Synthetic receptors for transition metal cations – tetrahydrazides on the basis of *p-tert*-butylthiacalix[4]arene

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Stereoisomers of tetrahydrazide on the basis of *p-tert*-butylthiacalix[4]arene have been synthesised and characterised by IR spectroscopy, ^{1}H and ^{13}C NMR spectroscopy and mass spectrometry; the receptor properties of novel compounds towards metal cations, including most dangerous environmental pollutants, have been characterised by picrate extraction.

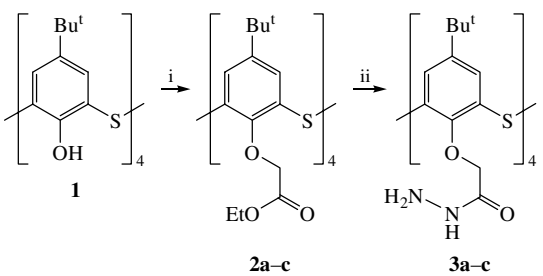
Recently, much attention has been paid to chemical separation techniques, which involve the design and synthesis of new extractants for transition metal ions.[1]

Calixarenes and thiacalixarenes are cyclic oligomers, prepared by condensation of *para*-substituted phenols and formaldehyde or sulfur under alkaline conditions.[2–4] These macrocycles are an excellent molecular platform for the design of sophisticated structures capable of molecular recognition of cations, anions and neutral molecules.[5,6] The calixarene structure provides a unique combination of a conformationally flexible macrocyclic ring, conformationally rigid aromatic units and easy-to-modify hydroxyls to construct multi-armed podand receptors with different geometries of binding sites.

p-tert-Butylthiacalix[4]arene **1** is known to bind transition metal cations by coordination with bridging sulfide fragments.[7] Nevertheless, there are only few publications concerning the extraction of transition metal cations by derivatives of **1**, substituted at the lower rim.[8] Miyano with coworkers reported on the facile synthesis[9] of three tetraester stereoisomers: cone **2a**, partial cone **2b**, 1,3-alternate **2c**, providing a direct synthetic route to stereoisomers of tetrasubstituted thiacalix[4]arenes. A usual synthetic approach to further modification consists of three stages: hydrolysis leading to an acid, its conversion into chloroanhydride and further modification with appropriate reagent.[10]

In this work, we report a one-step synthesis of three macrocyclic receptors: *cone* **3a**, *partial cone* **3b**, and 1,3-*alternate* **3c** stereoisomers of tetrahydrazide on the basis of thiacalix[4]arene by hydrazinolysis† of corresponding tetraesters **2a–c** (Scheme 1) with good to excellent yields (80, 95 and 90%, respectively). Note that the interconversion of stereoisomers does not occur under the conditions of hydrazinolysis.

Structures of the compounds obtained (Scheme 2) were characterised by a number of physical methods.† The conformation of tetrasubstituted thiacalix[4]arenes can be determined by signal patterns and chemical shifts of methylene and *tert*-butyl groups in ^{1}H NMR spectra.[8] Partial cone (**3b**) is the only stereoisomer possessing three nonequivalent groups of *tert*-butyl residues, which will give a 2:1:1 resonance pattern in NMR spectra (1.17, 1.30 and 1.37 ppm). Symmetrical structures of cone and 1,3-alternate stereoisomers should give the same pattern in NMR spectra; however, it is possible to distinguish between these stereoisomers considering chemical shifts of –OCH$_2$C(O)– units. In a 1,3-alternate conformation, these protons are located in a shielding zone of two adjacent benzene rings, and signals of these protons are located in a higher field than the signal of corresponding protons of cone stereoisomer (4.57 and 4.86 ppm, respectively). *tert*-Butyl protons of the 1,3-alternate stereoisomer are located in a deshielding zone of not only attaching phenyl unit but also two adjacent benzene rings. By that reason *tert*-butyl protons signal of 1,3-alternate should appear in a lower field, compared to *tert*-butyl protons signal of the cone stereoisomer (1.26 and 1.10 ppm, respectively). Thus, structures of compounds **3a** and **3c** could be unambiguously assigned for cone and 1,3-alternate stereoisomers, respectively.



Scheme 1 *Reagents and conditions*: i, see ref. 8; ii, see footnote.†

The signal of amide protons of compound **3a** in the ^{1}H NMR spectrum appears in a very weak field (9.90 ppm) indicating strong H-bonding between four amide moieties located on the same side of the macrocyclic plane. This is confirmed by the presence of only H-bonded amide group absorption band (3330 cm^{-1}) in IR spectra of **3a** in solid state and solution. The chemical shift (7.37 ppm) and sharp form of an amide proton peak in ^{1}H NMR spectrum of **3c** and IR spectra in solid state and solution, where both bonded (3330 cm^{-1}) and free (3416 cm^{-1}) amide absorption bands are present, indicate the existence of

† For **3a**. Solution of compound **2a** (1.00 g, 0.95 mmol) and $N_2H_4{\cdot}H_2O$ (0.96 ml, 19 mmol) in a mixture of Et_2O (20 ml) and ethanol (5 ml) was stirred at reflux for 20 h, concentrated at reduced pressure and dried *in vacuo*. The pure product was obtained by recrystallization from Pr^{i}OH. Yield 0.76 g (80%); mp 258 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.10 (s, 36H, Bu^t), 3.95 (br. s, 8H, NH_2), 4.86 (s, 8H, COCH), 7.34 (s, 8H, ArH), 9.90 (br. s, 4H, CONH). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 30.9, 34.1, 75.0, 128.2, 134.8, 147.9, 158.0, 168.8. IR (KBr pellet, ν/cm^{-1}): 3324 (NH-bonded), 1675 (CO), 1266 (COC). IR (0.05 M $CHCl_3$ solution, ν/cm^{-1}): 3330 (NH-bonded), 1670 (CO), 1265 (COC). MS ESI, *m/z*: 1031 (M + Na$^+$), 1047 (M + K$^+$).

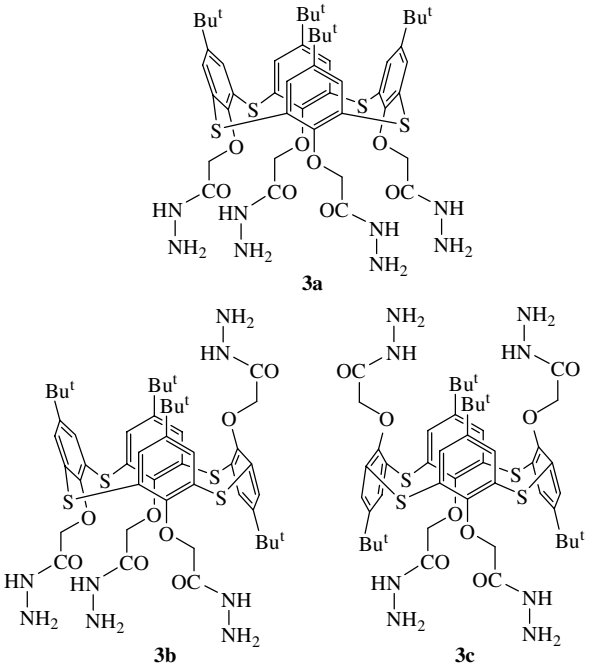
For **3b**. Suspension of compound **2b** (1.00 g, 0.95 mmol) and $N_2H_4{\cdot}H_2O$ (0.96 ml, 19 mmol) in ethanol (10 ml) was stirred at reflux for 40 h, concentrated at reduced pressure and dried *in vacuo*. The pure product was obtained by recrystallization from CH_2Cl_2–EtOH. Yield, 0.90 g (95%); mp 226 C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.17 (s, 18H, Bu^t), 1.30 (s, 9H, Bu^t), 1.37 (s, 9H, Bu^t), 2.26 (d, 2H, NH_2, $^3J_{HH}$ 4.3 Hz), 3.86 (br. s, 2H, NH_2), 3.94 (br. s, 4H, NH_2), 4.27 (s, 2H, O–CH$_2$), 4.45 (br. t, 1H, NH, $^3J_{HH}$ 4.3 Hz), 4.75, 4.64 (AB-q, 4H, O-CH$_2$, $^2J_{HH}$ 14.2 Hz), 4.80 (s, 2H, O–CH$_2$), 7.38 (d, 2H, ArH, $^4J_{HH}$ 2.6 Hz), 7.44 (s, 2H, ArH), 7.59 (d, 2H, ArH, $^4J_{HH}$ 2.6 Hz), 7.85 (s, 2H, ArH), 8.50 (br. s, 2H, NH), 8.96 (br. s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 31.2, 34.3, 34.5, 31.0, 34.7, 64.6, 72.6, 74.1, 126.0, 126.9, 127.8, 128.3, 128.4, 131.1, 135.5, 137.1, 148.8, 149.6, 152.4, 156.5, 158.4, 165.5, 168.3, 168.4. IR (KBr pellet, ν/cm^{-1}): 3434, 3416 (NH-free), 3323, 3278 (NH-bonded), 1680 (CO), 1268 (COC). IR (0.05 M $CHCl_3$ solution, ν/cm^{-1}): 3416 (NH-free), 3330 (NH-bonded), 1677 (CO), 1264 (COC). MS ESI, *m/z*: 1031 (M + Na$^+$), 1047 (M + K$^+$).

For **3c**. Suspension of compound **2c** (1.00 g, 0.95 mmol) and $N_2H_4{\cdot}H_2O$ (0.96 ml, 19 mmol) in a mixture of THF (15 ml) and ethanol (15 ml) was stirred at reflux for 50 h, concentrated at reduced pressure and dried *in vacuo*. The pure product was obtained by recrystallization from CH_2Cl_2–EtOH. Yield, 0.85 g (90%); mp 274 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.26 (s, 36H, Bu^t), 3.58 (br. s, 8H, NH_2), 4.57 (s, 8H, COCH), 7.37 (s, 4H, CONH), 7.41 (s, 8H, Ar*H*). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 31.3, 34.5, 68.3, 127.2, 128.5, 148.8, 154.7, 168.1. IR (KBr pellet, ν/cm^{-1}): 3416 (NH-free), 3320 (NH-bonded), 1676 (CO), 1270 (COC). IR (0.05 M $CHCl_3$ solution, ν/cm^{-1}): 3415 (NH-free), 3321 (NH-bonded), 1676 (CO), 1263 (COC). MS MALDI-TOF, *m/z*: 1009 (M + H$^+$), 1031 (M + Na$^+$).

Table 1 Extraction extent (*%E*) of alkali, alkaline earth and transition metal ions by stereoisomers **3a–c**.‡

Ligand	Li^+	Na^+	K^+	Cs^+	Mg^{2+}	Ca^{2+}	Ba^{2+}	Al^{3+}	Ni^{2+}	Cu^{2+}	Co^{3+}	Pb^{2+}	Hg^{2+}	Cd^{2+}
3a	n.e.[a]	n.e.	n.e.	4	12	14	21	28	99	98	96	88	96	96
3b	n.e.	n.e.	n.e.	n.e.	n.e.	n.e.	n.e.	5	89	89	19	17	97	24
3c	n.e.	n.e.	n.e.	n.e.	n.e.	n.e.	n.e.	9	9	12	7	8	45	9

[a]Not extracted (*%E* < 4).



Scheme 2 Structures of stereoisomers **3a–c**.

dynamic exchange between H-bonded and free NH moieties.

The structure of compound **3b** possesses symmetry of lower order than **3a** or **3c**, so in ^{1}H NMR spectrum amide protons appear as three signals. Signals of three associated amide moieties on one side of the macrocyclic plane appear as two singlets in a weak field (8.96 and 8.50) with an intensity ratio of 1:2. The isolated hydrazide residue on the other side of the macrocycle appears as a triplet (at 4.45 ppm) and doublet (at 2.26 ppm) for amide and amine groups, respectively. The upfield shift indicates that this hydrazide moiety is included into a macrocyclic cavity formed by benzene rings. Absorption bands of free (3416 cm^{-1}) and H-bonded (3323 cm^{-1}) amide moieties are present in IR spectra of **3b** in solid state and solution.

To estimate the receptor properties of synthesised compounds towards a large number of metal cations, including most dangerous environmental pollutants, picrate extraction experiments were performed.‡ Compounds **3a–c** possess binding sites of different nature: carbonyl groups of hydrazide moieties, as well as alkoxylic groups able to bind hard cations such as alkali and alkaline earth metal ions, and soft amine moieties capable of soft cation binding. The solutions of alkali and alkaline earth picrates, as well as transition metal picrates, were prepared by pH-metric titration from aqueous solutions of picric acid and metal hydroxides [LiOH, NaOH, KOH, CsOH, $Ca(OH)_2$ and $Ba(OH)_2$, pH 7] or metal nitrates [Ni^{2+}, Cu^{2+}, Mg^{2+}, Al^{3+}, Co^{3+}, Pb^{2+}, Hg^{2+} and Cd^{2+}; in these cases, the resulting solutions were weakly acidic (pH 4) to ensure that the metal cations do not undergo hydrolysis].

‡ *General method for picrate extraction.* Solutions of metal picrates were prepared by pH-metry from aqueous picric acid and metal hydroxide [LiOH, NaOH, KOH, CsOH, $Ca(OH)_2$ and $Ba(OH)_2$] or metal nitrate (Mg^{2+}, Al^{3+}, Ni^{2+}, Cu^{2+}, Hg^{2+}, Pb^{2+}, Co^{3+} and Cd^{2+}) solutions. In the latter case, solutions were weakly acidic (pH 4). An aqueous picrate solution (3 ml, 2.32×10^{-4} M) and a dichloromethane solution of the ligand (3 ml, 2.5×10^{-3} M) were stirred together for 0.5 h and then kept for 1 h for phase separation at 25 °C. The absorbance of the aqueous phase before (A_0) and after extraction (A_i) were measured at 355 nm. The percentage of cation extracted (*%E*) was calculated as the ratio $100(A_0 - A_i)/A_0$. The values presented are the result of three parallel runs, estimated standard deviations were under ±3%.

Extraction extent (*%E*) for alkali, alkaline earth and transition metal ions is presented in Table 1. It can be seen that all conformers **3a–c**, unlike tertiary amide analogues,[11] do not extract (*%E* < 4) alkali metal cations. Alkaline earth metal cations are only extracted by cone stereoisomer **3a** (12–26%) and extraction extent is increased with enlargening of cation size. Weak extractability of calixarenes **3a–c** towards alkali and alkaline-earth metal cations presumably results from strong H-bonding between the amide moieties of receptors **3a–c**, which competes with coordination of hard metal cations to carbonyl groups.

By contrast, calixarenes **3a–c** extract transition metal cations very well. Interestingly, the extractability of compounds **3a–c** towards environmentally dangerous transition metal cations (Ni^{2+}, Cd^{2+}, Pb^{2+}, Cu^{2+}, Hg^{2+} and Co^{3+}) is greatly influenced by receptor molecule conformation. Whereas 'four-armed' podand receptor **3a** is a highly effective, but not selective extractant of all the transition metal ions studied, 'three-armed' podand receptor **3b** effectively and selectively binds Ni^{2+}, Cu^{2+} and Hg^{2+}. 'Two-armed' podand receptor **3c** shows certain selectivity for Hg^{2+} among all ions studied. Dramatic difference in compounds affinity toward soft transition metal cations compared to hard alkali and alkaline-earth metal cations is presumably caused by coordination of soft cations with soft amine moieties of hydrazide group and/or sulfide bridging fragments of the parent macrocycle.

In conclusion, three new compounds **3a–c** bearing hydrazide moieties have been prepared from conformers of *p-tert*-butyltetrakis[(ethoxycarbonyl)methoxy]tetrathiacalix[4]arene. Complexation studies show that macrocycles **3a–c** are capable of transition metal ions recognition, whilst alkali, alkaline-earth metal and aluminium cations are weakly bound. Binding properties of the macrocycles are greatly influenced by the conformation of the receptor molecule.

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