Available online at www.sciencedirect.com
ScienceDirect
Mendeleev Commun., 2016, **26**, 508–510
Mendeleev Communications

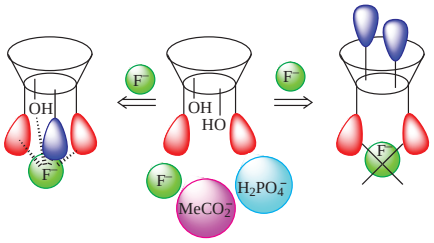
Selective fluoride ion recognition by a thiacalix[4]arene receptor containing *N*-(4-nitrophenyl)acetamide and 1-amidoanthraquinone fragments

Alena A. Vavilova, Roman V. Nosov and Ivan I. Stoikov*

A. M. Butlerov Institute of Chemistry, Kazan (Volga Region) Federal University, 420008 Kazan, Russian Federation. Fax: +7 8432 315 416; e-mail: ivan.stoikov@mail.ru

DOI: 10.1016/j.mencom.2016.11.016

New derivatives of thiacalix[4]arene, tri- and tetrasubstituted at the lower rim by *N*-(4-nitrophenyl)acetamide and 1-amidoanthraquinone fragments were synthesized. Their ability for recognition and binding of some anions (F^-, Cl^-, Br^-, I^-, $MeCO_2^-$, $H_2PO_4^-$, NO_3^-) was examined by UV spectroscopy, and a selective receptor for fluoride ion giving a 1 : 1 complex was invented.



A variety of objects of supramolecular chemistry and their ability to exhibit properties characteristic of highly organized biomolecules, such as molecular recognition, catalysis, active and selective transport has led to the rapid development of the chemistry of synthetic receptors.[1–5]

The design and synthesis of systems capable of recognizing anions continues to be one of the actual problems of organic chemistry. In particular, the fluoride ion plays an important role in living organisms, being one of the constituents of the mineral metabolism. It determines the bone status, its strength and toughness, correct formation of the skeleton, conditions and growth of hair, nails and teeth.[1] Usually, synthetic receptors for halide anions contain proton-donor groups, *e.g.*, amide, hydroxyl, urea.[6–10]

Calixarenes and thiacalixarenes are widely used as building blocks in the design of host molecules due to their unique three-dimensional structure as well as simplicity of functionalization of the macrocyclic platform[11–16] and possibility of existence of different conformational isomers (*cone*, *partial cone*, *1,2-alternate*, and *1,3-alternate*).

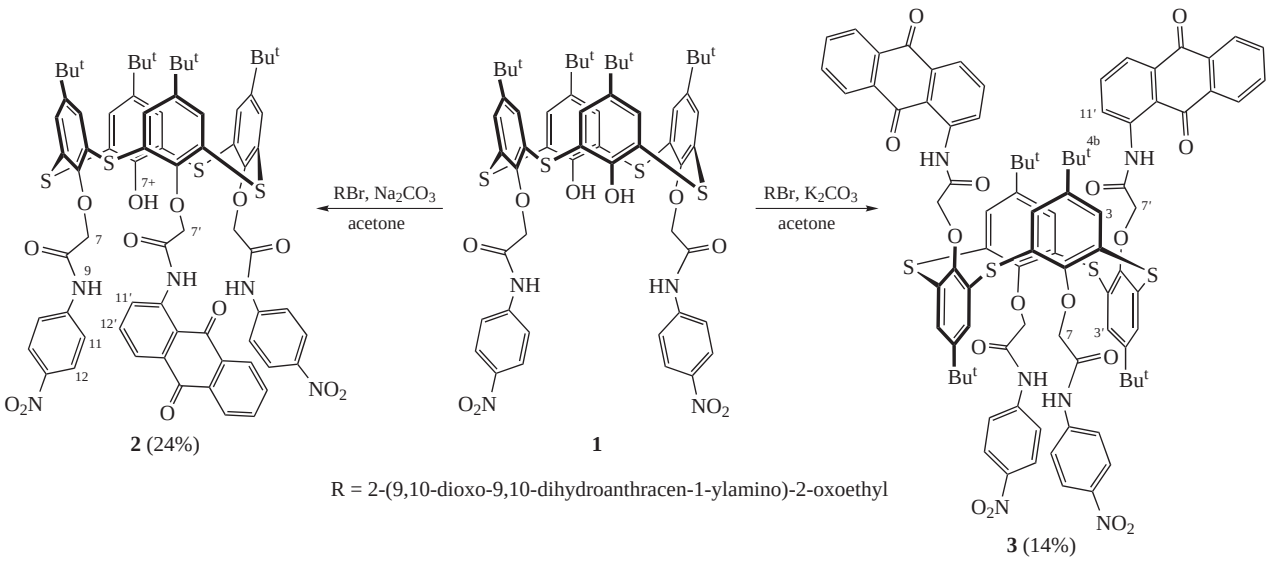
The synthesis of differently substituted at the lower rim *p-tert*-butylthiacalix[4]arene is more difficult than that of macrocycles substituted with the same fragments. Regioselective functionalization of the lower rim of thia-analogue of calix[4]arene is greatly complicated, because it requires comprehensive selection of the reaction conditions (ratio of reactants, temperature, and synthesis duration).

Development of selective 1,3-dialkylation of the lower rim of *p-tert*-butylthiacalix[4]arene with 2-bromo-*N*-(4-nitrophenyl)-acetamide[17] provided differently substituted synthetic receptors, allowing one to study the influence of the conditions on the functionalization of partially substituted derivatives with amide fragments. With the aim of the introduction of additional binding sites in thiacalixarene, special attention was paid to the functionalization of the macrocycle **1** with *N*-(9,10-dioxo-9,10-dihydroanthracen-1-yl)acetamide fragment containing polar NH group and chromophoric moiety required for spectrophotometrical detection of the complex formation. The 1-amidoanthraquinone fragment is also known as OFF–ON photo-switchable receptor realizing the ESIPT (excited-state intramolecular proton transfer) mechanism[18] including fluorescent sensors on its basis.[19] In this regard, we supposed to modify the thiacalixarene **1** structure with substituents containing 1-amidoanthraquinone fragment by alkylation of free phenolic hydroxyls and to study the complexation properties of the obtained compounds towards a variety of single-charged anions.

The interaction of the 1,3-disubstituted thiacalix[4]arene **1** with 2-bromo-*N*-(9,10-dioxo-9,10-dihydroanthracen-1-yl)acetamide according to the reported procedure[20] in the presence of alkali carbonates in acetone was studied. As a result, tri- and tetrasubstituted derivatives **2** and **3** were isolated from the reaction mixtures on using Na_2CO_3 and K_2CO_3, respectively (Scheme 1). The yields of products **2** and **3** (24 and 14%, respectively) were not as high, probably due to the steric hindrance of the reaction centre. In accordance with two-dimensional NMR data, macrocycle **2** possesses the *cone* conformation and macrocycle **3**, the *1,3-alternate* one. When cesium carbonate was used, only the starting compounds were quantitatively isolated instead of the expected tetrasubstituted product. Structures of products **2** and **3** were characterized by ^1H, ^{13}C, 2D NOESY NMR, IR spectroscopy, mass spectrometry, and their composition was confirmed by elemental analysis.[†]

The IR spectrum of trisubstituted thiacalix[4]arene **2** contained an absorption band of stretching vibrations of hydroxyl group

[†] *General procedure for the synthesis of compounds* **2** *and* **3**. The mixture of 5,11,17,23-tetra-*tert*-butyl-25,27-dihydroxy-26,28-bis[*N*-(4-nitrophenyl)aminocarbonylmethoxy]-2,8,14,20-tetrathiacalix[4]arene **1** (1.00 g, 0.93 mmol), an anhydrous alkali carbonate (0.39 g, 3.72 mmol Na_2CO_3 or 0.51 g, 3.72 mmol K_2CO_3) and 2-bromo-*N*-(9,10-dioxo-9,10-dihydroanthracen-1-yl)acetamide (1.28 g, 3.72 mmol) in 60 ml of dry acetone was refluxed for 60 h. After cooling, the solid residue from the reaction mixture was removed by filtration (in the case of Na_2CO_3, after evaporation under reduced pressure). The residue was dissolved in chloroform and washed with 2 M HCl. The organic layer was dried over molecular sieves, filtered and evaporated under reduced pressure. Crystallization of the resulting solid from tetrahydrofuran–methanol mixture gave pure samples of **2** and **3**.



Scheme 1

(3446 cm^{-1}), while in the spectrum of tetrasubstituted thiacalix[4]arene **3** it was absent. Stretching vibrations of N–H groups were observed in the form of broadened and narrow bands at 3292 and 3273 cm^{-1} in the IR spectrum of thiacalix[4]arene **2** and at 3329 and 3237 cm^{-1} in the IR spectrum of thiacalix[4]-arene **3** indicating hydrogen bond.

The receptor properties of the synthesized compounds **2** and **3** toward the tetrabutylammonium salts Bu_4NX ($X^- = F^-$, Cl^-, Br^-, I^-, $MeCO_2^-$, $H_2PO_4^-$, NO_3^-) were evaluated using UV spectroscopy and compared with the complexation ability of parent macrocycle **1**.[8] In these thiacalixarenes, proton donating secondary amide [*N*-(4-nitrophenyl)acetamide and 1-amidoanthraquinone fragments] and hydroxyl (phenolic) groups could participate in anion binding.

Preliminarily, the solutions of compounds **2** and **3** were studied in the presence of the 10-fold excess of Bu_4NX in $CDCl_3$ by ^1H NMR spectroscopy to estimate the possibility of binding tetrabutylammonium cations with the synthesized thiacalix[4]arenes. In ^1H NMR spectra, chemical shifts of the Bu_4N^+ protons did not change indicating the absence of this interaction.

The influence of the complex formation of compounds **2** and **3** with anions on the absorption spectra was investigated in the presence of 200-fold excess of the tetrabutylammonium salts in chloroform. The greatest changes, especially, hypochromic effect in the area of 290–330 nm, hyperchromic effect in the area of 330–420 nm and a bathochromic shift of the absorption band maximum at 315 nm, were detected for the interaction of macrocycle **2** with fluoride, acetate and dihydrogen phosphate salts. In addition, a new absorption maximum at 355 nm appeared. In the case of *p-tert*-butylthiacalix[4]arene **3**, such changes were not observed, indicating the absence of the interaction between this compound and the salts. Compound **3** is in the *1,3-alternate* conformation and probably, *tert*-butyl bulky groups hamper the complexation. It is also known that binding of substrates with *1,3-alternate* calix- and thiacalix[4]arenes can be complicated by negative allosteric effects.[21–25]

For the quantitative estimation of the complexation ability of compound **2** toward some anions ($X^- = F^-$, $MeCO_2^-$, $H_2PO_4^-$), the

5,11,17,23-Tetra-tert-*butyl-25-hydroxy-27-[*N*-(9,10-dioxo-9,10-dihydroanthracene-1-yl)aminocarbonylmethoxy]-26,28-bis[*N*-(4-nitrophenyl)-aminocarbonylmethoxy]-2,8,14,20-tetrathiacalix[4]arene* (*cone*-**2**, in the case of Na_2CO_3). Yield 0.30 g (24%), mp 198 °C. ^1H NMR ($CDCl_3$) δ: 1.03 (s, 9H, Me_3C), 1.13 (s, 18H, Me_3C), 1.23 (s, 9H, Me_3C), 4.69 [d, 2H, $OCH_2C(O)NHC_6H_4NO_2$, $^2J_{HH}$ 15.6 Hz], 5.00 [s, 2H, $OCH_2C(O)NH$], 5.48 [d, 2H, $OCH_2C(O)NHC_6H_4NO_2$, $^2J_{HH}$ 15.6 Hz], 7.27 (s, 2H, H_{Ar}), 7.43 (AB quadruplet, 4H, H_{Ar}, $^4J_{HH}$ 2.4 Hz), 7.51–8.90 (m, 7H, $H_{Ar'}$), 7.54 (s, 2H, H_{Ar}), 7.69 (AB part of AA′BB′ system, 4H, $H_{Ar'}$, $^3J_{AB}$ + + $^5J_{AB'}$ 9.0 Hz), 7.95 (A′B′ part of AA′BB′ system, 4H, $H_{Ar'}$, $^3J_{AB}$ + + $^5J_{AB'}$ 9.0 Hz), 9.01 (s, 1H, OH), 10.40 (s, 2H, $NHC_6H_4NO_2$), 12.85 (s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ: 25.63, 31.09, 31.30, 34.20, 34.37, 68.00, 73.90, 74.52, 118.23, 119.35, 120.86, 123.58, 124.59, 128.13, 128.44, 129.77, 132.59, 133.48, 134.19, 134.50, 134.80, 135.49, 135.57, 140.47, 143.30, 143.47, 148.01, 148.72, 156.25, 157.65, 167.90, 168.56. ^1H-^1H NOESY (most important cross-peaks are presented): $H^7/H^{7'}$, H^9/H^7, $H^9/H^{7'}$, $H^9/H^{11'}$, H^9/H^{7+}, H^9/H^{11}. IR (Nujol, ν/cm^{-1}): 3446 (OH), 3292, 3273 (NH), 1690 [C(O)NH], 1613, 1597 [C(O)NH], 1562, 1511, 1377, 1341 (NO_2). MS (MALDI-TOF), *m*/*z*: 1340.4 $[M + H]^+$, 1362.4 $[M + Na]^+$, 1378.4 $[M + K]^+$ (calc. for $[M^+]$, *m*/*z*: 1339.4). Found (%): C, 64.82; H, 4.85; N, 5.03; S, 9.60. Calc. for $C_{72}H_{69}N_5O_{13}S_4$ (%): C, 64.51; H, 5.19; N, 5.22; S, 9.57.

5,11,17,23-Tetra-tert-*butyl-25,27-bis[*N*-(9,10-dioxo-9,10-dihydroanthracene-1-yl)aminocarbonylmethoxy]-26,28-bis[*N*-(4-nitrophenyl)-aminocarbonylmethoxy]-2,8,14,20-tetrathiacalix[4]arene* (*1,3-alternate*-**3**, in the case of K_2CO_3). Yield 0.20 g (14%), mp 196 °C. ^1H NMR ($CDCl_3$) δ: 0.66 (s, 18H, Me_3C), 1.16 (s, 18H, Me_3C), 4.08 [s, 4H, $OCH_2C(O)NH$], 4.91 [s, 4H, $OCH_2C(O)NH$], 7.42 (s, 4H, H_{Ar}), 7.67 (s, 4H, H_{Ar}), 7.71– 9.26 (m, 14H, $H_{Ar'}$), 7.77 (AB part of AA′BB′ system, 4H, $H_{Ar'}$, $^3J_{AB}$ + $^5J_{AB'}$ 9.1 Hz), 8.21 (A′B′ part of AA′BB′ system, 4H, $H_{Ar'}$, $^3J_{AB}$ + $^5J_{AB'}$ 9.1 Hz), 9.05 (s, 2H, NH), 12.67 (s, 2H, NH). ^{13}C NMR ($CDCl_3$) δ: 29.70, 30.41, 30.80, 34.03, 34.51, 70.56, 70.81, 118.02, 119.41, 122.86, 125.07, 127.42, 128.61, 130.31, 132.42, 134.53, 135.60, 141.49, 142.98, 143.96, 147.98, 149.15, 155.66, 156.10, 166.87, 167.49. ^1H-^1H NOESY (the most important cross-peaks are presented): $H^{4b}/H^{11'}$, $H^3/H^{7'}$, $H^7/H^{3'}$. IR (Nujol, ν/cm^{-1}): 3329, 3237 (NH), 1671 [C(O)NH], 1611, 1596 [C(O)NH], 1542, 1512, 1378, 1340 (NO_2). MS (MALDI-TOF), *m*/*z*: 1603.6 $[M + H]^+$, 1625.6 $[M + Na]^+$, 1641.7 $[M + K]^+$ (calc. for $[M^+]$, *m*/*z*: 1602.4). Found (%): C, 65.75; H, 4.68; N, 5.07; S, 8.07. Calc. for $C_{88}H_{78}N_6O_{16}S_4$ (%): C, 65.90; H, 4.90; N, 5.24; S, 8.00.

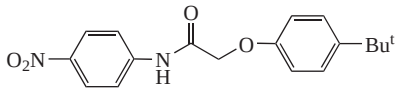
‡ *Determination of the stoichiometry by isomolar series method*.[26] The stoichiometry was determined by plotting curves of isomolar series. The solutions of the host and guest in chloroform with a concentration of 2.5×10^{-5} mol dm^{-3} were prepared. The receptor was dissolved in 100 ml of chloroform. The tetrabutylammonium salt weighed sample of the same concentration was dissolved in 25 ml of chloroform. The spectra of the initial solutions and their mixtures (0.6 ml + 2.4 ml; 0.75 ml + 2.25 ml; 1 ml + 2 ml; 1.2 ml + 1.8 ml; 1.5 ml + 1.5 ml; 1.8 ml + 1.2 ml; 2 ml + 1 ml; 2.25 ml + 0.75 ml; 2.4 ml + 0.6 ml) were recorded. The optical density values were used to calculate data required for plotting the complex absorption *vs.* concentration changes. According to the X-coordinate of the curve maximum, the stoichiometry of the complexes was determined. For all the systems studied the X-coordinate of the curve maximum was equal to 0.5. This indicates the presence of host–guest complexation in a 1 : 1 ratio. The measurements were carried out twice under the same conditions. Statistical analysis was performed using Student's *t*-test.

Table 1 The logarithms of the association constant ($\log K_{as}$) of the complexation of the test compounds with anions (at 25 °C).

Compound	Host : guest ratio	$\log K_{as}$						
		F^-	Cl^- [a]	Br^- [a]	I^- [a]	$H_2PO_4^-$	$MeCO_2^-$	NO_3^- [a]
1	1:1	3.67±0.19	–	–	–	3.41±0.09	3.50±0.32	–
2	1:1	4.77±0.19	–	–	–	3.37±0.09	3.30±0.32	–
4	1:1	2.52±0.48	–	–	–	2.81±0.27	2.32±0.56	–

[a] No changes in UV spectra.

association constants (Table 1) and stoichiometry of the complexes formed were determined.[‡,§] Isomolar series method showed that in $CHCl_3$ thiacalix[4]arene **2** formed the 1 : 1 complexes with the tetrabutylammonium salts studied (Figure 1). The stoichiometry of the complexation was also confirmed by measuring Job's plots (see Figure 1). The association constants of the test complexes were estimated in chloroform by the dilution method. The appropriate complexation constants (Table 1) were calculated using the Benesi–Hildebrand method.[26]



4

For estimation of thiacalixarene platform contribution to the anion binding, the properties of model compound **4**[8] were studied, whose logarithms of the association constant with anions were found to be lower by at least an order of magnitude as compared with those of the macrocycles **1**, **2** (Table 1). The introduction of additional amide proton donating fragment into the lower rim of

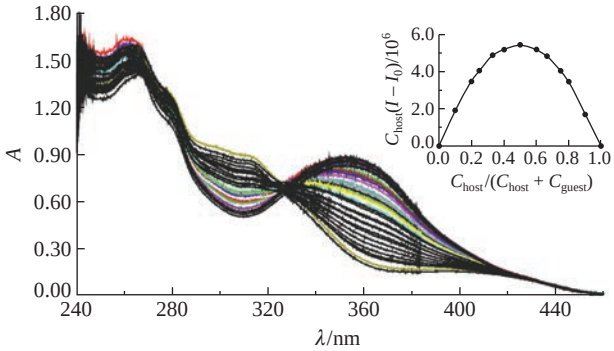


Figure 1 UV spectra of the system thiacalix[4]arene **2** (2.5×10^{-5} mol dm^{-3}) with the fluoride ion ($C_{initial} = 2.5\times10^{-5}$ mol dm^{-3}, $C_{final} = 5\times10^{-3}$ mol dm^{-3}) in $CHCl_3$: determination of the association constant of the complex by the dilution method and the Job's plot for the system **2** + Bu_4NF.

§ *Determination of the association constant.*[26] Absorption properties of compounds **2** and **3** were studied in chloroform solution (2.5×10^{-5} M). The efficiency of anion binding was estimated by addition of a 200-fold excess of tetrabutylammonium salt in chloroform. The concentration of the anion in titration experiment was varied from 2.5×10^{-5} to 5.0×10^{-3} mol dm^{-3}. The calculation of association constants values were carried out according the intensity change of the absorption wavelength maximum having the highest hyperchromic effect upon complexation, for which absorption intensity change was the maximum, and according the change of the ratio of two wavelengths intensities having a maximum hypo- and hyperchromic effects upon complexation.[26]

The association constants of the complexes were calculated by the formula $\beta = \alpha C_h/[(C_h - a\alpha C_h)^a(C_g - b\alpha C_h)^b]$, where C_g is the anion concentration, C_h is the receptor concentration, α is the saturation constant of the complex, a is the stoichiometric coefficient of the receptor molecule, b is the stoichiometric coefficient of the salt molecule.

the 1,3-disubstituted *p-tert*-butylthiacalix[4]arene **1** in the case of compound **2** resulted in selective binding of the fluoride anion. Tetrasubstituted macrocycle **3** in *1,3-alternate* conformation did not bind the anions studied, presumably because of the negative allosteric effect that hindered the complexation.

In conclusion, selective receptor for fluoride ion based on trisubstituted thiacalix[4]arene containing *N*-(4-nitrophenyl)acetamide and 1-amidoanthraquinone fragments at the lower rim was synthesized.

This work was supported by the Russian Science Foundation (grant no. 16-13-00005).

References

1 *Anion Sensing*, ed. I. Stibor, Springer, Berlin, 2005, vol. 255.
2 V. V. Gorbatchuk, A. K. Gatiatulin, M. A. Ziganshin, A. T. Gubaidullin and L. S. Yakimova, *J. Phys. Chem. B*, 2013, **117**, 14544.
3 C. D. Gutsche, in *Calixarenes Revisited – Monographs in Supramolecular Chemistry*, ed. J. F. Stoddart, The Royal Society of Chemistry, Cambridge, 1998, vol. 6.
4 L. S. Yakimova, J. B. Puplampu, A. A. Vavilova and I. I. Stoikov, in *Advances in Chemistry Research*, ed. J. C. Taylor, Nova Science Publishers, New York, 2015, vol. 28, p. 145.
5 G. M. Mamardashvili, N. Zh. Mamardashvili and O. I. Koifman, *Russ. Chem. Rev.*, 2015, **84**, 275.
6 I. I. Stoikov, O. A. Mostovaya, L. S. Yakimova, A. A. Yantemirova, I. S. Antipin and A. I. Konovalov, *Mendeleev Commun.*, 2010, **20**, 359.
7 S. Naher, K. Hiratani and S. Ito, *J. Inclusion Phenom. Macrocycl. Chem.*, 2006, **55**, 151.
8 I. I. Stoikov, A. A. Yantemirova, R. V. Nosov, I. Kh. Rizvanov, A. R. Julmetov, V. V. Klochkov, I. S. Antipin, A. I. Konovalov and I. Zharov, *Org. Biomol. Chem.*, 2011, **9**, 3225.
9 N. Pelizzi, A. Casnati, A. Friggeri and R. Ungaro, *J. Chem. Soc., Perkin Trans. 2*, 1998, 1307.
10 P. Curinova, I. Stibor, J. Budka, J. Sykora, K. Lang and P. Lhotak, *New J. Chem.*, 2009, **33**, 612.
11 I. I. Stoikov, A. A. Yantemirova, R. V. Nosov, A. R. Julmetov, V. V. Klochkov, I. S. Antipin and A. I. Konovalov, *Mendeleev Commun.*, 2011, **21**, 41.
12 I. I. Stoikov, O. A. Mostovaya, A. A. Yantemirova, I. S. Antipin and A. I. Konovalov, *Mendeleev Commun.*, 2012, **22**, 21.
13 A. A. Vavilova, R. V. Nosov, A. N. Yagarmina, O. A. Mostovaya, I. S. Antipin, A. I. Konovalov and I. I. Stoikov, *Macroheterocycles*, 2012, **5**, 396.
14 A. A. Vavilova, R. V. Nosov, L. S. Yakimova, I. S. Antipin and I. I. Stoikov, *Macroheterocycles*, 2013, **6**, 219.
15 J. B. Puplampu, L. S. Yakimova, A. A. Vavilova, D. A. Fayzullin, Y. F. Zuev and I. I. Stoikov, *Macroheterocycles*, 2014, **7**, 337.
16 J. B. Puplampu, L. S. Yakimova, A. A. Vavilova, I. Kh. Rizvanov and I. I. Stoikov, *Macroheterocycles*, 2015, **8**, 75.
17 I. I. Stoikov, D. Sh. Ibragimova, N. V. Shestakova, D. B. Krivolapov, I. A. Litvinov, I. S. Antipin, A. I. Konovalov and I. Zharov, *Supramol. Chem.*, 2009, **21**, 564.
18 T. P. Smith, K. A. Zaklika, K. Thakur, G. C. Walker, K. Tominaga and P. F. Barbara, *J. Phys. Chem.*, 1991, **95**, 10465.
19 S. J. Hyo, J. K. Hyun, V. Jacques and S. K. Jong, *Tetrahedron Lett.*, 2009, **50**, 983.
20 J. R. Etukala and J. S. Yadav, *Heteroatom Chem.*, 2008, **19**, 221.
21 I. I. Stoikov, O. A. Omran, S. E. Solovieva, S. K. Latypov, K. M. Enikeev, A. T. Gubaidullin, I. S. Antipin and A. I. Konovalov, *Tetrahedron*, 2003, **59**, 1469.
22 J. Budka, P. Lhotak, V. Michlova and I. Stibor, *Tetrahedron Lett.*, 2001, **42**, 1583.
23 A. V. Galukhin, K. V. Shabalin, I. S. Antipin, A. I. Konovalov and I. I. Stoikov, *Mendeleev Commun.*, 2013, **23**, 41.
24 A. V. Galukhin, E. A. Andreyko, I. H. Rizvanov and I. I. Stoikov, *Mendeleev Commun.*, 2013, **23**, 196.
25 A. V. Galukhin and I. I. Stoikov, *Mendeleev Commun.*, 2014, **24**, 82.
26 K. Hirose, *J. Inclusion Phenom. Macrocycl. Chem.*, 2001, **39**, 193.

Received: 28th March 2016; Com. 16/4891