboxylic and hydroxylic groups of a substrate and binding sites of a receptor (amide group and pyridine fragment). In the case of binding of malonic acid (*cone* **6a**, log K_a=3.7, 1,3-*alternate* **6c**, log K_a=4.5) and oxalic acid (*cone* **6a**, log K_a=3.8, 1,3-*alternate* **6c**, log K_a=5.5), both the geometric correspondence of binding centers and the acid strength play important roles. Also, significant differences in complexation ability were observed for synthetic receptors **6a** and **6c** toward two isomers, maleic (*cone* **6a**, log K_a=5.5, 1,3-*alternate* **6c**, log K_a=5.4) and fumaric acids (*cone* **6a**, log K_a=3.9, 1,3-*alternate* **6c**, log K_a=4.9). Thus, for the cis-isomer (maleic acid) high association constant values are due to steric pre-organization of the substrate structure.

The influence of the methylene bridge between the amide group and the pyridine fragment on efficiency of interaction of *p-tert*-butyl thiacalixarenes **3–8** with the studied acids is mostly pronounced for maleic acid. While amidopyridines show logarithms of association constants in the range 2.3–2.5, for amidopyridines they shifted to 5.2–6.8. *p-tert*-Butyl thiacalix[4]arenes **6b–8b** with (amido)methyl pyridine fragments in *partial cone* conformation bind maleic acid the most effectively (log K_a=6.7) in the series of

Table 1
Association constant (log K_a) for complexation of *p-tert*-butyl thiacalix[4]arene derivatives **3–8** with different α-hydroxy and dicarboxylic acids in CH_2Cl_2 (at 25 °C)

Compound	log K_a, M^{-1}						
	Tartaric acid	Oxalic acid	Glycolic acid	Malonic acid	Succinic acid	Fumaric acid	Maleic acid
3a	4.2±0.2	4.6±0.1	4.8±0.3	3.5±0.3	4.6±0.2	4.5±0.1	4.8±0.1
3b	3.9±0.1	4.6±0.1	4.1±0.2	4.1±0.0	4.4±0.2	4.9±0.2	5.5±0.1
3c	2.5±0.2	3.3±0.2	2.3±0.1	3.1±0.1	2.7±0.2	2.4±0.2	4.7±0.1
4a	3.5±0.2	2.6±0.12	2.4±0.1	3.2±0.2	3.2±0.2	3.0±0.3	4.9±0.1
4b	5.1±0.1	4.8±0.2	5.2±0.2	5.1±0.2	5.0±0.1	4.1±0.2	3.7±0.1
4c	5.8±0.2	6.7±0.1	5.7±0.0	5.4±0.2	4.2±0.1	2.8±0.1	5.3±0.1
5a	4.8±0.1	5.9±0.2	4.7±0.2	5.2±0.2	4.8±0.1	4.8±0.1	4.3±0.2
5b	3.7±0.1	6.3±0.2	3.9±0.2	5.6±0.2	3.9±0.2	4.0±0.2	2.3±0.1
5c	5.5±0.2	7.1±0.1	4.2±0.0	6.1±0.1	5.1±0.2	4.3±0.0	4.9±0.1
6a	4.9±0.2	3.8±0.0	4.9±0.3	3.7±0.2	3.2±0.1	3.9±0.2	5.5±0.1
6b	5.9±0.0	5.6±0.0	5.9±0.2	5.4±0.0	5.1±0.1	4.9±0.1	6.7±0.1
6c	7.0±0.2	5.5±0.1	7.4±0.2	4.5±0.2	4.9±0.2	4.9±0.2	5.4±0.1
7a	3.9±0.2	4.9±0.0	3.9±0.1	4.7±02	3.2±0.3	3.7±0.2	5.8±0.1
7b	3.9±0.1	5.4±0.0	4.8±0.0	5.3±01	4.6±0.3	2.7±0.0	6.7±0.1
7c	4.9±0.2	4.8±0.2	5.5±0.0	5.2±0.2	4.4±0.2	4.8±0.2	6.3±0.2
8b	3.0±0.2	5.4±0.0	2.5±0.2	5.4±0.2	2.5±0.2	3.3±0.0	6.8±0.1
8c	5.2±0.1	6.2±0.1	5.2±0.0	5.4±0.2	4.4±0.2	4.9±0.0	5.2±0.1

±, Standard deviation.

the investigated macrocycles. Among compounds **6b–8b**, the maximum selectivity of binding in the cis- and trans-isomer pair (fumaric and maleic acids, log K_a=2.7 and 6.7, respectively) was achieved for **7b** with *m*-substituted pyridine fragments.

For oxalic acid, macrocycle **4c** with *m*-amidopyridine fragments in 1,3-*alternate* conformation is the most effective and selective receptor (log K_a=6.7). Obtained data (Table 1) can be considered as evidence in favor of the absence of general relationships between the effective binding of studied acids by the *p-tert*-butyl thiacalix[4]arenes **3–8** and macrocycle configuration. Nevertheless, in the case of compound **3** with *o*-amidopyridine fragments, the association constants for tartaric, glycolic, and succinic acids increase in the range 1,3-*alternate*<*partial cone*<*cone*. The reverse relationship (*cone*<*partial cone*<1,3-*alternate*) of association constants was observed for the following host and guest systems: compounds **4** with tartaric, oxalic, glycolic, and malonic acids, **5** with oxalic and malonic acids, **6** with tartaric and glycolic acid, and **7** with the glycolic acid. In addition, significant difference of the complexation ability for the investigated synthetic receptors **3–8** toward two isomers—maleic acid (cis) and fumaric (trans)—acids was observed. This is due to steric pre-organization of the substrate structure (cis-isomer). Therefore, high association constants are achieved for almost all the macrocycles in comparison with the trans-isomer.

3. Conclusion

Novel derivatives of *p-tert*-butyl thiacalix[4]arene with *o*-, *m*-, *p*-amido and *o*-, *m*-, *p*-(amidomethyl)pyridine fragments at the lower rim in *cone*, *partial cone*, and 1,3-*alternate* configuration were synthesized. The complexation ability of *p-tert*-butyl thiacalix[4]-arene derivatives toward some hydroxylic (tartaric, glycolic) and dicarboxylic acids (malonic, maleic, fumaric, oxalic, and succinic) was studied by UV-spectroscopy. The values of association constant (10^2 to 10^7 M^{-1}) of the formation of the complexes were determined and 1:1 stoichiometry of the complex between *p-tert*-butyl thiacalix[4]arenes and the acid was established by UV–vis spectroscopy.

Also, it is stated that *p-tert*-butyl thiacalix[4]arenes with (amidomethyl)pyridine substitutes are more effective for binding the studied substrates. Effective and selective receptors for tartaric, oxalic, glycolic, and malonic acids were found. In addition, the efficiency and selectivity of complexation of the synthesized compounds were characterized. The established relationships make it possible to directly change the receptor ability of tetra-substituted thiacalix[4]arenes by varying their substituents and the macrocycle configuration.

The obtained compounds offer opportunities for developing sensory devices for the detection of organic acids, among other, for multisensory systems ('electronic tongue') and solid-phase extraction of components in industry, and solid waste treatment.

4. Experimental

4.1. General

Melting points were determined using Boetius Block apparatus. Most chemicals were purchased from Aldrich and used as received without additional purification. Organic solvents were purified by standard procedures. The ^{1}H and ^{13}C NMR spectra were recorded with 300 MHz Varian XL-300 spectrometer. IR spectra (KBr pellets or Nujol) were recorded with Vector 22 (Bruker) IR spectrometer. ESI mass spectra were recorded with Bruker Esquire MS. Elemental analysis was performed with Perkin–Elmer 2400 Series II instruments.

4.2. General procedure of the synthesis of compounds 3(a–c)–8(b–c)

Acids **2**(**a**–**c**) (1 g, 1.05×10^{-3} mol) were put into a round-bottom flask and $SOCl_2$ (10 mL, 0.084 mol) was added. The mixture was refluxed for 1.5 h, excess of $SOCl_2$ was removed; remainder was dried under reduced pressure for 2 h. A solution of aminopyridine (methylaminopyridine) (9.0×10^{-3} mol) in 50 mL of methylene chloride was added. The mixture was stirred at rt overnight, the remainder was separated, and organic layer was evaporated in vacuo. The remainder was crystallized from the ethanol/dichloromethane.

*4.2.1. 5,11,17,23-Tetra-tert-butyl-25,26,27,28-tetrakis[(2-pyridylamidocarbonyl)-methoxy]-2,8,14,20-tetrathiacalix[4]arene (cone-**3a**).* White powder, yield: 0.92 g (70%). Mp: 245 °C. ^{1}H NMR (300 MHz, 373 K, $CDCl_3$) δ 10.59 (s, 4H, NH), 7.39 (s, 8H, ArH), 6.90–6.95, 7.50–7.56, 7.96–7.99, 8.23–8.26 (m, 16H, PyH), 5.15 (s, 8H, OCH_2CO), 1.11 (c, 36H, $(CH_3)_3C$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.4, 157.6, 151.1, 147.9, 147.7, 137.8, 135.1, 128.3, 119.6, 114.4, 75.1, 34.3, 31.1. IR (KBr) ν_{max} 1698, 2870, 2962, 3288. MS (ESI): calcd for $[M]^+$ m/z=1257.6, $[M+Na]^+$ m/z=1280.6, found m/z=1257.5, 1280.4. El. Anal. Calcd for $C_{68}H_{72}N_8O_8S_4$: C, 64.94; H, 5.77; N, 8.91; S, 10.20. Found: C, 64.87; H, 5.73; N, 8.99; S, 10.45.

*4.2.2. 5,11,17,23-Tetra-tert-butyl-25,26,27,28-tetrakis[(2-pyridylamidocarbonyl)-methoxy]-2,8,14,20-tetrathiacalix[4]arene (partial cone-**3b**).* White powder, yield: 1.08 g (82%). Mp: 226 °C. ^{1}H NMR (300 MHz, 373 K, $CDCl_3$) δ 10.66 (s, 1H, NH), 9.94 (s, 2H, NH), 9.22 (s, 1H, NH), 6.91–7.04, 7.33–8.01, 8.22–8.34 (m, 16H, Py–H), 7.96 (s, 2H, ArH), 7.74 (s, 2H, ArH), 7.57 (d, J=14.4 Hz, 2H, ArH), 7.47 (d, J=14.4 Hz, 2H, ArH), 5.26 (d, J=15.2 Hz, 2H, OCH_2CO), 5.00 (s, 2H, OCH_2CO), 4.96 (d, J=15.2 Hz, 2H, OCH_2CO), 3.81 (s, 2H, OCH_2CO), 1.31 (s, 9H, $(CH_3)_3C$), 0.98 (s, 18H, $(CH_3)_3C$), 0.95 (s, 9H, $(CH_3)_3C$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.3, 167.2, 166.0, 157.8, 150.8, 148.3, 148.1, 148.0, 137.9, 137.8, 137.7, 136.5, 135.5, 133.8, 131.9, 128.3, 127.6, 127.4, 127.3, 119.9, 119.7, 119.6, 114.2, 114.0, 113.8, 75.4, 73.5, 71.3, 34.5, 34.3, 34.2, 31.2, 30.8, 30.6. IR (KBr) ν_{max} 1700, 2870, 2961, 3287, 3374, 3457. MS (ESI): calcd for $[M]^+$ m/z=1257.6, found m/z=1257.4. El. Anal. Calcd for $C_{68}H_{72}N_8O_8S_4$: C, 64.94; H, 5.77; N, 8.91; S, 10.20. Found: C, 64.94; H, 5.61; N, 8.71; S, 10.16.

*4.2.3. 5,11,17,23-Tetra-tert-butyl-25,26,27,28-tetrakis[(2-pyridylamidocarbonyl)-methoxy]-2,8,14,20-tetrathiacalix[4]arene (1,3-alternate-**3c**).* White powder, yield: 1.06 g (80%). Mp: 272 °C. ^{1}H NMR (300 MHz, 373 K, $CDCl_3$) δ 8.95 (s, 4H, NH), 7.66 (s, 8H, ArH), 6.96–7.01, 7.69–7.72, 8.28–8.29, 8.30–8.33 (m, 16H, PyH), 5.09 (s, 8H, OCH_2CO), 0.74 (s, 36H, $(CH_3)_3C$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1, 155.5, 150.9, 148.1, 138.0, 130.2, 126.5, 120.2, 114.6, 68.9, 34.1, 30.5. IR (KBr) ν_{max} 1710, 2893, 2959, 3298. MS (MALDI-TOF): calcd for $[M]^+$ m/z=1257.6, $[M+Na]^+$ m/z=1280.6, found m/z=1257.7, 1280.0. El. Anal. Calcd for $C_{68}H_{72}N_8O_8S_4$: C, 64.94; H, 5.77; N, 8.91; S, 10.20. Found: C, 64.84; H, 5.92; N, 8.77; S, 10.06.

*4.2.4. 5,11,17,23-Tetra-tert-butyl-25,26,27,28-tetrakis[(3-pyridylamidocarbonyl)-methoxy]-2,8,14,20-tetrathiacalix[4]arene (cone-**4a**).* White powder, yield: 0.79 g (60%). Mp: 202 °C. ^{1}H NMR (300 MHz, 373 K, $CDCl_3$) δ 10.35 (s, 4H, NH), 7.40 (s, 8H, ArH), 7.15–7.20, 7.15–7.20, 7.98–8.29, 8.18–8.85 (m, 16H, PyH), 5.19 (s, 8H, OCH_2CO), 1.13 (s, 36H, $(CH_3)_3C$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.5, 157.6, 147.7, 145.1, 141.5, 135.0, 134.6, 127.9, 123.6, 46.1, 34.3,31.1. IR (KBr) ν_{max} 1685, 3272. MS (ESI): calcd for $[M+Na]^+$ m/z=1280.6, found m/z=1279.3. El. Anal. Calcd for $C_{68}H_{72}N_8O_8S_4$:

C, 64.94; H, 5.77; N, 8.91; S, 10.20. Found: C, 64.74; H, 5.86; N, 8.68; S, 10.35.

*4.2.5. 5,11,17,23-Tetra-tert-butyl-25,26,27,28-tetrakis[(3-pyridylamidocarbonyl)-methoxy]-2,8,14,20-tetrathiacalix[4]arene (partial cone-**4b**).* White powder, yield: 0.90 g (68%). Mp: 258 °C. ^{1}H NMR (300 MHz, 373 K, $CDCl_3$) δ 10.36 (s, 1H, NH), 9.83 (s, 2H, NH), 8.48 (s, 1H, NH), 7.12–7.15, 7.16–7.21, 7.36–7.41, 7.86–8.09, 7.89–8.12, 8.20–8.33, 8.22–8.34, 8.41–8.69 (m, 16H, Py–H), 7.96 (s, 2H, ArH), 7.56 (d, J=2.2 Hz, 2H, ArH), 7.42 (d, J=2.2 Hz, 2H, ArH), 7.34 (s, 2H, ArH), 4.82 (s, 2H, OCH_2CO), 4.71 (d, J=13.2 Hz, 2H, OCH_2CO), 4.60 (d, J=13.2 Hz, 2H, OCH_2CO), 4.39 (s, 2H, OCH_2CO), 1.43 (s, 9H, $(CH_3)_3C$), 0.77 (s, 18H, $(CH_3)_3C$), 0.75 (s, 9H, $(CH_3)_3C$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.3, 166.5, 166.3, 157.4, 157.1, 156.8, 148.2, 147.7, 147.3, 145.0, 144.9, 144.6, 141.6, 140.9, 135.6, 135.1, 134.5, 134.2, 133.4, 132.4, 128.5, 127.5, 127.1, 126.5, 126.3, 123.6, 123.5, 123.2, 40.1, 40.0, 39.7, 34.4, 34.1, 34.0, 31.0, 30.6. IR (Nujol) ν_{max} 1540, 1698, 3303, 3368. MS (ESI): calcd for $[M]^+$ m/z=1257.6, $[M+Na]^+$ m/z=1279.8, found m/z=1257.8, 1280.4. El. Anal. Calcd for $C_{68}H_{72}N_8O_8S_4$: C, 64.94; H, 5.77; N, 8.91; S, 10.20. Found: C, 64.61; H, 5.78; N, 8.66; S, 10.43.

*4.2.6. 5,11,17,23-Tetra-tert-butyl-25,26,27,28-tetrakis[(3-pyridylamidocarbonyl)-methoxy]-2,8,14,20-tetrathiacalix[4]arene (1,3-alternate-**4c**).* White powder, yield: 0.86 g (65%). Mp: 249 °C. ^{1}H NMR (300 MHz, 373 K, $CDCl_3$) δ 9.20 (s, 4H, NH), 8.39–8.41, 8.51–8.55, 7.35–7.40, 8.27 (m, 16H, PyH), 7.29 (s, 8H, ArH), 4.70 (s, 8H, OCH_2CO), 0.70 (s, 36H, $(CH_3)_3C$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.7, 155.1, 148.4, 144.5, 140.9, 135.1, 129.8, 128.8, 127.1, 124.2, 118.7, 34.0, 30.4. IR (KBr) ν_{max} 1539, 1699, 3259, 3377. MS (MALDI-TOF): calcd for $[M]^+$ m/z=1257.6, found m/z=1257.4. El. Anal. Calcd for $C_{68}H_{72}N_8O_8S_4$: C, 64.94; H, 5.77; N, 8.91; S, 10.20. Found: C, 64.79; H, 5.98; N, 8.85; S, 10.18.

*4.2.7. 5,11,17,23-Tetra-tert-butyl-25,26,27,28-tetrakis[(4-pyridylamidocarbonyl)-methoxy]-2,8,14,20-tetrathiacalix[4]arene (cone-**5a**).* White powder, yield: 0.73 g (55%). Mp: 152 °C. ^{1}H NMR (300 MHz, 373 K, DMSO-d_6) δ 10.54 (s, 4H, NH), 8.31 (d, J=6.2 Hz, 8H, PyH), 7.55 (d, J=6.2 Hz, 8H, PyH), 7.45 (s, 8H, ArH), 5.12 (s, 8H, OCH_2CO), 1.09 (s, 36H, $(CH_3)_3C$). ^{13}C NMR (75 MHz, DMSO-d_6) δ 166.8, 165.8, 156.1, 148.4, 145.6, 143.5, 133.1, 126.3, 112.6, 112.5, 38.6, 32.6, 29.5. IR (KBr) ν_{max} 1521, 1702, 3279. MS (ESI): calcd for $[M]^+$ m/z=1257.6, found m/z=1257.7. El. Anal. Calcd for $C_{68}H_{72}N_8O_8S_4$: C, 64.94; H, 5.77; N, 8.91; S, 10.20. Found: C, 64.81; H, 5.66; N, 9.11; S, 10.31.

*4.2.8. 5,11,17,23-Tetra-tert-butyl-25,26,27,28-tetrakis[(4-pyridylamidocarbonyl)-methoxy]-2,8,14,20-tetrathiacalix[4]arene (partial cone-**5b**).* White powder, yield: 0.70 g (53%). Mp: 207 °C. ^{1}H NMR (300 MHz, 373 K, $CDCl_3$) δ 9.77 (s, 2H, NH), 9.56 (s, 4H, NH), 9.39 (s, 2H, NH), 8.42–8.51, 8.23–8.29, 7.65–7.69, 7.38–7.54, 7.17–7.22 (m, 16H, PyH), 7.74 (s, 2H, ArH), 7.71 (s, 2H, ArH), 7.65 (d, J=2.6 Hz, 2H, ArH), 7.51 (d, J=2.6 Hz, 2H, ArH), 5.07 (d, J=15.04 Hz, 2H, OCH_2CO), 4.85 (s, 2H, OCH_2CO), 4.82 (s, 2H, OCH_2CO), 4.61 (d, J=15.0 Hz, 2H, OCH_2CO), 1.36 (s, 9H, $(CH_3)_3C$), 1.10 (s, 9H, $(CH_3)_3C$), 0.94 (s, 18H, $(CH_3)_3C$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 168.6, 159.3, 157.9, 157.5, 157.0, 156.9, 155.0, 149.4, 148.9, 148.7, 147.4, 146.6, 145.7, 136.8, 136.7, 136.4, 136.3, 135.0, 134.7, 133.6, 128.3, 127.1, 126.2, 122.5, 122.0, 121.7, 44.7, 44.2, 34.3, 34.1, 31.3, 30.1. IR (Nujol) ν_{max} 1540, 1684, 3363. MS (ESI): calcd for $[M]^+$ m/z=1257.6, found m/z=1256.2. El. Anal. Calcd for $C_{68}H_{72}N_8O_8S_4$: C, 64.94; H, 5.77; N, 8.91; S, 10.20. Found: C, 64.82; H, 5.76; N, 8.61; S, 10.05.

*4.2.9. 5,11,17,23-Tetra-tert-butyl-25,26,27,28-tetrakis[(4-pyridylamidocarbonyl)-methoxy]-2,8,14,20-tetrathiacalix[4]arene (1,3-alternate-**5c**).* White powder, yield: 0.85 g (64%). Mp: 106 °C. ^{1}H NMR (300 MHz, 373 K, $CDCl_3$) δ 8.53 (s, 4H, NH), 8.56 (d, J=6.2 Hz, 8H, PyH), 7.49 (s, 8H, ArH), 7.48 (d, J=6.2 Hz, 8H, PyH), 4.85 (s, 8H, OCH_2CO), 0.74 (s, 36H, $(CH_3)_3C$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4, 156.0, 151.0, 149.5, 143.9, 130.7, 127.0, 113.4, 70.4, 34.2, 30.3. IR (KBr) ν_{max} 1539, 1699, 3381, 3234. MS (ESI): calcd for $[M]^+$ m/z=1257.6, found m/z=1257.7. El. Anal. Calcd for $C_{68}H_{72}N_8O_8S_4$: C, 64.94; H, 5.77; N, 8.91; S, 10.20. Found: C, 64.95; H, 5.83; N, 8.72; S, 10.17.

*4.2.10. 5,11,17,23-Tetra-tert-butyl-25,26,27,28-tetrakis[(2-pyridylmethylamidocarbonyl)-methoxy]-2,8,14,20-tetrathiacalix[4]arene (cone-**6a**).* White powder, yield: 1.04 g (75%). Mp: 126 °C. ^{1}H NMR (300 MHz, 373 K, $CDCl_3$) δ 8.93 (t, J=5.3 Hz, 4H, NH), 8.40–8.41, 7.57–7.63, 7.05–7.12 (m, 16H, PyH), 7.30 (s, 8H, ArH), 4.92 (8H, s, OCH_2CO), 4.55 (d, J=5.3 Hz, 8H, $NHCH_2$), 1.09 (s, 36H, $(CH_3)_3C$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9, 157.7, 157.4, 149.0, 147.2, 136.8, 134.8, 128.3, 122.1, 122.0, 44.5, 34.2, 31.1. IR (Nujol) ν_{max} 1541, 1648, 3336. MS (ESI): calcd for $[M+Na]^+$ m/z=1335.5, found m/z=1335.4. El. Anal. Calcd for $C_{72}H_{80}N_8O_8S_4$: C, 65.83; H, 6.14; N, 8.53; S, 9.76. Found: C, 65.57; H, 6.22; N, 8.45; S, 9.65.

*4.2.11. 5,11,17,23-Tetra-tert-butyl-25,26,27,28-tetrakis[(2-pyridylmethylamidocarbonyl)-methoxy]-2,8,14,20-tetrathiacalix[4]arene (partial cone-**6b**).* White powder, yield: 0.76 g (55%). Mp: 239 °C. ^{1}H NMR (300 MHz, 373 K, $CDCl_3$) δ 9.17 (t, J=5.4 Hz, 1H, NH), 8.99 (t, J=6.2 Hz, 2H, NH), 8.24 (t, J=5.4 Hz, 1H, NH), 7.80 (s, 2H, ArH), 7.54 (s, 2H, ArH), 7.53 (d, J=2.7 Hz, 2H, ArH), 6.99 (d, J=2.7 Hz, 2H, ArH), 6.92–6.97, 7.03–7.10, 7.14–7.21, 7.27–7.35, 7.44–7.69 (m, 16H, PyH), 5.04 (d, J=14.3 Hz, 2H, OCH_2CO), 5.03 (s, 2H, OCH_2CO), 4.82 (d, J=6.6 Hz, 1H, CH_2NH), 4.77 (d, J=6.6 Hz, 1H, CH_2NH), 4.73 (d, J=5.5 Hz, 2H, CH_2NH), 4.53 (d, J=4.8 Hz, 1H, CH_2NH), 4.47 (d, J=4.8 Hz, 1H, CH_2NH), 4.40 (d, J=14.3 Hz, 2H, OCH_2CO), 4.38 (s, 2H, OCH_2CO), 4.18 (d, J=5.4 Hz, 1H, CH_2NH), 1.32 (s, 9H, $(CH_3)_3C$), 1.16 (s, 18H, $(CH_3)_3C$), 0.98 (s, 9H, $(CH_3)_3C$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.0, 168.6, 159.3, 157.9, 157.5, 157.0, 156.9, 155.0, 149.4, 149.0, 148.7, 147.4, 146.6, 145.7, 136.8, 136.7, 136.4, 136.3, 135.0, 134.7, 133.6, 128.3, 127.1, 126.2, 122.5, 122.1, 122.0, 121.7, 44.7, 44.2, 34.3, 34.1, 31.3, 31.0. IR (Nujol) ν_{max} 1540, 1681, 3350, 3270. MS (ESI): calcd for $[M+Na]^+$ m/z=1335.5, found m/z=1335.4. El. Anal. Calcd for $C_{72}H_{80}N_8O_8S_4$: C, 65.83; H, 6.14; N, 8.53; S, 9.76. Found: C, 65.64; H, 6.39; N, 8.40; S, 9.81.

*4.2.12. 5,11,17,23-Tetra-tert-butyl-25,26,27,28-tetrakis[(2-pyridylmethylamidocarbonyl)-methoxy]-2,8,14,20-tetrathiacalix[4]arene (1,3-alternate-**6c**).* White powder, yield: 0.97 g (70%). Mp: 219 °C. ^{1}H NMR (300 MHz, 373 K, $CDCl_3$) δ 8.58 (t, J=5.3 Hz, 4H, NH), 7.54 (s, 8H, ArH), 7.15–7.21, 7.24–7.28, 7.60–7.69, 8.53–8.58 (m, 16H, PyH), 4.64 (d, J=5.3 Hz, 8H, CH_2NH), 4.13 (s, 8H, OCH_2CO), 1.05 (s, 36H, $(CH_3)_3C$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.3, 156.9, 156.6, 149.0, 147.2, 136.4, 133.4, 127.2, 122.0, 121.3, 44.4, 33.91, 30.7. IR (Nujol) ν_{max} 1533, 1668, 3316. MS (ESI): calcd for $[M+H]^+$ m/z=1313.5, found m/z=1313.5. El. Anal. Calcd for $C_{72}H_{80}N_8O_8S_4$: C, 65.83; H, 6.14; N, 8.53; S, 9.76. Found: C, 65.78; H, 6.01; N, 8.55; S, 9.80.

*4.2.13. 5,11,17,23-Tetra-tert-butyl-25,26,27,28-tetrakis[(3-pyridylmethylamidocarbonyl)-methoxy]-2,8,14,20-tetrathiacalix[4]arene (cone-**7a**).* White powder, yield: 0.87 g (63%). Mp: 206 °C. ^{1}H NMR (300 MHz, 373 K, $CDCl_3$) δ 8.37 (t, J=5.9 Hz, 4H, NH), 7.18–7.21, 7.57–7.61, 8.43–8.46, 8.54 (m, 16H, PyH), 7.30 (s, 8H, ArH), 4.80 (8H, s, OCH_2CO), 4.45 (d, J=5.9 Hz, 8H, $NHCH_2$), 1.09 (s, 36H, $(CH_3)_3C$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.7, 157.3, 147.4, 147.2, 146.6, 137.0, 134.8, 134.4, 127.9, 123.8, 40.1, 34.0, 30.8. IR (Nujol) ν_{max} 1540, 1648, 1670, 3267, 3363. MS (ESI): calcd for $[M+H]^+$ m/z=1313.5, found $[M+H]^+$ m/z=1313.8. El. Anal. Calcd for $C_{72}H_{80}N_8O_8S_4$: C, 65.83; H, 6.14; N, 8.53; S, 9.76. Found: C, 65.59; H, 6.12; N, 8.42; S, 9.93.

*4.2.14. 5,11,17,23-Tetra-tert-butyl-25,26,27,28-tetrakis[(3-pyridylmethylamidocarbonyl)-methoxy]-2,8,14,20-tetrathiacalix[4]arene (partial cone-**7b**).* White powder, yield: 0.94 g (68%). Mp: 118 °C. ^{1}H NMR

(300 MHz, 373 K, $CDCl_3$) δ 9.12 (t, J=5.7 Hz, 1H, NH), 8.22 (t, J=5.6 Hz, 2H, NH), 7.79 (t, J=5.7 Hz, 1H, NH), 7.04–7.23, 7.68–7.76, 8.27–8.75 (m, 16H, PyH), 7.66 (s, 2H, ArH), 7.52 (s, 2H, ArH), 7.23 (d, J=2.6 Hz, 2H, ArH), 6.98 (d, J=2.6 Hz, 2H, ArH), 5.02 (s, 2H, OCH_2CO), 4.93 (d, J=14.6 Hz, 2H, OCH_2CO), 4.34–4.65 (m, 8H, CH_2NH), 4.17 (s, 2H, OCH_2CO), 4.15 (d, J=14.6 Hz, 2H, OCH_2CO), 1.31 (s, 9H, $(CH_3)_3C$), 1.14 (s, 9H, $(CH_3)_3C$), 0.94 (s, 18H, $(CH_3)_3C$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.7, 168.1, 159.0, 157.6, 155.1, 149.2, 149.2, 148.9, 148.4, 148.3, 147.6, 136.3, 135.7, 135.2, 134.9, 134.2, 134.0, 133.4, 132.9, 128.1, 127.1, 125.7, 125.6, 123.5, 123.4, 123.1, 40.5, 40.4, 40.2, 34.2, 33.9, 31.1, 30.8. IR (Nujol) ν_{max} 1541, 1653, 1670, 3301. MS (ESI): calcd for $[M+Na]^+$ m/z=1335.5, found m/z=1335.4. El. Anal. Calcd for $C_{72}H_{80}N_8O_8S_4$: C, 65.83; H, 6.14; N, 8.53; S, 9.76. Found: C, 65.74; H, 6.08; N, 8.67; S, 9.88.

*4.2.15. 5,11,17,23-Tetra-tert-butyl-25,26,27,28-tetrakis[(3-pyridylmethylamidocarbonyl)-methoxy]-2,8,14,20-tetrathiacalix[4]arene (1,3-alternate-**7c**).* White powder, yield: 0.90 g (65%). Mp: 212 °C. ^1H NMR (300 MHz, 373 K, $CDCl_3$) δ 8.17 (t, J=5.9 Hz, 4H, NH), 7.43 (s, 8H, ArH), 7.23–7.30, 7.64–7.70, 8.51–8.61 (m, 16H, PyH), 4.50 (d, J=5.9 Hz, 8H, CH_2NH), 4.08 (s, 8H, OCH_2CO), 1.03 (s, 36H, $(CH_3)_3C$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 156.4, 149.4, 149.0, 147.7, 135.7, 133.4, 127.2, 123.6, 40.7, 34.1, 30.9. IR (Nujol) ν_{max} 1539, 1661, 3298, 3387. MS (ESI): calcd for $[M+Na]^+$ m/z=1335.5, found m/z=1335.5. El. Anal. Calcd for $C_{72}H_{80}N_8O_8S_4$: C, 65.83; H, 6.14; N, 8.53; S, 9.76. Found: C, 65.83; H, 6.07; N, 8.49; S, 9.96.

*4.2.16. 5,11,17,23-Tetra-tert-butyl-25,26,27,28-tetrakis[(4-pyridylmethylamidocarbonyl)-methoxy]-2,8,14,20-tetrathiacalix[4]arene (partial cone-**8b**).* White powder, yield: 0.75 g (54%). Mp: 118 °C. ^1H NMR (300 MHz, 373 K, $CDCl_3$) δ 9.10 (t, J=5.9 Hz, 1H, NH), 8.26 (t, J=5.9 Hz, 2H, NH), 7.88 (t, J=5.9 Hz, 1H, NH), 7.71 (s, 2H, ArH), 7.56 (s, 2H, ArH), 7.36 (d, J=2.4 Hz, 2H, ArH), 7.02 (d, J=2.4 Hz, 2H, ArH), 6.70–6.74, 7.14–7.22, 7.24–7.30, 8.32–8.37, 8.45–8.57 (m, 16H, PyH), 5.07 (s, 2H, OCH_2CO), 5.03 (d, J=14.7 Hz, 2H, OCH_2CO), 4.45 (s, 2H, OCH_2CO), 4.34–4.63 (m, 6H, CH_2NH), 4.19 (d, J=14.7 Hz, 2H, OCH_2CO), 4.10 (d, J=5.9 Hz, 2H, CH_2NH), 1.32 (s, 9H, $(CH_3)_3C$), 1.19 (s, 9H, $(CH_3)_3C$), 0.97 (s, 18H, $(CH_3)_3C$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 168.3, 158.9, 157.7, 155.1, 150.0, 149.4, 149.3, 147.7, 147.5, 147.3, 146.9, 146.3, 146.1, 136.4, 134.9, 134.0, 132.8, 128.3, 127.1, 125.8, 122.4, 122.3, 121.9, 41.8, 41.4, 34.2, 33.9, 31.1, 30.8. IR (Nujol) ν_{max} 1541, 1653, 1670, 3301. MS (ESI): calcd for $[M+H]^+$ m/z=1313.5, $[M+Na]^+$ m/z=1335.5, $[M+K]^+$ m/z=1351.5, found m/z=1313.7, 1335.7, 1351.7. El. Anal. Calcd for $C_{72}H_{80}N_8O_8S_4$: C, 65.83; H, 6.14; N, 8.53; S, 9.76. Found: C, 65.74; H, 6.03; N, 8.64; S, 9.77.

*4.2.17. 5,11,17,23-Tetra-tert-butyl-25,26,27,28-tetrakis[(4-pyridylmethylamidocarbonyl)-methoxy]-2,8,14,20-tetrathiacalix[4]arene (1,3-alternate-**8c**).* White powder, yield: 0.84 g (61%). Mp: 189 °C. ^1H NMR (300 MHz, 373 K, $CDCl_3$) δ 8.22 (t, J=5.9 Hz, 4H, NH), 7.48 (s, 8H, ArH), 7.21–7.29, 8.52–8.63 (m, 16H, PyH), 4.51 (d, J=5.9 Hz, 8H, CH_2NH), 4.13 (s, 8H, OCH_2CO), 1.06 (s, 36H, $(CH_3)_3C$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 156.2, 150.0, 147.7, 147.3, 133.3, 127.1, 122.3, 41.8, 34.0, 30.7. IR (Nujol) ν_{max} 1538, 1660, 3283. MS (ESI): calcd for $[M+H]^+$ m/z=1313.5, $[M+Na]^+$ m/z=1335.5, found m/z=1313.5, 1335.5. El. Anal. Calcd for $C_{72}H_{80}N_8O_8S_4$: C, 65.83; H, 6.14; N, 8.53; S, 9.76. Found: C, 65.74; H, 6.08; N, 8.55; S, 9.98.

4.3. Materials and general methods

The studies of the receptor abilities of thiacalix[4]arene derivatives **3**–**8** were carried out in CH_2Cl_2 (analytical grade). UV–vis spectra were obtained on a Perkin Elmer spectrophotometer Lambda 35.

4.3.1. Job plots. The series of solutions of thiacalix[4]arene derivatives **3**–**8**, α-hydroxylic, and dicarboxylic acids in CH_2Cl_2 was prepared from 1×10^{-5} M solutions of the substrate and receptor mixed in the ratio from 2.75:0.25 to 0.25:2.75 so that their total concentration remained constant and equal to 1×10^{-5} M. The solutions were shaken for 4 h at room temperature (20 °C). The absorbance A_i of the solution was measured at the wavelength of the maximum of the complex absorbance and then used for calculation as shown in Figures 7–9. The stoichiometry of the complexes was determined from the diagram maximum. Three independent experiments were carried out for each system.

4.3.2. Acid recognition studies. Because of the solubility problem, which existed for some substrates in CH_2Cl_2, the experimental procedure used assumed a significant excess of one of the components.[38] Standard solution contained equimolar amounts of *p-tert*-butyl thiacalix[4]arene and an acid in CH_2Cl_2 was prepared by addition of 1×10^{-5} M of *p-tert*-butyl thiacalix[4]arene in CH_2Cl_2 to 1000-fold excess of an acid. Then the mixture was shaken for 4 h at room temperature (20 °C). After that the series of dilutions was prepared in 5 mL calibrated flasks by mixing this stock solution and CH_2Cl_2 in ratio 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, and 9:1. Their UV–vis spectra were recorded and the absorbance measured at the wavelength corresponded to the maximum shift of the absorbance against that of 1×10^{-5} M of *p-tert*-butyl thiacalix[4]arene. The dilution series and absorbance measurements were repeated several times so that three datasets (concentration, d; absorbance, A_C) were obtained. K_a was calculated from derived data as described by Colquhoun.[38] Briefly, assuming the formation of 1:1 complex between the *p-tert*-butyl thiacalix[4]arene and the acid (CA·HA), the association constant, K_a, is defined by Eq. 1.

$$K_a = \frac{[CA\cdot HA]}{[CA][HA]} \tag{1}$$

Taken the initial concentrations of CA and HA equal to d, equilibrium concentrations can be expressed as follows:

$$[HA] + [CA\cdot HA] = d \tag{2}$$

$$[CA] + [CA\cdot HA] = d \tag{3}$$

For the equilibrium concentration of the complex equal to x, Eq. 1 is converted to Eq. 4.

$$K_a = \frac{x}{(d-x)^2} \tag{4}$$

The solution absorbance, A, is a sum of those related to thiacalix[4]arene, acid, and complex (A_{CA}, A_{HA}, and A_x, respectively),

$$A = A_{CA} + A_{HA} + A_x \tag{5}$$

Assuming that the Beer–Lambert law is obeyed for all the components considered Eq. 6, the absorbance A_i is expressed

$$A_i = c_i\varepsilon_i l \tag{6}$$

where c_i is a molar concentration of i-species, ε_i the molar absorptivity, and l the cell thickness. For complexation between the *p-tert*-butyl thiacalix[4]arene and acid the absorbance measurement is commonly conducted at the wavelength of absorbance maximum in the charge-transfer region where A_{HA}=0. This gives Eq. 7,

$$A = \varepsilon_{CA}(d-x)l + \varepsilon_x x l \tag{7}$$

where ε_{CA} and ε_x are the molar absorptivities of thiacalix[4]arene and the complex, respectively. Hence we obtain Eq. 8:

$$x = \frac{A - \varepsilon_{CA} dl}{(\varepsilon_x - \varepsilon_{CA})l} \quad (8)$$

Assuming $A-\varepsilon_{CA}dl=A_C$ and $\varepsilon_x-\varepsilon_{CA}=\varepsilon_C$, Eq. 8 is converted to Eq. 9:

$$x = \frac{A_C}{\varepsilon_C l} \quad (9)$$

Combining Eqs. 4 and 9 gives Eq. 10.

$$\frac{d}{A_C} = \left[\frac{1}{K_a \varepsilon_C}\right]^{1/2} \frac{1}{(A_C)^{1/2}} + \frac{1}{\varepsilon_C l} \quad (10)$$

The association constants for receptor and substrate were calculated by linear curve fitting of the plot of d/A_C against $1/(A_C)^{1/2}$ for a series of solutions of different concentrations d. Origin 7.0 (OriginLab Corporation) was used for all the calculations.

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Supplementary data

Supplementary data associated with this article can be found in online version, at doi:10.1016/j.tet.2009.10.075.

References and notes

1. Sorensen, U. S.; Bleisch, T. J.; Kingston, A. E.; Wright, R. A.; Johnson, B. G.; Schoepp, D. D.; Ornstein, P. L. *Bioorg. Med. Chem.* **2003**, *11*, 197–205.
2. Atwood, J. L.; Steed, J. W. *Organic Nanostructures*; Wiley-VCH: Weinheim, Germany, 2008.
3. Kayser, O.; Lemke, A.; Hernandez-Trejo, N. *Curr. Pharm. Biotechnol.* **2005**, *6*, 3–5.
4. Stoikov, I. I.; Fitseva, N. A.; Akhmetzyanova, L. R.; Gafioullina, L. I.; Antipin, I. S.; Zheltukhin, V. F.; Devyaterikova, A. I.; Alfonsov, V. A.; Konovalov, A. I. *Russ. Chem. Bull.* **2004**, *53*, 1577–1583.
5. Mascini, M.; Tombelli, S. *Biomarkers* **2008**, *13*, 637–657.
6. Stoikov, I. I.; Khrustalev, A. A.; Antipin, I. S.; Konovalov, A. I. *Dokl. Chem.* **2000**, *374*, 179–182.
7. Koner, A. L.; Schatz, J.; Nau, W. M.; Pischel, U. *J. Org. Chem.* **2007**, *72*, 3889–3895.
8. Schug, K.; Lindner, W. *Chem. Rev.* **2005**, *105*, 67–113.
9. Mutihac, L.; Buschmann, H. J.; Diacuc, E. *Desalination* **2002**, *148*, 253–256.
10. Dondoni, A.; Kleban, M.; Hu, X.; Marra, A.; Banks, H. D. *J. Org. Chem.* **2002**, *14*, 4722–4733.
11. Tomapatanaget, B.; Tuntulani, T. *Tetrahedron Lett.* **2001**, *42*, 8105–8109.
12. Clark, J. L.; Peinado, J.; Stezowski, J. J.; Vold, R. L.; Huang, Y.; Hoatson, G. L. *J. Phys. Chem.* **2006**, *110*, 26375–26387.
13. Jain, R. R.; Hamilton, A. D. *Org. Lett.* **2000**, *12*, 1721–1723.
14. Kolusheva, S.; Zadmard, R.; Schrader, T.; Jelinek, R. *J. Am. Chem. Soc.* **2006**, *41*, 13592–13598.
15. Peczuh, M. W.; Hamilton, A. D. *Chem. Rev.* **2000**, *100*, 2479–2494.
16. Zadmard, R.; Schrader, T. *J. Am. Chem. Soc.* **2005**, *127*, 904–915.
17. Verma, A.; Rotello, V. M. *Chem. Commun.* **2005**, 303–312.
18. You, C.-C.; De, M.; Rotello, V. M. *Curr. Opin. Chem. Biol.* **2005**, *9*, 639–646.
19. Ariga, K.; Kunitake, T. *Acc. Chem. Res.* **1998**, *31*, 371–378.
20. Atwood, J. L.; Davies, J. E. D.; MacNicol, D. D.; Vogtle, F.; Lehn, J. M.; Gokel, G. W. *Comprehensive Supramolecular Chemistry*; Pergamon: London, 1996.
21. Schneider, H.-J.; Yatsimirsky, A. K. *Principles and Methods in Supramolecular Chemistry*; John Wiley: Chichester, UK, 2000.
22. Park, H. S.; Lin, Q.; Hamilton, A. D. *J. Am. Chem. Soc.* **1999**, *121*, 8–13.
23. Stoikova, E. E.; Evtugyn, G. A.; Beljakova, S. V.; Khrustalev, A. A.; Stoikov, I. I.; Antipin, I. S.; Budnikov, H. C.; Konovalov, A. I. *J. Inclusion Phenom.* **2001**, *39*, 339–346.
24. Morohashi, N.; Narumi, F.; Iki, N.; Hattori, T.; Miyano, S. *Chem. Rev.* **2006**, *106*, 5291–5316.
25. Zlatuskova, P.; Stibor, I.; Tkadlecova, M.; Lhotak, P. *Tetrahedron Lett.* **2004**, *60*, 11383–11390.
26. Lamartine, R.; Bavoux, C.; Vocanson, F.; Martin, A.; Senlis, G.; Perrin, M. *Tetrahedron Lett.* **2001**, *42*, 1021–1024.
27. Stoikov, I. I.; Gafiullina, L. I.; Ibragimova, D. Sh.; Antipin, I. S.; Konovalov, A. I. *Russ. Chem. Bull.* **2004**, *53*, 1172–1180.
28. Stoikov, I. I.; Yushkova, E. A.; Zhukov, A. Yu.; Zharov, I.; Antipin, I. S.; Konovalov, A. I. *Tetrahedron* **2008**, *64*, 7489–7497.
29. Lhotak, P. *Eur. J. Org. Chem.* **2004**, 1675–1692.
30. Iki, N.; Miyano, S. *J. Inclusion. Phenom. Macrocyclic Chem.* **2001**, *41*, 99–105.
31. Evtugyn, G. A.; Stoikov, I. I.; Beljyakova, S. V.; Shamagsumova, R. V.; Stoikova, E. E.; Zhukov, A. Yu.; Antipin, I. S.; Budnikov, H. C. *Talanta* **2007**, *71*, 1720–1727.
32. Evtugyn, G. A.; Stoikov, I. I.; Belyakova, S. V.; Stoikova, E. E.; Shamagsumova, R. V.; Zhukov, A. Yu.; Antipin, I. S.; Budnikov, H. C. *Talanta* **2008**, *76*, 441–447.
33. Iki, N.; Narumi, F.; Fujimoto, T.; Morohashi, N.; Miyano, S. *J. Chem. Soc., Perkin Trans. 2* **1998**, 2745–2750.
34. Iki, N.; Narumi, F.; Suzuki, T.; Sugawara, A.; Miyano, S. *Chem. Lett.* **1998**, 1065–1066.
35. Stoikov, I. I.; Yushkova, E. A.; Zhukov, A. Y.; Zharov, I.; Antipin, I. S.; Konovalov, A. I. *Tetrahedron* **2008**, *64*, 7112–7121.
36. Stoikov, I.; Smolentsev, V.; Antipin, I.; Habicher, W.; Gruner, M.; Konovalov, A. *Mendeleev Commun.* **2006**, *16*, 294–297.
37. Joule, J.; Mills, K. *Heterocyclic Chemistry*; Blackwell Science: Oxford, 2000.
38. Colquhoun, H. N.; Goodings, E. P.; Maud, J. M.; Stoddart, J. F.; Wolstenholme, J. B.; Williams, D. J. *J. Chem. Soc., Perkin Trans. 2* **1985**, 607–624.