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The synthesis and complexation of novel azosubstituted calix[4]arenes and thiacalix[4]arenes

Kamil Lang [a,*], Petra Prošková [a], Jan Kroupa [b], Jiří Morávek [b], Ivan Stibor [b], Michaela Pojarová [b], Pavel Lhoták [b,**]

[a] *Institute of Inorganic Chemistry, v.v.i., Academy of Sciences of the Czech Republic, 250 68 Řež, Czech Republic*
[b] *Department of Organic Chemistry, Institute of Chemical Technology, Technická 5, 16628 Prague 6, Czech Republic*

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Abstract

Novel calix[4]arene/thiacalix[4]arene derivatives bearing arylazo moieties were prepared via a diazo-coupling reaction. Subsequent alkylation with ethyl bromoacetate via the template effect of alkali metal carbonates resulted in arylazo substituted calix[4]arene/thiacalix[4]arene tetraacetates. UV–vis spectroscopy revealed that in terms of their binding affinity towards alkali metal cations, the tetraacetate derivative displayed considerable selectivity for sodium cations ($K_{Na^+}/K_{K^+} > 100$, $K_{Na^+}/K_{Li^+} > 175$).

Keywords: Calix[4]arene; Thiacalix[4]arene; Alkylation; Cation complexation; UV–vis titration

1. Introduction

Calixarenes, a well-known family of macrocyclic phenol–formaldehyde oligomers, have been attracting the interest of chemists for more than three decades. As these compounds represent readily available and precisely defined three-dimensional structures, they found numerous applications in supramolecular chemistry [1]. The unproblematic derivatization of the calix[4]arene skeleton **1** together with the controllable shape of the cavity makes this molecule an ideal molecular scaffold for the construction of various receptors. Due to their excellent complexation abilities, calix[4]arenes are frequently used for the design of novel selective complexation agents. Depending on the substitution pattern and the conformation, calix[4]arenes bind cations [2], anions [3] and/or neutral compounds [4] via noncovalent interactions (cation–π interactions, π–π interactions, hydrogen bonds, electrostatic interactions, coordination bonds, van der Waals interactions, etc.). While the chemistry of classical calix[4]arenes **1** has been already well established, the chemistry of thiacalix[4]arenes [5] **2** with sulfur atoms substituted for methylene bridges is still underdeveloped and not fully understood (Fig. 1). The presence of heteroatoms in the macrocyclic skeleton causes unusual chemical behavior and different conformational preferences. As we have demonstrated recently, structurally identical molecules differing only in the bridging group can have dramatically different binding affinity towards neutral molecules [6]. In this paper we report on the comparative study of alkali metal receptors based on the calix[4]arene and/or thiacalix[4]arene scaffolds.

2. Experimental

Melting points are uncorrected and were determined using a Boetius Block apparatus (Carl Zeiss Jena, Germany). The NMR spectra were recorded at 300 MHz (^{1}H) and at 75 MHz (^{13}C). Elemental analyses were measured on Elementar vario EL instruments (Elementar, Germany). The mass

* Corresponding author. Tel.: +420 266 172 193; fax: +420 220 941 502.
** Corresponding author. Tel.: +420 220 445 055; fax: +420 220 444 288.
E-mail addresses: lang@iic.cas.cz (K. Lang), lhotakp@vscht.cz (P. Lhoták).

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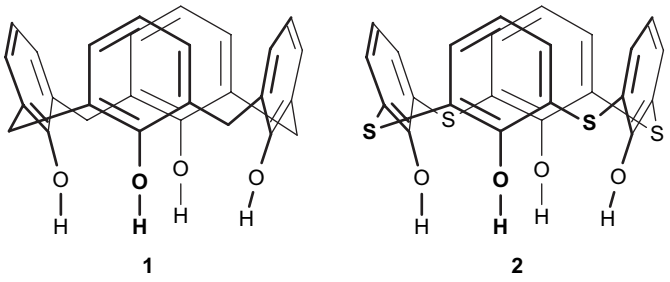


Fig. 1. Calix[4]arene and thiacalix[4]arene.

spectra were measured using the ESI technique on a Q-TOF spectrometer (Micromass) or the MALDI-TOF technique on an HP G2030A spectrometer (Hewlett–Packard) with delayed extraction option. The IR spectra were measured on an FT-IR spectrometer Nicolet 740 in $CHCl_3$ and/or in KBr. The purity of the substances and the courses of reactions were monitored by TLC using TLC aluminum sheets with Silica gel 60 F_{254} (Merck). The preparative TLC chromatography was carried out on 20×20 cm glass plates covered by Silica gel 60 GF_{254} (Merck) or Al_2O_3 type G (Fluka). The column chromatography was performed using Silica gel 60 (Merck).

2.1. Preparation of 4-methylbenzenediazonium tetrafluoroborate

p-Toluidine (8.0 g, 0.08 mol) was dissolved in 55 ml of water and 16 ml of conc. aqueous hydrochloric acid was added under stirring. The solution was cooled to 3 °C and a solution of $NaNO_2$ (5.6 g, 0.08 mol) in 15 ml of water was added dropwise at such a rate to maintain temperature below 5 °C. The reaction mixture was then stirred with active carbon, filtered and treated with a solution of $NaBF_4$ (8.78 g, 0.08 mol) in 55 ml of water. The precipitate was collected by filtration and washed with water and methanol to yield 6.0 g (67%) of the title compound in the form of white micro-crystals with m.p. 109–111 °C (Ref. [12] 110 °C).

2.2. Preparation of 5,11,17,23-tetrakis-[(4-methylphenyl)azo]calix[4]arene **3**

The mixture of calix[4]arene **1** (0.5 g, 1 mmol) and 4-methylbenzenediazonium tetrafluoroborate (0.8 g, 4 mmol) was dissolved in 20 ml of THF, cooled to 0 °C by an ice/NaCl cooling bath, and 2 ml of pyridine was added. The reaction mixture was stirred for 3 h at 0–5 °C. A yellow precipitate was collected by filtration and redissolved in 70 ml of pyridine. The solution was stirred with charcoal for 15 min at room temperature, then filtered and evaporated to dryness. The yellow residue was stirred with 10 ml of conc. HCl and 10 ml of water. The resulting precipitate was filtered off, washed sequentially with water and methanol and dried overnight at 80 °C to yield 0.95 g of the title compound (95%) as orange crystals with m.p. 303–305 °C (decomp.) (Ref. [13] 305 °C). ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 2.34 (s, 12H, CH_3), 7.28 (d, 8H, $J = 8.2$ Hz, H-arom *p*-tolyl), 7.66 (d, 8H, $J = 8.2$ Hz, H-arom *p*-tolyl), 7.72 (s, 8H, H-arom calix). ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm): 20.93, 32.66, 122.68, 123.51, 128.12, 131.57, 139.82, 144.37, 150.39, 159.08. IR (KBr) ν_{max} (cm^{-1}): 3442 (w), 2924 (s), 1631 (m), 1502 (s), 1471 (m).

2.3. Preparation of 5,11,17,23-tetrakis-[(4-methylphenyl)azo]thiacalix[4]arene **4**

The mixture of thiacalix[4]arene **2** (1.5 g, 3 mmol) and 4-methylbenzenediazonium tetrafluoroborate (2.5 g, 12 mmol) was dissolved in 60 ml of THF, and 2 ml of pyridine was added. The reaction mixture was stirred for 4 days at room temperature. A yellow precipitate was filtered off and dissolved in 225 ml of pyridine. The solution was stirred for 1 h with charcoal, filtered and evaporated to dryness. The orange precipitate was dispersed in 30 ml of conc. HCl and 15 ml of water, and the mixture was stirred overnight at room temperature. The remaining precipitate was filtered and washed with water and methanol to yield 2.14 g (78%) of the title compound as orange crystals with m.p. >350 °C. The product was insoluble in most of the common organic solvents and was used in the next step without further purification. ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 2.37 (s, 12H, CH_3), 7.31 (d, 8H, $J = 8.2$ Hz, H-arom *p*-tolyl), 7.66 (d, 8H, $J = 8.2$ Hz, H-arom *p*-tolyl), 8.10 (s, 8H, H-arom calix). ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm): 21.00, 122.28, 122.62, 125.60, 126.76, 129.80, 138.86, 140.70, 150.02. TOF-MS ES^- $m/z = 967.2$ [M − H]. Raman (KBr) ν_{max} (cm^{-1}): 1459 (m), 1444 (m), 1178 (m), 1148 (w).

2.4. Small-scale screening of the alkylation reaction with ethyl bromoacetate

A mixture of **3** or **4** (0.03 mmol), alkali metal carbonate (0.15 mmol) and ethyl bromoacetate (0.12 mmol) was stirred under reflux in 1.5 ml of acetone for 5 days. The reaction mixture was cooled to room temperature, quenched with aqueous HCl (9 ml of water + 1 ml of conc. HCl), and extracted with CH_2Cl_2. The organic layer was washed with water to neutral pH, dried over anhydrous $MgSO_4$, and evaporated to dryness to yield crude products. The overall yields of alkylation and the product distribution were obtained by analyzing ^{1}H NMR spectra in $CDCl_3$ (Table 1).

^{1}H NMR spectrum of ***5c*** ($CDCl_3$, 298 K, 300 MHz) δ (ppm): 0.76, 0.86, 1.29 (3t, 6H, 3H, 3H, $-CH_2CH_3$), 2.36, 2.38, 2.41 (3s, 6H, 3H, 3H, MeC_6H_4-), 3.38 (d, 2H, $J = 13.2$ Hz, Ar–CH_2–Ar), 3.93 (m, 4H, Ar–CH_2–Ar), 3.88, 4.23 (2d, 2H, 2H, $-OCH_2COOEt$), 3.92, 4.25 (q, m, 2H, 6H, $-OCH_2CH_3$), 4.30 (d, 2H, $J = 13.19$ Hz, Ar–CH_2–Ar), 4.81, 5.14 (2s, 2H, 2H, $-OCH_2COOEt$), 6.92, 7.06, 7.21, 7.27, 7.44, 7.74, 7.79, 7.99, 8.03, 8.05 (8d, 2s, 4H, 2H, 2H, 4H, 2H, 2H, 2H, 2H, 2H, H-arom calix and *p*-tolyl).

^{1}H NMR spectrum of ***6c*** ($CDCl_3$, 298 K, 300 MHz) δ (ppm): 0.89 (t, 3H, $J = 7.14$ Hz, $-CH_2CH_3$), 1.16 (t, 3H, $J = 7.14$ Hz, $-CH_2CH_3$), 1.27 (t, 6H, $J = 7.1$ Hz, $-CH_2CH_3$), 2.33 (s, 3H, MeC_6H_4-), 2.44 (s, 3H, MeC_6H_4-),

Table 1
Alkylation of derivatives **3** and **4** with the ethyl bromoacetate/M_2CO_3/acetone system

Compound	M_2CO_3	Overall yield[a] (%)	Conformer distribution in the crude reaction mixture (%)			
			5b/6b	**5c/6c**	**5a/6a**	**5d/6d**
			Cone	*Partial cone*	*1,3-Alternate*	*1,2-Alternate*
3	Na_2CO_3	86	95	5	0	[b]
3	K_2CO_3	79	76	24	0	[b]
3	Cs_2CO_3	88	0	30	70	[b]
4	Na_2CO_3	66	9	64	27	[b]
4	K_2CO_3	60	4	50	29	17
4	Cs_2CO_3	78	4	30	57	9

[a] For reaction conditions see Section 2.
[b] Not observed in the reaction mixture.

2.45 (s, 3 H, *Me*C_6H_4–), 2.47 (s, 3H, *Me*C_6H_4–), 3.84 (q, 2H, $J = 7.14$ Hz, –O*CH*$_2$CH$_3$), 4.21 (m, 6H, –O*CH*$_2$CH$_3$), 4.46 (s, 2H, –O–*CH*$_2$–COOEt), 4.83 (s, 2H, –O–*CH*$_2$–COOEt), 4.96 (s, 2H, –O–*CH*$_2$–COOEt), 4.91 (m, 6H, –O–*CH*$_2$–COOEt), 6.94 (d, 4H, $J = 8.2$ Hz, H-arom), 7.33 (d, 2H, $J = 8.2$ Hz, H-arom), 7.35 (d, 2H, $J = 8.2$ Hz, H-arom), 7.40 (d, 4H, $J = 8.2$ Hz, H-arom), 7.55 (d, 2H, $J = 2.2$ Hz, H-arom), 7.84 (d, 2H, $J = 8.2$ Hz, H-arom), 7.91 (d, 2H, $J = 7.7$ Hz, H-arom), 8.09 (d, 2H, $J = 2.7$ Hz, H-arom), 8.18 (s, 2H, H-arom), 8.49 (s, 2H, H-arom).

^{1}H NMR spectrum of ***6d*** ($CDCl_3$, 298 K, 300 MHz) δ (ppm): 0.88 (t, 12H, $J = 7.03$ Hz, –CH_2CH_3), 2.39 (s, 12H, *Me*C_6H_4–), 3.82 (m, 8H, –*CH*$_2$–CH$_3$), 4.17 (d, 4H, $J = 15.83$ Hz, –O*CH*$_2$–COOEt), 4.83 (d, 4H, $J = 15.83$ Hz, –O*CH*$_2$–COOEt), 7.21 (d, 8H, $J = 8.21$ Hz, H-tolyl), 7.73 (d, 8H, $J = 8.21$ Hz, H-tolyl), 8.07 (d, 4H, $J = 2.35$ Hz, H-arom), 8.17 (d, 4H, $J = 2.35$ Hz, H-arom).

*2.5. Preparation of 5,11,17,23-tetrakis[(4-methylphenyl)azo]-25,26,27,28-tetrakis(ethoxycarbonylmethoxy)calix[4]arene (1,3-alternate) (**5a**)*

To a suspension of calix[4]arene **3** (300 mg, 0.3 mmol) and Cs_2CO_3 (994 mg, 4.5 mmol) in dry acetone (10 ml) was added ethyl bromoacetate (0.47 ml, 4.0 mmol). The reaction mixture was refluxed for 7 days, cooled to room temperature and diluted with water. A crude product was extracted with CH_2Cl_2 and organic extracts were washed with water and dried over $MgSO_4$. Evaporation of the solvent and subsequent precipitation with methanol gave 262 mg of the product as an orange powder (62% yield) with m.p. 216–218 °C (ethyl acetate). ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 0.97 (t, 12H, $J = 6.60$ Hz, –CH_2CH_3), 2.40 (s, 12H, *Me*C_6H_4–), 3.88 (q, 8H, $J = 7.14$ Hz, –O–*CH*$_2$CH$_3$), 3.92 (s, 8H, Ar–*CH*$_2$–Ar), 4.22 (s, 8H, –O*CH*$_2$–COOEt), 7.24 (d, 8H, $J = 8.2$ Hz, H-tolyl), 7.73 (d, 8H, $J = 8.2$ Hz, H-tolyl), 7.76 (s, 8H, H-arom). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 13.61, 21.44, 37.72, 60.80, 68.64, 122.57, 125.22, 129.63, 134.63, 141.07, 148.16, 150.63, 158.23, 168.97. IR (KBr) ν_{max} (cm^{-1}): 1762 (w). EA calcd for $C_{72}H_{72}N_8O_{12}$: C, 69.66; H, 5.85; N, 9.03. Found: C, 69.43; H, 5.61; N, 8.84. UV–vis ($CHCl_3$–$CH_3CN = 4:1$) λ_{max} (nm), ε (M^{-1} cm^{-1}) in parentheses: 348 (8.86×10^4), 436 (3.71×10^3).

*2.6. Preparation of 5,11,17,23-tetrakis[(4-methylphenyl)azo]-25,26,27,28-tetrakis(ethoxycarbonylmethoxy)thiacalix[4]arene (1,3-alternate) (**6a**)*

Ethyl bromoacetate (0.43 ml, 3.9 mmol) was added to a suspension of thiacalix[4]arene **4** (300 mg, 0.3 mmol) and Cs_2CO_3 (994 mg, 4.2 mmol) in 10 ml of dry acetone. The reaction mixture was refluxed for 7 days and allowed to cool to room temperature. After evaporation of the solvent in vacuum, the solid residue was taken up in $CHCl_3$ and washed with water (15 ml). The organic layer was dried over $MgSO_4$ and evaporated to half volume. The addition of methanol yielded the product as an orange powder (44% yield) with m.p. 203–205 °C (ethyl acetate). ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 0.83 (t, 12H, $J = 7.0$ Hz, –CH_2–*CH*$_3$), 2.38 (s, 12H, *CH*$_3$–C_6H_4), 3.82 (q, 8H, $J = 7.0$ Hz, –*CH*$_2$–CH$_3$), 4.73 (s, 8H, –O–*CH*$_2$–COOEt), 7.16 (d, 8H, $J = 8.3$ Hz, arom *p*-tolyl), 7.68 (d, 8H, $J = 8.3$ Hz, arom *p*-tolyl), 7.98 (s, 8H, H-arom calix). ^{13}C NMR ($CDCl_3$, 298 K, 75 MHz) δ (ppm): 13.41, 21.51, 60.94, 67.12, 122.81, 128.80, 129.22, 129.76, 141.85, 147.98, 150.32, 160.46, 167.91. IR (KBr) ν_{max} (cm^{-1}): 1770 (m), 1732 (w). UV–vis ($CHCl_3$–$CH_3CN = 4:1$) λ_{max} (nm), ε (M^{-1} cm^{-1}) in parentheses: 292 (5.11×10^4), 350 (9.67×10^4), 437 (3.82×10^3). TOF-MS ES$^+$ $m/z = 1335.4$ [M – Na]$^+$.

*2.7. Preparation of 5,11,17,23-tetrakis[(4-methylphenyl)azo]-25,26,27,28-tetrakis(ethoxycarbonylmethoxy)calix[4]arene (cone) (**5b**)*

To a suspension of calix[4]arene **3** (300 mg, 0.3 mmol) and Na_2CO_3 (488 mg, 4.5 mmol) in dry acetone (10 ml) was added ethyl bromoacetate (0.47 ml, 4.0 mmol). The reaction mixture was refluxed for 7 days and then allowed to cool to room temperature. After evaporation of the solvent with a rotary evaporator, the mixture was taken up in $CHCl_3$ and washed with water (15 ml). The organic layer was dried over $MgSO_4$ and evaporated to half volume. The addition of methanol yielded the product as an orange powder (87% yield) with m.p. 283–285 °C (ethyl acetate). ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 1.25 (t, 12H, $J = 7.0$ Hz, –CH_2–*CH*$_3$), 2.30 (s, 12H, *CH*$_3$–C_6H_4), 3.42 (d, 4H, $J = 13.8$ Hz, eq. –CH_2–), 4.18 (q, 8H, $J = 7.0$ Hz, –*CH*$_2$–CH$_3$), 4.78 (s, 8H, –O–*CH*$_2$–COOEt), 4.98 (d, 4H, $J = 13.8$ Hz, ax. –CH_2–), 7.01 (d, 8H, $J = 8.2$ Hz, H-arom *p*-tolyl), 7.30 (s, 8H, H-arom calix), 7.49 (d, 8H, $J = 8.2$ Hz, H-arom *p*-tolyl). ^{13}C NMR ($CDCl_3$, 298 K, 75 MHz) δ (ppm): 14.20, 21.42, 31.72, 60.75, 71.49, 122.55, 123.47, 129.40, 134.89, 140.45, 148.73, 150.66, 158.17, 169.74. IR (KBr) ν_{max} (cm^{-1}): 1756 (w). EA calcd for $C_{72}H_{72}N_8O_{12}$: C, 69.66; H, 5.85; N, 9.03. Found: C, 68.86; H, 5.58; N, 8.87. UV–vis ($CHCl_3$–$CH_3CN = 4:1$) λ_{max} (nm), ε (M^{-1} cm^{-1}) in parentheses: 331

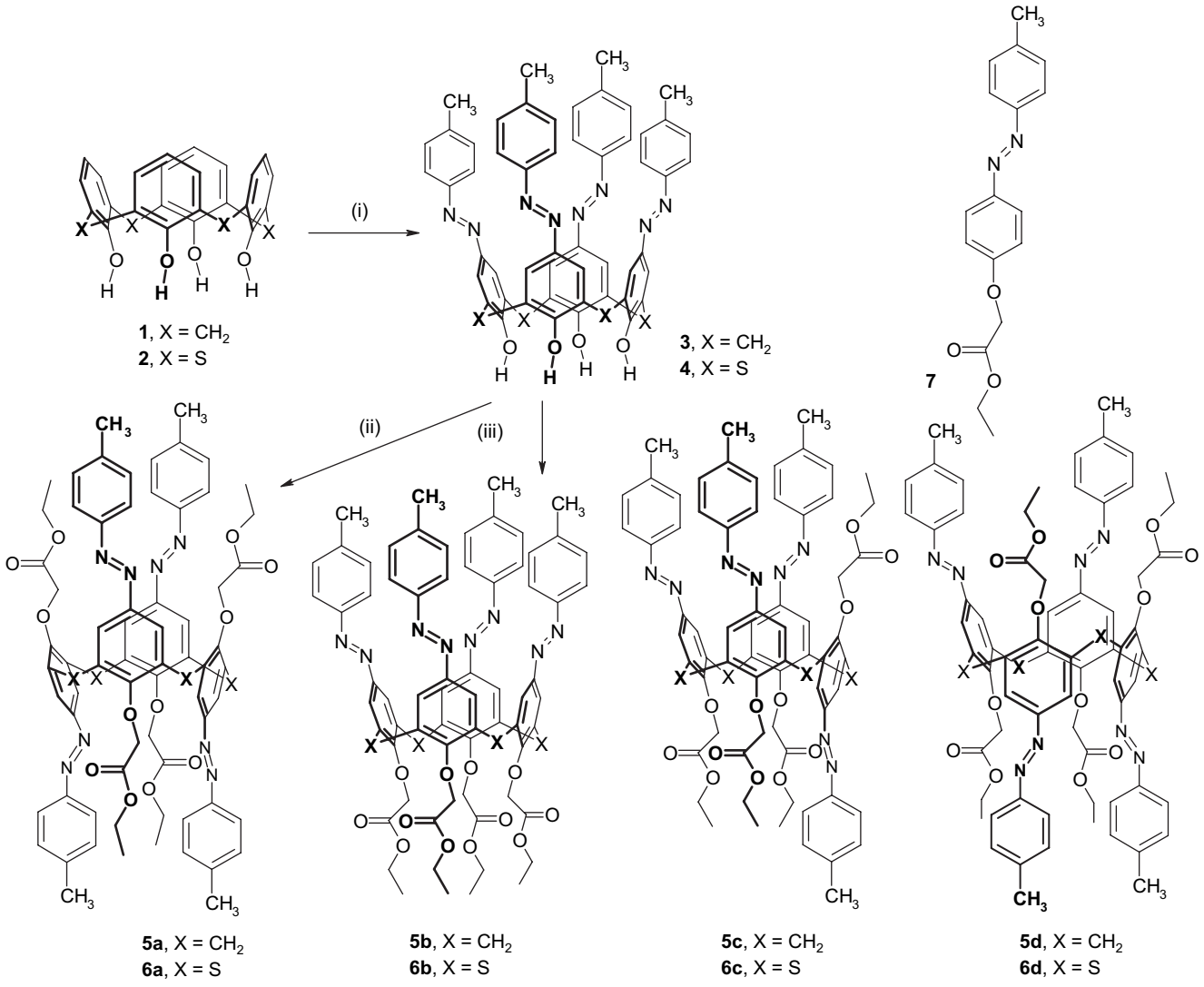
(8.47×10^4), 436 (3.81×10^3). TOF-MS ES$^+$ $m/z = 1263.7$ $[M - Na]^+$.

2.8. Preparation of ethyl 4-[(4-methylphenyl)azo]-phenoxyacetate (7)

To 300 mg (1.41 mmol) of 4-[(4-methylphenyl)azo]phenol [14] in 10 ml of acetone were added 0.5 ml (4.58 mmol) of ethyl bromoacetate and 676 mg (4.9 mmol) of potassium carbonate. The reaction mixture was refluxed overnight and then allowed to cool to room temperature. After evaporation of the solvent with a rotary evaporator, the mixture was taken up in $CHCl_3$ and washed with water (15 ml). The organic layer was dried over $MgSO_4$ and evaporated. The addition of ethyl acetate gave the solid product (91% yield) in the form of an orange powder with m.p. 76–77 °C (ethyl acetate). ^{1}H NMR ($CDCl_3$, 298 K, 300 MHz) δ (ppm): 1.30 (t, 3H, $J = 7.0$ Hz, $-CH_2CH_3$), 2.42 (s, 3H, $CH_3-C_6H_4$), 4.30 (q, 2H, $J = 7.0$ Hz, $-CH_2CH_3$), 4.70 (s, 2H, $-O-CH_2-COOEt$), 7.02 (d, 2H, $J = 9.1$ Hz), 7.30 (d, 2H, $J = 8.2$ Hz), 7.78 (d, 2H, $J = 8.2$ Hz), 7.91 (d, 2H, $J = 8.8$ Hz). ^{13}C NMR ($CDCl_3$, 298 K, 75 MHz) δ (ppm): 14.14, 21.45, 61.52, 65.46, 114.84, 122.59, 124.52, 129.67, 141.02, 147.64, 150.73, 159.81, 168.48. IR (KBr): 2977 (s), 2916 (s), 1763 (w), 1500 (m), 1387 (s), 1205 (w), 1111 (m). UV–vis ($CHCl_3$–$CH_3CN = 4{:}1$) λ_{max} (nm), ε ($M^{-1}\,cm^{-1}$) in parentheses: 346 (2.66×10^4), 433 (1.15×10^3). TOF-MS ES$^+$ $m/z = 299.2$ $[M - H]^+$.

2.9. Crystallographic data for derivative 6a

$C_{70}H_{66}Cl_6N_8O_{12}S_4$, $M = 1552.25$ g mol^{-1}, triclinic system, space group P-1, $a = 12.182(2)$ Å, $b = 16.968(3)$ Å, $c = 18.573(4)$ Å, $\alpha = 75.10(3)°$, $\beta = 87.65(3)°$, $\gamma = 89.63(3)°$, $Z = 2$, $V = 3706.9(13)$ Å^3, Dc = 1.391 g cm^{-3}, μ (Mo Kα) = 0.409 mm^{-1}, crystal dimensions of $0.32 \times 0.37 \times 0.40$ mm. Data were collected at 150(2) K on a Nonius KappaCCD diffractometer with graphite monochromated Mo Kα



Scheme 1. (i) p-$CH_3C_6H_4N_2^+BF_4^-$/THF/pyridine, r.t., **3** (95%), **4** (78%); (ii) $BrCH_2COOEt/Cs_2CO_3$/acetone, reflux, **5a** (62%), **6a** (44%); (iii) $BrCH_2COOEt/K_2CO_3$/acetone, reflux, **5b** (82%).

radiation. The structure was solved by direct methods [15] using the SHELX suite of programs [16] and anisotropically refined by full-matrix least-squares on F^2 values to final $R = 0.0824$ and $R_w = 0.2267$ using 12 046 independent reflections ($\theta_{max} = 55.02°$) and 1081 parameters. The positions of disordered groups were found from the electron density maps. Disordered fragments were then placed in appropriate positions and all distances between the neighbouring atoms and angles were fixed. Site occupancies were refined for the different parts with the same thermal parameters for the same atoms in the various fragments. At the end of refinement, site occupancies were fixed and hydrogen atoms were placed in calculated positions.

2.10. Binding experiments

All UV–vis experiments were performed in a mixture $CHCl_3$–CH_3CN (4:1) at 293 K by adding aliquots of a stock solution of respective cations. Cations Li^+ and Na^+ were used as perchlorates, K^+ and Cs^+ in the form of $CF_3SO_3^-$ and $SB_9H_{12}^-$ salts, respectively. The recorded sets of the absorption spectra were globally analyzed using the Specfit program (v. 3.0, Spectrum Software Associates) to get the corresponding binding constants. The stoichiometry of the complexes was determined by the Job method of continuous variations. The experiments were performed in the dark in order to eliminate *trans*-to-*cis* photoisomerization of the azobenzene units.

3. Results and discussion

Our design of receptors is based on the well-recognized complexation ability of calix[4]arene tetraacetates. If immobilized in the *cone* conformation, these compounds exhibit high complexation affinity [7] towards alkali metal cations. To visualize the complexation phenomenon we appended chromophore groups on the opposite upper rim [8]. This functionalization allows the monitoring of complexation using UV–vis spectroscopy.

The synthesis of the receptors was started by a diazocoupling reaction between pristine calix[4]arenes [9] **1** or thiacalix[4]arene [10] **2** and *p*-methylbenzenediazonium tetrafluoroborate. The reaction proceeded smoothly in a THF solution under pyridine catalysis and yielded the corresponding tetraazo compounds **3** and **4** in high yields (Scheme 1). Subsequent alkylation with ethyl bromoacetate can theoretically lead to four different conformations: *cone*, *partial cone*, *1,3-alternate* and *1,2-alternate*. It is known that metal cation used as a base dramatically influences the conformational outcome of the reaction [11]. Hence, the template effect of alkali metal carbonates (Na_2CO_3, K_2CO_3, Cs_2CO_3) was screened using small scale alkylation of **3** and **4** with an excess of ethyl bromoacetate (acetone, **5d** reflux) followed by the subsequent ^1H NMR analysis of crude reaction mixtures. As follows from Table 1, three conformers **5a–c** of the tetraalkylated product (with exception of *1,2-alternate* **5d**) could be detected in the classical calix[4]arene series. On the other hand, all four conformations of thiacalix[4]arenes **6a–d** were identified in the reaction mixtures. As expected, the template effect enabled the stereoselective synthesis of the calix[4]arene and thiacalix[4]arene conformations. Thus, alkylation of compound **3** using Na_2CO_3 as a base led almost exclusively to the corresponding *cone* conformer **5b** (82% isolated yield), while the same reaction in the presence of Cs_2CO_3 gave predominantly *1,3-alternate* **5a** (62% yield). The template effect of Cs_2CO_3 is similar in the thiacalix[4]arene series. As both the *cone* and the *1,3-alternate* conformations represent well-preorganised cavities for cation recognition (monotopic versus ditopic receptors), only these two conformations were selected for the complexation study. Unfortunately, despite several attempts we were unable to isolate thiacalix[4]arene **6b** in a sufficiently pure form.

The structure of thiacalix[4]arene **6a** was unequivocally proven by X-ray crystallography. The single crystals were grown by slow evaporation of a solvent mixture $CHCl_3$–ethyl acetate. Compound **6a** in the *1,3-alternate* conformation was crystallised with two chloroform molecules in the triclinic form, space group *P*-1. As expected, the azo bonds –N=N– adopt the *trans*-configuration with almost coplanar tolyl substituents (Fig. 2a). The chloroform molecules are located outside the thiacalix[4]arene cavities (Fig. 2b).

The azobenzene chromophore in the calix[4]arene series exhibited the $S_2(\pi,\pi^*)$ band at 331–350 nm and the low lying $S_1(n,\pi^*)$ band at 436–437 nm. The absorption maxima λ_{max} of cone **5b** are shifted by 15 nm (331 nm) to a shorter wavelength and by 3 nm (436 nm) to a longer wavelength when compared to those of **7** (346, 433 nm). On the other hand, λ_{max} of **5a** (348, 436 nm) and **6a** (350, 437 nm) are very close to those of the model compound **7**. The sulfur bridges in **6a** have no effect on the position of the absorption bands. Clearly, the spectral features depend on the overall orientation of the azobenzene units as their intermolecular interactions are much stronger in the cone conformation than in the pinched *1,3-alternates* with only two units oriented to the same half plane. As was expected, the molar absorption coefficients of the absorption bands increased approximately 3.5 times when compared to those of **7** since the number of the azobenzene units increases four times in the calixarene derivatives.

Complexation of Li^+, Na^+, K^+ and Cs^+ was studied by UV–vis titration experiments. The addition of cations into a solution of **5b** resulted in a shift of about 4 nm and in a small hyperchromicity of the $S_2(\pi,\pi^*)$ band (Fig. 3). The appearance of a clear isosbestic point is typical for the presence of two forms in a solution – the free receptor and receptor–cation complex. These findings together with the Job plots that had the maxima at the mole fraction of 0.5 (Fig. 4) confirmed the formation of 1:1 receptor–cation complexes. Complexation of Na^+ is exceptional since the binding isotherms exhibited a sharp saturation beyond the molar ratio of Na^+/**5b** = 1. It indicates the high affinity and selectivity of **5b** for Na^+ that is expressed by the large binding constant of $(1.0 \pm 0.2) \times 10^6\ M^{-1}$ (Table 2). The spectral changes of alternate **5a** upon the addition of cations were much smaller than those for **5b**. Similar to **5b**, the Job plots confirmed the

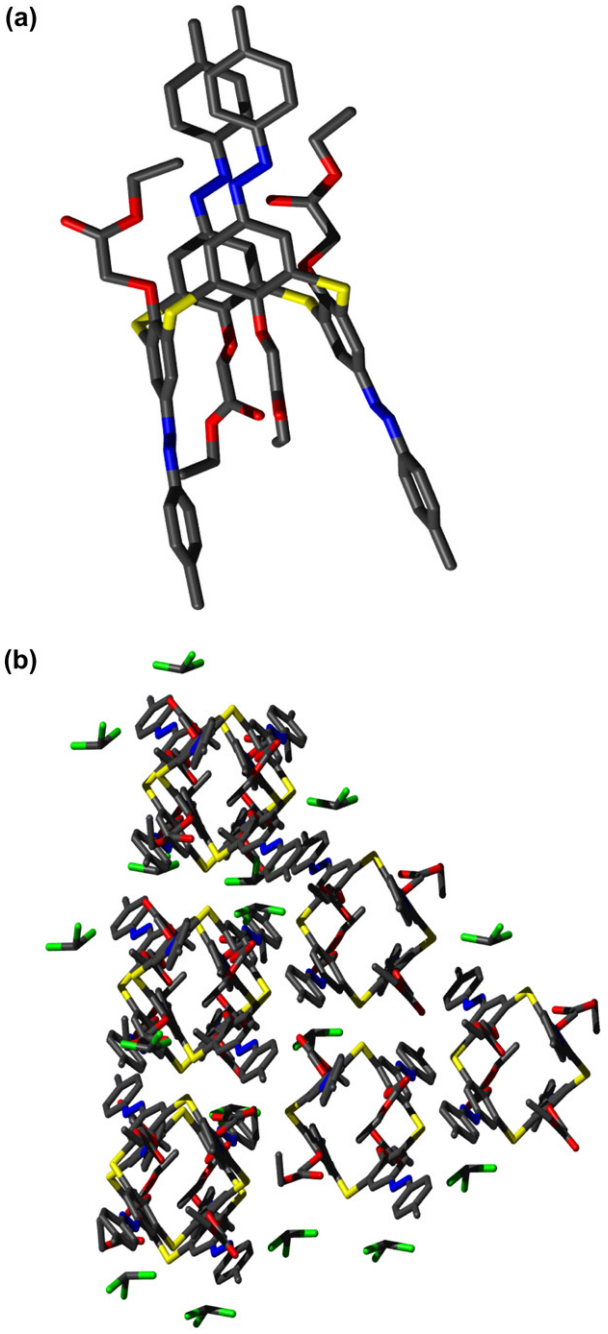


Fig. 2. (a) X-ray structure of **6a**; (b) crystal packing of **6a**·2$CHCl_3$ (hydrogen atoms were removed for better clarity).

stoichiometry of 1:1 for **5a**-cation complexes with exception of Li^+. In this case no spectral evidence of complexation was found. The spectra of thiacalix[4]arene **6a** did not indicate any cation complexation. All calculated binding constants are listed in Table 2. Quite interesting is the comparison of our results with literature data for the corresponding calix[4]arene tetraacetates having *tert*-butyl groups instead of arylazo moieties on the upper rim [17]. Thus, analogue of **5b** – tetrakis(ethoxycarbonyl-methoxy)calix[4]arene (*cone*) – shows the same trend in the complexation constants ($Na^+ > K^+ > Cs^+$) with only weak selectivity towards Na^+ (log $K = 3.95$) versus

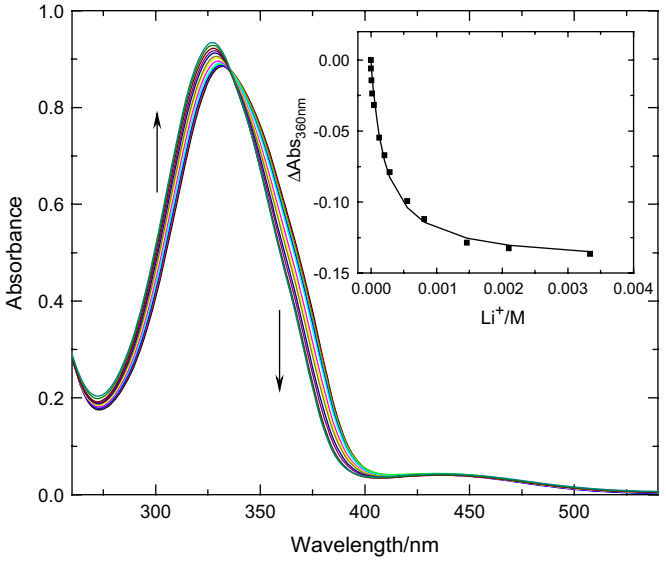


Fig. 3. Absorption spectra of **5b** (1.1×10^{-5} M) induced by Li^+ in $CHCl_3$–CH_3CN = 4:1. The arrows show changes due to increasing concentration of Li^+. Concentration of Li^+ varies from 0 to 3.3×10^{-3} M. Inset: Binding isotherm at 360 nm, the solid line represents the least-squares fit to the experimental data.

K^+ cations (log $K = 3.08$) as measured by UV–vis titrations in THF. On the other hand, the corresponding *1,3-alternate* analogue of **5a** exhibits the different selectivity trend ($K^+ > Cs^+ > Na^+$) with much higher association constants (log $K = 4.98$, 4.41 and 4.10, respectively). Interestingly, the complexation ability in thiacalixarene series was entirely lost after the introduction of arylazo moiety (compared to parent *1,3-alternate* thiacalix[4]arene tetraacetate) [11c].

In conclusion, the diazo-coupling reaction followed by alkylation with ethyl bromoacetate yields new arylazo substituted calix[4]arene and thiacalix[4]arene derivatives. These compounds possess well-preorganised acetate cavity on the lower rim, while the upper rim is occupied by the

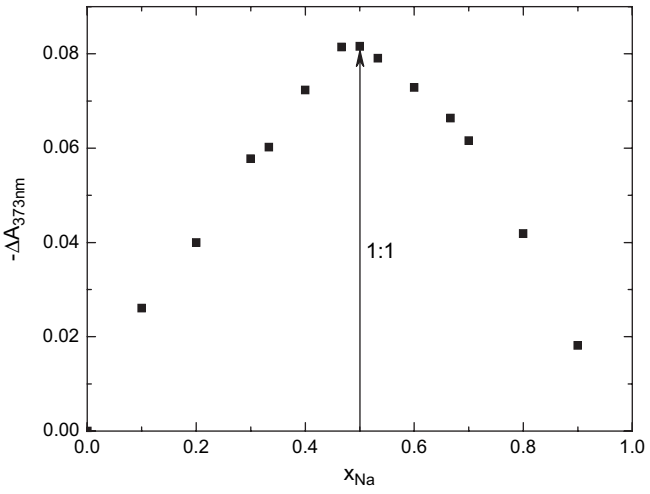


Fig. 4. The Job plot documenting the stoichiometry of 1:1 for complexation of Na^+ by **5b** in $CHCl_3$–CH_3CN = 4:1. The plot was constructed from absorbance changes at 373 nm using the sum of concentrations 1.1×10^{-5} M.

Table 2
Binding constants (M^{-1}) based on UV–vis titration experiments in $CHCl_3$–CH_3CN (4:1) at 293 K

	Li^+	Na^+	K^+	Cs^+
5b	4700 ± 400	$(1.0 \pm 0.2) \times 10^6$	6800[a]	200 ± 30
5a	[b]	3500 ± 300	8600 ± 500	1200 ± 100
6a	[b]	[b]	[b]	[b]

[a] Estimated error 30% due to the limited solubility of the K^+ salt in a solvent mixture.
[b] No spectral evidence of binding.

chromophore groups. As demonstrated by UV–vis measurements, the receptor **5b** shows pronounced selectivity towards sodium cations.

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