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Chemo- and stereocontrolled alkylation of 1,2-disubstituted at the lower rim 1,2-*alternate p-tert*-butylthiacalix[4]arene

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1,2-*Alternate p-tert*-butylthiacalix[4]arene bearing at the lower rim 1,2-positioned acetamide fragments reacts with ethyl bromoacetate to give mono-O-alkylation product when Na_2CO_3 is used as a base and O,O′,N,N′-tetraalkylation one in the case of K_2CO_3.

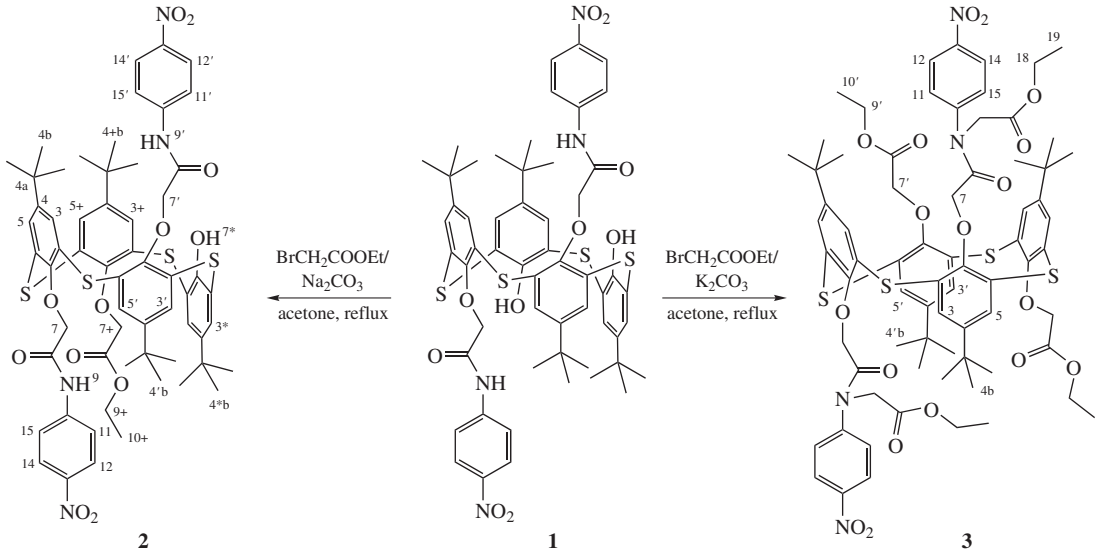
The common approach to design of synthetic receptors is modification of macrocyclic molecular platform by variation of substituents which provides optimal spatial orientation of binding sites.[1] To choose such substituents, one should consider a number of requirements: availability of starting macrocycle, sufficient conformation rigidity of the molecular platform providing optimal spatial orientation of binding sites, existence of highly effective common procedures for functionalization of the molecular platform.[2,3] Products of cyclocondensation of phenols and sulfur, namely thiacalix[4]arenes, are in a good agreement with these requirements.[4,5]

Carboxamide fragment, which contains two different binding sites – proton-donor NH group and lone electron pair of carbonyl group is very promising for this purpose. Depending on the substitution pattern of amide group, such thiacalixarenes either can serve as hosts for anion binding (in the case of secondary amide group),[6] or as extragents of metal cations (in the case of tertiary amide group).[7–9] Thus, interest to N-alkylation of secondary amide fragments attached to thiacalix[4]arene platform is obvious.

In the literature, there are only several examples of partially substituted at the lower rim thiacalix[4]arenes in 1,2-*alternate* conformation.[4] Therefore, studying of reactivity of 1,2-disubstituted 1,2-*alternate p-tert*-butylthiacalix[4]arene **1** bearing *N*-(4-nitrophenyl)acetamide fragments[10] seemed topical. Macrocycles modified by ester fragments are known to recognize alkali metal cations due to their coordination with carbonyl and alkoxyl oxygen atoms.[11] Ethyl bromoacetate is a favourable reactant for the introduction of ester group into the macrocyclic platform.[12–14]

In this work, macrocycle **1** was modified by its treatment with ethyl bromoacetate in acetone using sodium and potassium carbonates as the bases, in analogy with the published data.[15] In the case of sodium carbonate, monosubstitution product **2** is formed in 87% yield, with the 1,2-*alternate* conformation of the macrocycle being retained, whereas the use of potassium carbonate leads to formation of O,O′,N,N′-tetrasubstitution product **3** accompanied by a conformation change of thiacalix[4]arene platform into 1,3-*alternate* stereoisomer (Scheme 1).

The structures of new thiacalix[4]arene derivatives **2** and **3** were established based on ^1H, ^{13}C NMR and IR spectroscopy, mass spectrometry (EI, ESI) and elemental analysis. The 2D NOESY ^1H–^1H NMR spectrum of compound **2** displays cross-peaks between spatially close protons, namely, between *tert*-butyl and aryl protons (H^{4*b}/H^{11}, H^{15}/H^{4*b}, $H^{11}/H^{4'b}$, $H^{15}/H^{4'b}$, $H^{11'}/H^{4b}$, $H^{15'}/H^{4b}$), between oxymethylene protons and aromatic protons of the macrocycle ($H^{7a}/H^{5'}$, $H^{7'a}/H^{3}$, H^{7+a}/H^{5*}), and between hydroxyl proton and nitrophenylamide protons ($H^{7*}/H^{9'}$, $H^{7*}/H^{11'}$, $H^{7*}/H^{15'}$), which clearly testifies that macrocycle **2** has 1,2-*alternate* conformation.



2 **1** **3**

Scheme 1

The NOESY ^{1}H–^{1}H spectrum of compound **3** contains cross-peaks between *tert*-butyl protons and aryl protons ($H^{11}/H^{4'b}$, $H^{15}/H^{4'b}$), between *tert*-butyl protons and oxymethylene protons ($H^{7'}/H^{4b}$), which confirm that macrocycle **3** has 1,3-*alternate* conformation.

Selective formation of 1,2-*alternate* mono-O-alkylation product in the presence of Na_2CO_3 can be due to retaining of intramolecular hydrogen bonds between hydroxyl and amide groups[10] in the starting compound **1** having also 1,2-*alternate* conformation. The formation of O,O′,N,N′-tetrasubstituted 1,3-*alternate* stereoisomer upon treatment with K_2CO_3 can be explained either by strong binding or total absence of the interaction between 1,3-*alternate* compound **3** and K^+ ion. Tetrasubstituted at the lower rim thiacalix[4]arenes with amide or ester groups in 1,3-*alternate* positions usually show binding ability toward K^+ and Cs^+ ions.[4,15] Generally, template effect of cesium cation is used in syntheses of thiacalix[4]arene 1,3-*alternate* stereoisomers, while template effect of potassium cation is used to prepare tetrasubstituted product in *partial cone* configuration.[4,15] However, formation of tetra-O-alkylated *p-tert*-butylthiacalix[4]arenes in 1,3-*alternate* configuration regardless of the bases used is common for alkylating reagents which do not contain coordination sites capable of binding metal ions.[4]

Nevertheless, we proposed here that formation of compound **3** in 1,3-*alternate* configuration is caused by template effect of alkali metal cation. For verification of this hypothesis, complexation ability of synthesized macrocycles **2** and **3** towards some monocharged metal cations (Li^+, Na^+, K^+, Cs^+) was studied. Thiacalix[4]arenes **2** and **3**, containing electron-donating binding sites of different nature (carbonyl groups of amide fragments and ester groups), according to literature data,[4,5] can be capable of complexation with metal cations. To estimate the ability of synthesized compounds to recognize alkali metal cations, picrate extraction was investigated in mutually saturated water–dichloromethane system.‡ To compare extraction ability of macrocycles **2**, **3**, and thiacalix[4]arene **4** depriving of amide moieties,[15] the percent extraction (*E*%) of alkali metal cations were measured (Figure 1).

As predicted, introduction of additional electron-donating binding sites, such as ester group (compound **3**), leads to binding of K^+ and Cs^+ cations. However, thiacalix[4]arene **2** does not extract studied alkaline metal picrates which is obviously caused by formation of intramolecular hydrogen bonds between amide and ester groups.

It is interesting to compare properties of tetraester **4** in 1,3-*alternate* configuration with those of tetrasubstituted *p-tert*-butyl thiacalix[4]arene **3** in 1,3-*alternate* configuration. Although the structures of substituents at the lower rim of the macrocycle of these compounds considerably differ, their ability to bind alkali

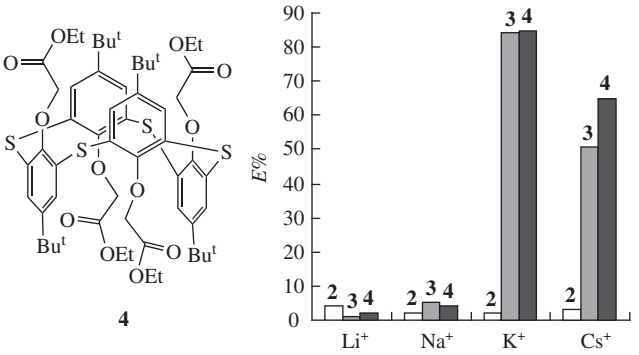


Figure 1 The percent extraction (*E*%) of alkali metal cations by thiacalix[4]arenes **2**–**4**. Extraction conditions: [L] = 2.5×10^{-3} mol dm^{-3}, [MPic] = = 2.32×10^{-4} mol dm^{-3}.

† *Synthesis of compounds* **2** *and* **3** (*general procedure*). 5,11,17,23-Tetra-*tert*-butyl-25,26-dihydroxy-27,28-bis[*N*-(4-nitrophenyl)aminocarbonylmethoxy]thiacalix[4]arene **1** (1 g, 1.39 mmol) was suspended in 30 ml of dry acetone containing anhydrous alkali metal carbonate (0.29 g, 2.78 mmol Na_2CO_3 or 0.38 g, 2.78 mmol K_2CO_3). Then ethyl bromoacetate (0.4 ml, 3.72 mmol) and 40 ml of dry acetone were added. The mixture was refluxed for 50 h (TLC monitoring). After cooling, the solid was removed by filtration, the filtrate was evaporated to dryness under reduced pressure. Ethanol (30 ml) was added and the solid was filtered off. Crystallization of the resulting solid from dichloromethane–ethanol gave pure samples of **2** and **3**.

5,11,17,23-Tetra-tert-*butyl-25-hydroxy-26-(ethoxycarbonylmethoxy)-27,28-bis[*N-*(4′-nitrophenyl)aminocarbonylmethoxy]thiacalix[4]arene* **2**. White powder, yield 0.93 g (87%), mp 236 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.67 s (9H, Me_3C), 0.72 (s, 9H, Me_3C), 0.92 (t, 3H, OCH_2*Me*, $^3J_{HH}$ 7.2 Hz), 1.29 (s, 9H, Me_3C), 1.49 (s, 9H, Me_3C), 3.53 (m, 2H, O*C*H_2Me, $^3J_{HH}$ 7.2 Hz), 4.07 (d, 1H, O*C*H_2CONH, $^2J_{HH}$ 15.0 Hz), 4.22 (d, 1H, O*C*H_2CONH, $^2J_{HH}$ 15.0 Hz); 4.73 (q, AB system, 2H, OCH_2COO, $^2J_{HH}$ 14.7 Hz), 4.98 (d, 1H, O*C*H_2CONH, $^2J_{HH}$ 15.0 Hz), 5.31 (d, 1H, OCH_2CONH, $^2J_{HH}$ 15.0 Hz), 6.26 (AB part of AA′BB′ system, 2H, $H_{Ar'}$, $^3J_{AB}$ + $^5J_{AB'}$ 9.1 Hz), 6.30 s (1H, NH), 7.22 (d, 1H, H_{Ar}, $^4J_{HH}$ 2.6 Hz), 7.24 (d, 1H, H_{Ar}, $^4J_{HH}$ 2.6 Hz), 7.35 (d, 1H, H_{Ar}, $^4J_{HH}$ 2.6 Hz), 7.37 (d, 1H, H_{Ar}, $^4J_{HH}$ 2.6 Hz), 7.39 (d, 1H, H_{Ar}, $^4J_{HH}$ 2.6 Hz), 7.63 (d, 1H, H_{Ar}, $^4J_{HH}$ 2.6 Hz), 7.71 (A′B′ part of AA′BB′ system, 2H, $H_{Ar'}$, $^3J_{AB}$ + $^5J_{AB'}$ 9.1 Hz), 7.75 (AB part of AA′BB′ system, 2H, $H_{Ar''}$, $^3J_{AB}$ + $^5J_{AB'}$ 9.1 Hz), 7.83 (d, 1H, H_{Ar}, $^4J_{HH}$ 2.6 Hz), 7.89 (d, 1H, H_{Ar}, $^4J_{HH}$ 2.6 Hz), 8.11 (A′B′ part of AA′BB′ system, 2H, $H_{Ar''}$, $^3J_{AB}$ + $^5J_{AB'}$ 9.1 Hz), 9.17 (s, 1H, OH), 10.52 (s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.85, 14.10, 30.29, 30.55, 30.62, 31.05, 31.45, 34.05, 34.25, 34.61, 60.82, 61.57, 64.63, 66.59, 68.21, 69.15, 71.21, 118.40, 119.22, 120.03, 120.20, 124.21, 124.50, 125.10, 126.52, 126.71, 127.47, 127.89, 128.03, 128.10, 128.40, 128.51, 129.10, 129.30, 129.52, 130.01, 131.17, 133.79, 134.91, 135.70, 142.23, 142.91, 143.15, 143.61, 144.20, 144.59, 147.83, 148.75, 149.11, 149.83, 150.30, 152.72, 153.61, 154.65, 156.50, 157.32, 157.51, 165.78, 166.21, 166.41, 167.82, 168.01. ^{1}H–^{1}H NOESY spectrum: H^{4b}/H^3, $H^{4'b}/H^{3'}$, H^{4+b}/H^{3+}, H^{4b}/H^5, H^{4+b}/H^{5+}, $H^{4'b}/H^{5'}$, H^{3*}/H^{4*b}, H^{4*b}/H^{5*}, $H^{11}/H^{4'b}$, $H^{15}/H^{4'b}$, H^{4*b}/H^{11}, H^{15}/H^{4*b}, $H^{11'}/H^{4b}$, $H^{15'}/H^{4b}$, $H^{11'}/H^{12'}$, $H^{14'}/H^{15'}$, H^{11}/H^{12}, H^{14}/H^{15}, H^{7+a}/H^{5*}, $H^{7a}/H^{5'}$, $H^{7'a}/H^3$, H^{5+}/H^5, H^{3+}/H^{5*}, $H^{3*}/H^{3'}$, $H^{11'}/H^{9'}$, $H^{15'}/H^{9'}$, $H^{7*}/H^{9'}$, $H^{7*}/H^{11'}$, $H^{7*}/H^{15'}$, H^{9+}/H^{10+}. IR (Nujol, ν/cm^{-1}): 3378 (NH), 3321 (OH), 1734 [C(O)OEt], 1715, 1613, 1600 [C(O)NH], 1541, 1508, 1378, 1328 (NO_2), 1111, 1088 (Ar–H). MS (EI), *m*/*z*: 1162.3 (calc. for [M$^+$], *m*/*z*: 1162.4). Found (%): C, 60.95; H, 5.48; N, 4.76. Calc. for $C_{60}H_{66}N_4O_{12}S_4$ (%): C, 61.94; H, 5.72; N, 4.82.

5,11,17,23-Tetra-tert-*butyl-25,26-bis(ethoxycarbonylmethoxy)-27,28-bis[*N-*(ethoxycarbonylmethyl)-*N*-*(4-nitrophenyl)aminocarbonylmethoxy]-thiacalix[4]arene* **3**. White powder, yield 0.49 g (38%), mp 227 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.18 (s, 18H, Me_3C), 1.20 (s, 18H, Me_3C), 1.26 (t, 12H, OCH_2*Me*, $^3J_{HH}$ 7.2 Hz), 4.18 (m, 8H, O*C*H_2Me, $^3J_{HH}$ 7.2 Hz), 4.41 (AB quadruplet, 4H, OCH_2CON, $^2J_{HH}$ 17.7 Hz), 4.55 (s, 4H, OCH_2COOEt), 4.60 (AB quadruplet, 4H, OCH_2COO, $^2J_{HH}$ 13.4 Hz), 7.33 (AB part of AA′BB′ system, 4H, $H_{Ar'}$, $^3J_{AB}$ + $^5J_{AB'}$ 8.8 Hz), 7.38 (s, 4H, H_{Ar}), 7.39 (d, 2H, H_{Ar}, $^4J_{HH}$ 2.6 Hz), 7.42 (d, 2H, H_{Ar}, $^4J_{HH}$ 2.6 Hz), 8.13 (A′B′ part of AA′BB′ system, 4H, $H_{Ar'}$, $^3J_{AB}$ + $^5J_{AB'}$ 8.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.18, 14.29, 31.03, 31.09, 34.15, 34.19, 51.11, 60.55, 61.59, 67.58, 68.02, 125.05, 127.20, 127.30, 127.40, 127.61, 128.71, 133.35, 133.55, 133.69, 146.29, 146.37, 146.59, 147.41, 156.91, 157.14, 157.25, 167.06, 167.71, 168.69. ^{1}H–^{1}H NOESY spectrum: $H^{11}/H^{4'b}$, $H^{15}/H^{4'b}$, $H^{7'}/H^{4b}$, H^{4b}/H^3, H^{4b}/H^5, $H^{4'b}/H^{3'}$, $H^{4'b}/H^{5'}$, $H^{9'}/H^{10'}$, H^{18}/H^{19}. IR (Nujol, ν/cm^{-1}): 1735 [C(O)OEt], 1649 [C(O)N], 1509, 1377, 1344 (NO_2), 1112, 1074 (Ar–H). MS (ESI), *m*/*z*: 1438.7 (calc. for [M + NH_4^+], 1438.5). Found (%): C, 61.40; H, 4.98; N, 3.95. Calc. for $C_{72}H_{84}N_4O_{18}S_4$ (%): C, 60.83; H, 5.96; N, 3.94.

‡ *General method for picrate extraction.* Solutions of metal picrates were prepared from aqueous picric acid solution and aqueous solution of metal hydroxide (LiOH, NaOH, KOH, CsOH) by pH-metric titration method; final concentration of alkali metals was 0.1 mol dm^{-3}. Aqueous picrate solution (3 ml, 2.32×10^{-4} mol dm^{-3}) and dichloromethane solution of ligand (L) **2**–**4** (3 ml, 2.5×10^{-3} mol dm^{-3}) were stirred together for 0.5 h and then kept for 1 h for phase separation at 25 °C. Absorbance of the aqueous phase prior to (A_0) and after extraction (A_i) was measured at 355 nm. The percentage of cation extracted (%*E*) was calculated as ratio $100(A_0 - A_i)/A_0$. The values presented in Figure 1 resulted from three parallel runs, estimated standard deviation was less than ±3%.

metal cations does not change, except for Cs^+ cation (Figure 1). The replacement of two ester groups on the different sides of the macrocycle in thiacalix[4]arene **4** with two bulky tertiary amide groups lowers its binding ability towards cesium cation, and leads to increase in selectivity of potassium ion extraction by the macrocycle **3**. The obtained results indirectly confirm that formation of the product **3** in 1,3-*alternate* configuration is caused by template effect of potassium cation.

Thus, a new example of template effect of a cation on chemo- and stereoselectivity of alkylation of thiacalix[4]arene derivatives was discovered manifesting the change from 1,2-*alternate* conformation to 1,3-*alternate*.

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