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Regioselective alkylation of the lower rim of *p-tert*-butylthiacalix[4]arene with *N*-(*p*-nitrophenyl)-α-bromoacetamide

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The preparation of partially substituted thiacalix[4]arenes **2**–**6** has been accomplished by conducting the reaction of the thiacalixarene **1** with *N*-(*p*-nitrophenyl)-α-bromoacetamide in acetone or acetonitrile in the presence of M_2CO_3 (M = Na, K and Cs). The influence of the reaction conditions (temperature, time, solvent, ratio of the reagents and the nature of the alkali metal carbonate) on regio- and stereoselectivity of this reaction is described.

Keywords: thiacalix[4]arene; regioselective alkylation; synthesis; conformations; secondary amides

Introduction

Calix[*n*]arenes are macrocyclic compounds that are remarkably easy to obtain and functionalise on the lower and upper rims, and in the bridge positions (*1*, *2*). Calix[*n*]arenes are key building blocks in the design of new types of three-dimensional architectures such as molecular tubes, in the preparation of selective receptors and new types of drug delivery agents (*3*–*5*). Replacing the methylene bridges between the aromatic units in calix[4]-arenes with sulphur atoms leads to thiacalix[4]arenes (*3*–*5*). The presence of four sulphur atoms results in many new features when compared to 'classical' calixarenes, including different coordination behaviours, facile oxidation of bridge sulphur atoms and different sizes and different conformational behaviours. Thiacalix[4]arenes exhibit a broad range of interesting functions, which make these compounds fundamentally interesting and promising for a variety of applications. For example, derivatives of the *p-tert*-butylthiacalix[4]arene **1** (Chart 1) are selective and efficient extractants for metal cations, as well as artificial receptors for both anions and neutral molecules (*4*–*6*).

To create thiacalix[4]arene-based complexation agents selective for different types of guests, effective synthetic methods for the preparation of partially and completely substituted derivatives of thiacalix[4]arenes with controlled conformation are required (*7*). Recently, it has been shown that thiacalixarenes containing electronegative groups such as ethoxycarbonyl are capable of coordination with metal cations, which allows stereoselective alkylation due to the templating effect. Miyano and co-workers (*8*) have developed the templating approach for the lower rim alkylation of thiacalixarenes by ethyl bromoacetate. It was based on using alkali carbonates M_2CO_3 (M = Na, K and Cs) as bases in acetone or dimethylformamide. Reaction of thiacalixarenes with ethyl bromoacetate in the presence of Na_2CO_3, K_2CO_3 and Cs_2CO_3 gave the cone, partial cone and 1,3-alternate of tetra-*O*-alkylation product 5,11,17,23-tetra-*tert*-butyl-25,26,27,28-tetrakis[(ethoxy-carbonyl)methoxy]-2,8,14,20-tetrathiacalix[4]arene, with yields ranging from 58 to 78% (after column chromatography). Later, Hosseini and co-workers (*9*) and Stibor and co-workers (*10*) investigated this reaction and the structure of the products in more detail.

Recently, we reported the preparation of disubstituted thiacalix[4]arene **2** in the *cone* conformation as a precursor for the synthesis of organic nanotubes (*11*). Compound **2** was obtained in 77% yield by the regioselective alkylation of the *p-tert*-butylthiacalix[4]arene with *N*-(*p*-nitro-phenyl)-α-bromoacetamide (NPNBA) in acetonitrile in the presence of caesium hydroxide as a base. The reaction stopped at the stage of the 1,3-disubstituted thiacalix[4] arene as a result of its low solubility in acetonitrile. Thus, we decided to further investigate the alkylation of *p-tert*-butylthiacalix[4]arene **1** with NPNBA with the expectation that the resulting alkylation products could provide convenient precursors for other functionalised thiacalix-arenes. For example, the hydrolysis of the amide fragment could lead to the corresponding carboxylic acid, and the reduction of nitro group could result in an aromatic amine (*6*). Furthermore, the accumulation of amide protons on the lower rim of thiacalix[4]arene could lead to the binding of anions (*12*). Finally, thiacalixarenes that contain the amide fragments could be used for binding of carboxylate and carboxyl moieties (*13*).

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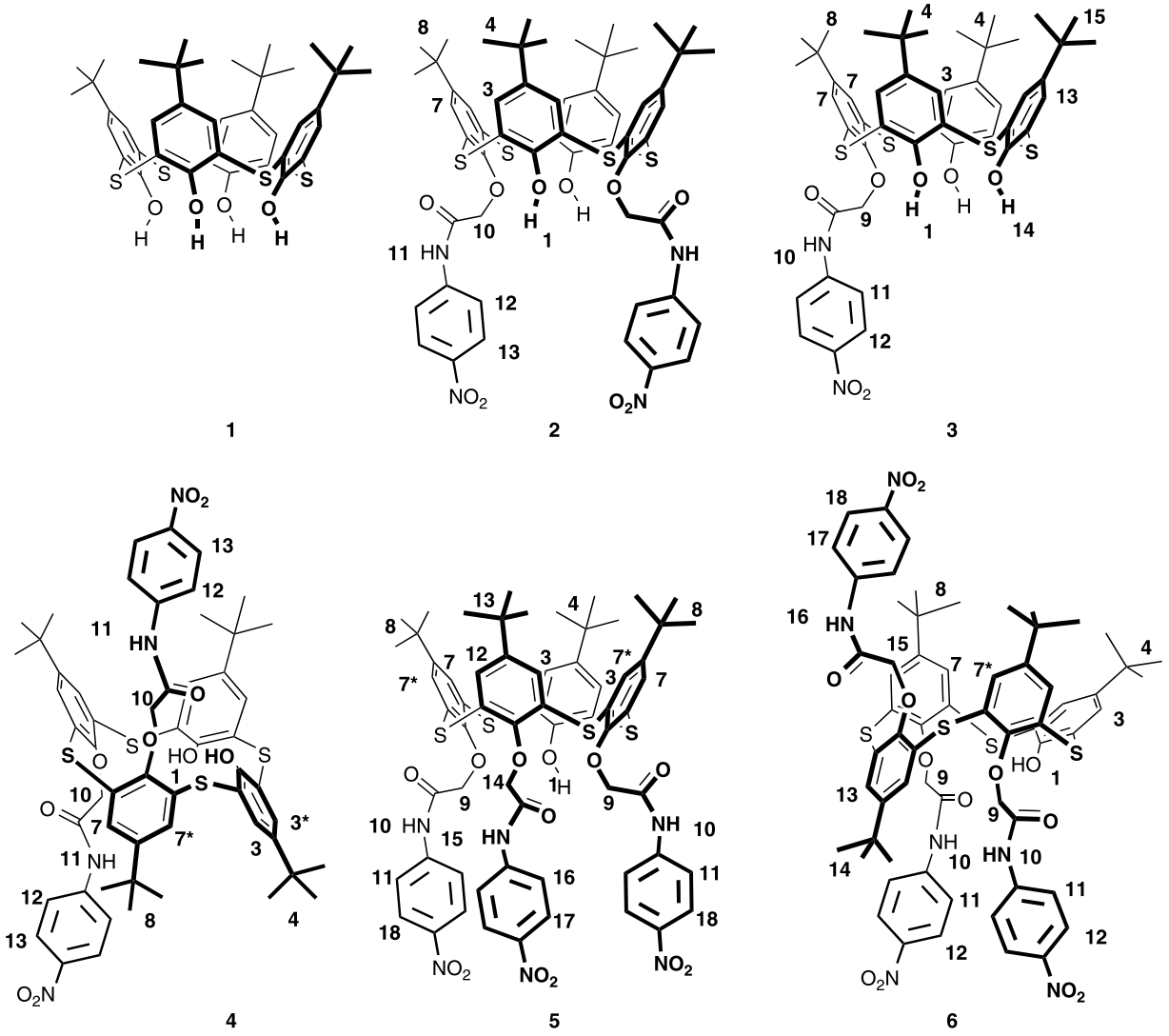

Chart 1. Structures of thiacalix[4]arenes **1**–**6**.

In the present paper, we report the tetra-alkylation of thiacalix[4]arene with NPNBA in acetone or acetonitrile in the presence of alkali metal carbonates leading to substituted thiacalixarenes in different conformations, and the effect of solvent, temperature, reagent ratio and metal cation on the regio- and stereoselectivity of the reaction.

Results and discussion

Synthesis of the thiacalix[4]arene derivatives

Five products can be expected in terms of the alkylation regioselectivity: one tetra- and four partially substituted products (mono-, 1,2-di-, 1,3-di- and trisubstituted) are possible upon the alkylation of the lower rim of the thiacalix[4]arene. In order to obtain the partially substituted derivatives of the thiacalix[4]arene, the alkylation reagent can be used in sub-stoichiometric quantity with respect to the phenol groups of the thiacalix[4]arene.

We studied the alkylation of the thiacalix[4]arene with the reagents *p-tert*-butylthiacalix[4]arene/NPNBA/M_2CO_3 in the ratio of 1:2:4 (Table 1), leading to the formation of compounds **2**–**6**. The reactions were monitored

Table 1. Yields of isolated products and regioisomer distribution for the alkylation reaction of thiacalix[4]arene with *p-tert*-butylthiacalix[4]arene/NPNBA/M_2CO_3 in a 1:2:4 ratio.

			Product distribution (%)					
M_2CO_3	Solvent	Time (h)	**1**[a]	**2**	**3**	**4**	**5**	**6**
Na	Me_2CO	72	63	11	–	–	26	–
K	Me_2CO	72	40	–	54	6	–	–
Cs	Me_2CO	72	48	–	10	42	–	–
Na	MeCN	20	44	51	–	–	–	5
K	MeCN	20	49	–	44	7	–	–
Cs	MeCN	20	27	–	20	53	–	–

[a] The starting material isolated from the reaction mixture.

by thin layer chromatography (TLC) and were continued until the disappearance of one of the starting materials. Initially, the reactions were carried out at reflux for 72 h using acetone as a solvent. Replacing acetone with acetonitrile and increasing the reaction temperature led to the change in both the structure and the yield of the alkylation products. Reactions in acetonitrile were carried out at reflux for 20 h. Reaction products were isolated from the reaction mixture and purified by fractional recrystallisation. Table 1 lists the yields of isolated products as well as regioisomer distributions.

The alkylation of thiacalix[4]arene in acetone using sodium carbonate as a base leads to the formation of the trisubstituted thiacalix[4]arene **5** in the *cone* conformation in 26% yield as a major product and 1,3-disubstituted thiacalixarene **2** as a by-product in 11% yield (Table 1), whereas using potassium and caesium carbonates leads to the monosubstituted (**3**) and 1,2-disubstituted (**4**) products. Using potassium carbonate as a base leads to the formation of monosubstituted compound **3** as the main product (54%) and 1,2-disubstituted compound **4** as a by-product (6%), whereas using caesium carbonate results in a different ratio of the products: 1,2-disubstituted (42%) as the main product and monosubstituted (10%) as a by-product. In acetonitrile, using Na_2CO_3 results in the 1,3-disubstituted thiacalixarene **2** as the main product (51%) and the trisubstituted thiacalix[4]arene **6** in the partial *cone* conformation in 5% yield as a by-product. The alkylation of thiacalix[4]arene in the presence of potassium carbonate furnishes the monosubstituted compound **3** in 44% yield; furthermore, 1,2-disubstituted thiacalixarene **4** was isolated from the reaction mixture by fractional recrystallisation in 7% yield. Finally, using caesium carbonate instead of sodium or potassium carbonate allows to increase the yields of compounds **3** and **4** to 20 and 53%, respectively.

Although the alkylation of thiacalixarene with NPNBA showed reasonable regioselectivity at the reagent ratio of *p-tert*-butylthiacalix[4]arene/NPNBA/M_2CO_3 equal to 1:2:4, the total yields of isolated products are not higher than 37–73%. In order to improve the yields, we decided to increase the amount of the base and to use the reagents *p-tert*-butylthiacalix[4]arene/NPNBA/M_2CO_3 in the ratio of 1:2:6 (Table 2). We observed two trends under these conditions: the yields increased when using sodium carbonate and decreased when using potassium or caesium carbonate. We have found (Tables 1 and 2) the distinct influence of solvents and nature of base on the regioselectivity of the lower rim alkylation of the thiacalix[4]arene.

Table 2. Yields of isolated products and regioisomer distribution for the alkylation reaction of thiacalix[4]arene with the reagents *p-tert*-butylthiacalix[4]arene/NPNBA/M_2CO_3 in a 1:2:6 ratio.

			Product distribution (%)					
M_2CO_3	Solvent	Time (h)	**1**[a]	**2**	**3**	**4**	**5**	**6**
Na	Me_2CO	72	51	20	12	–	12	6
K	Me_2CO	72	46	–	46	8	–	–
Cs	Me_2CO	72	57	–	12	32	–	–
Na	MeCN	20	31	52	14	–	–	3
K	MeCN	20	50	–	27	23	–	–
Cs	MeCN	20	50	–	40	10	–	–

[a] The starting material isolated from the reaction mixture.

Characterisation

The structure and composition of compounds **2**–**6** was confirmed using ^{1}H and 2D NMR, IR spectroscopy, mass spectrometry (MALDI-TOF, CI, EI and ESI) and elemental analysis. Moreover, the structure of the monosubstituted compound **3** was also confirmed by X-ray crystallography.

The ^{1}H NMR spectrum of monosubstituted compound **3** shows three singlets for the *tert*-butyl protons (relative intensity 1:2:1), singlet for the $OCH_2C(O)$ methylene protons, two singlets of equal intensity and two similar AB systems ($^4J_{HH} = 2.5$ Hz) for the aromatic protons of the thiacalixarene macrocycle, two AA′BB′ systems ($^3J_{HH} = 9.3$ Hz) for the aromatic protons of the substituent, two singlets (relative intensity 2:1) for the protons of hydroxy groups and singlet for the NH proton in the weak-field region. The relative intensity of the proton signals strongly suggests that compound **3** is a monosubstituted thiacalixarene. This is also consistent with ESI and MALDI-TOF mass spectra, which possess molecular ion signals, with $m/z = 898.3$ (M^+), 899 ($M + H^+$), 922 ($M + Na^+$) and 938 ($M + K^+$). The 2D NMR spectrum (NOESY) of monosubstituted compound **3** exhibits the cross-peaks between the protons of the hydroxy groups and the methylene group, as well as the cross-peaks between the aromatic protons of the macrocycle, which confirms its *cone* conformation.

The crystals of compound **3** are monoclinic in the space group *Ia*. The asymmetric unit consists of one independent molecule of **3** and a molecule of acetonitrile (Figure 1). Compound **3** is a monosubstituted thiacalix[4]arene in the *cone* conformation, with all C—S—C angles having similar values. The dihedral angles between adjacent aromatic rings, i.e. C2–C7 and C16–C21, and C9–C14 and C23–C28, are 3.7° and 7.4°, respectively. The analysis of geometric parameters (bond length, valence and torsion angles) in molecule **3** shows that they are close to their standard values. The *cone* conformation of macrocycle **3** is stabilised by the cyclic hydrogen bond of O—H···O and N—H···O types (*14*). The hydrogen bonds are formed by four protons, one belonging to the NH group of the substituent. The parameters of the hydrogen bonds are shown in Table 3. The strong hydrogen bonding was also confirmed by the IR spectroscopy. The IR spectrum of monosubstituted

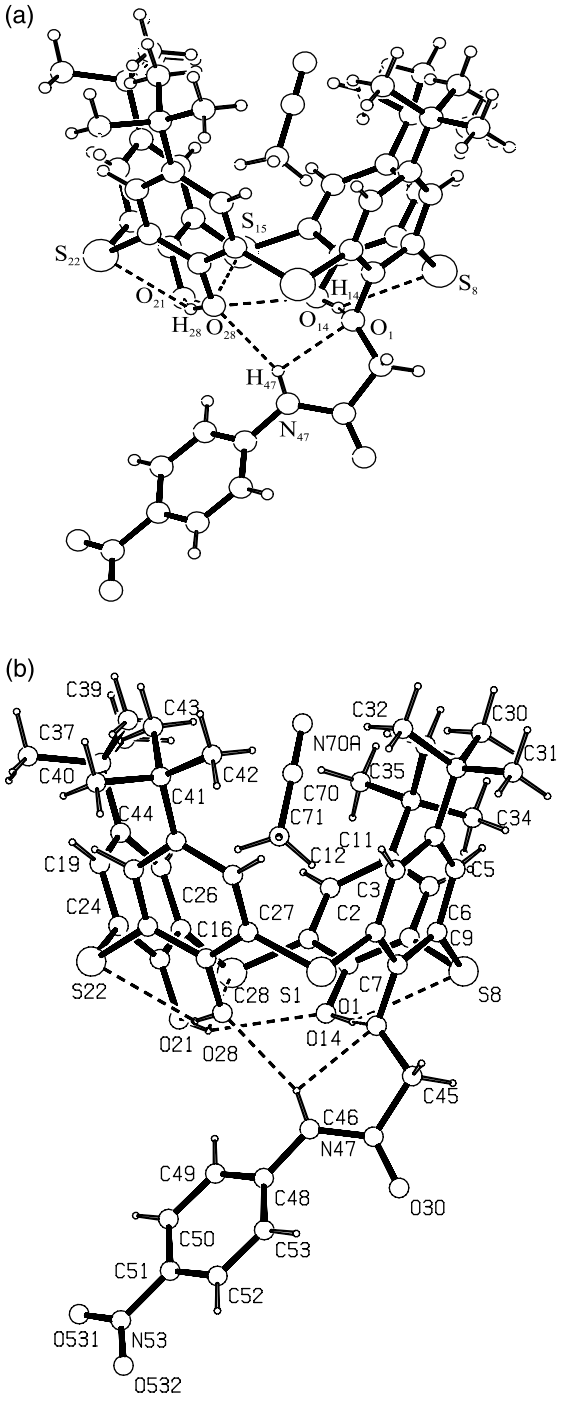

Figure 1. X-ray structure of compound **3** with acetonitrile clathrate. Selected bond lengths (Å) and bond angles (deg): S(1)–C(2) 1.790(4), S(1)–C(27) 1.783(4), S(8)–C(6) 1.780(4), S(8)–C(9) 1.788(4), S(15)–C(13) 1.777(4), S(15)–C(16) 1.784(4), S(22)–C(20) 1.780(4), S(22)–C(23) 1.794(4), O(1)–C(7) 1.376(4), O(1)–C(45) 1.448(5), O(14)–C(14) 1.360(5), O(21)–C(21) 1.359(5), O(28)–C(28) 1.347(5), O(30)–C(46) 1.214(5), N(47)–C(46) 1.357(5), N(47)–C(48) 1.405(5), N(53)–C(51) 1.464(6), C(2)–S(1)–C(27) 100.4(2), C(6)–S(8)–C(9) 100.5(2), C(13)–S(15)–C(16) 102.1(2), C(20)–S(22)–C(23) 99.3(2), C(7)–O(1)–C(45) 114.4(3), C(46)–N(47)–C(48) 126.2(4).

Table 3. The parameters of hydrogen bonds (Å) in the crystal structure of acetonitrile clathrate of compound **3**.

D—H···A	$d_{D—H}$ (Å)	$d_{H\cdot\cdot\cdot A}$ (Å)	$d_{D\cdot\cdot\cdot A}$ (Å)	D—H···A (deg)
O_{14}—H_{14}···S_8	0.82	2.54	3.054(3)	122.0
O_{14}—H_{14}···O_1	0.82	2.18	2.913(4)	148.0
O_{21}—H_{21}···S_{15}	0.82	2.48	2.992(3)	121.0
O_{21}—H_{21}···O_{14}	0.82	2.48	3.100(4)	134.0
O_{28}—H_{28}···S_{22}	0.82	2.50	3.019(3)	123.0
O_{28}—H_{28}···O_{21}	0.82	2.22	2.904(4)	142.0
N_{47}—H_{47}···O_1	0.86	2.16	2.596(4)	111.0
N_{47}—H_{47}···O_{28}	0.86	2.26	3.036(5)	150.0

compound **3** shows a band at 3326 cm^{-1} for the OH group and a band at 3375 cm^{-1} for the NH group, which indicates the presence of a strong hydrogen bond formation. The molecule of solvent (acetonitrile) is found inside the macrocycle cavity, with the nitrogen atom of acetonitrile turned away from the thiacalix[4] arene cavity. Similar structures have been previously reported (*2*, *15–18*).

It is noteworthy that the solvent molecule is retained well in the crystals of **3**. Even prolonged drying under vacuum (3 days) does not lead to the removal of acetonitrile. The 1:1 stoichiometry of thiacalix[4]arene **3**/acetonitrile clathrate was also confirmed by NMR.

Compound **4** is disubstituted as confirmed by its ESI and MALDI-TOF mass spectra. The ^{1}H NMR spectrum of compound **4** shows two singlets of equal intensity for the *tert*-butyl protons, an AA′BB′ system for the aromatic substituents and an AB system for the methylene protons. Only two structures could correspond to this spectrum: 1,3-disubstituted thiacalixarene in *1,2-alternate* conformation and 1,2-disubstituted thiacalixarene in *1,2-alternate* conformation. The structure of thiacalixarene **4** was established by the 2D NMR spectroscopy. The 2D spectrum of compound **4** shows that protons of the *tert*-butyl group (CH_3^8) are situated nearer to protons (CH_2^{10}) of lateral fragments than to the hydroxy group's proton OH^1. Only 1,2-disubstituted thiacalix[4]arene in *1,2-alternate* conformation could correspond to that spectrum. The formation of 1,2-disubstituted thiacalixarene in *1,2-alternate* conformation could result from the thermodynamic stabilisation of the structure as a result of the intramolecular hydrogen bond formation between the amide fragment and the phenol group. It is necessary to emphasise that the intramolecular hydrogen bond prevents the rotation of the unsubstituted phenol units of the macrocyclic ring. In the IR spectrum, the absorption bands of the OH and NH groups appear at 3336 and 3385 cm^{-1}, respectively, which strongly support a strong hydrogen bond formation.

In the ^{1}H NMR spectra of **5** and **6**, the signals of the methylene protons are observed as a singlet in an AB system (integral intensity 1:2). However, the singlet of the

methylene protons is shifted upfield by 0.5 ppm in **6** compared to **5**, which confirms the shielding of the protons of the $-OCH_2-C(O)-$ group by the aromatic moieties of the thiacalixarene ring. At the same time, no difference in the chemical shifts for the AB system of the methylene protons was found. These observations suggest a partial *cone* conformation for the trisubstituted compound **6**. The structure of compounds **5** and **6** was further investigated by the 2D NOESY NMR spectroscopy. The NOESY spectrum of compound **5** shows the cross-peaks corresponding to the dipole–dipole interactions between the protons of the *tert*-butyl groups and the aromatic protons of the macrocycle (H_8/H_3, H_8/H_{12}, H_{13}/H_3, H_4/H_{12} and H_7/H_3), and the cross-peaks between the methylene protons (H_{9a}/H_{14} and H_{9b}/H_{14}) and the protons (H_{17}/H_{18}) of the aromatic group of the substituent, which confirms the *cone* conformation of the macrocycle. The 2D NOESY spectrum of compound **6** showed the cross-peaks between the protons (H_{15}, H_{16} and H_{17}) of the substituent and the protons (H_4 and H_8) of the *tert*-butyl groups ($H_8/H_{15} \approx H_8/H_7$, H_{17}/H_4, H_{15}/H_7), as well as the cross-peaks between the aromatic protons and the methylene protons of the substituent (H_9/H_{13}), which strongly support the partial cone conformation of the macrocycle.

The IR spectra of compounds **5** and **6** show different intensity and frequency of absorption bands corresponding to the OH and NH groups. The IR spectrum of **5** displays the absorption bands at 3316 cm^{-1} for νOH and at 3369 cm^{-1} for νNH, which indicates the presence of a strong hydrogen bond in **5**, which is also observed for the 1,2-disubstituted compound **4**. The IR spectrum of **6** shows a band at 3380 cm^{-1} for the NH group and a broad band of the hydrogen-bonded OH group at 3319 cm^{-1}, in agreement with the proposed structure.

Mechanistic considerations

The formation of mono-, 1,2- and 1,3-disubstituted is controlled by a number of factors. The first step of the alkylation reaction results in the monosubstituted compound **3**, which is stabilised by the cyclic hydrogen bond (Figure 1). Further abstraction of the protons from the phenol group and their subsequent alkylation depend on the nature of the base used, as well as on the stability of the resulting anions.

The formation of two monoanions A and B is possible (Figure 2). The anion A is stabilised by two H bonds formed with the adjacent phenolic hydrogen and the NH group of the substituent, while, in structure B, the phenolate anion is stabilised by the hydrogen bonding to the neighbouring phenolic hydrogens. Obviously, monoanion B is more stable. As a result, distal

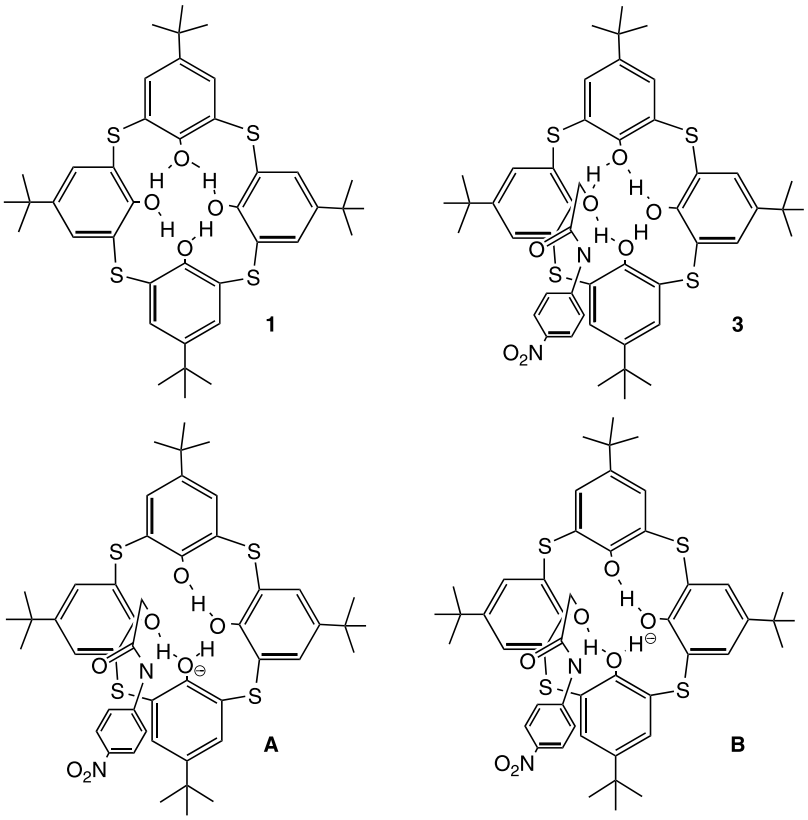

Figure 2. Stabilisation of distal and proximal anions of monosubstituted thiacalix[4]arene by hydrogen bonding.

disubstitution of thiacalix[4]arenes is being achieved when using Na_2CO_3, which forms a tighter ion pair in acetonitrile or acetone. On the other hand, potassium and caesium cations form looser ion pairs with the phenolate anion, whose charge, as a result, is less shielded. The yield of the 1,2-disubstituted product increases depending on the nature of the metal cation as follows: $Na_2CO_3 < K_2CO_3 < Cs_2CO_3$. The nature of the solvent also has a distinct influence on the reaction. In addition, it appears that the solubility plays a role. In acetonitrile, the reaction stops at the second step because of a low solubility of the 1,3-disubstituted compound **2**, which slows down its further alkylation. However, the products of mono-, 1,2-di- or 1,3-disubstition are soluble in acetone, and the alkylation of the lower rim of the thiacalix[4]arene does not stop at this stage but proceeds to provide the trisubstituted products.

Conclusions

We developed a regioselective synthesis of new thiacalix[4]arenes in *cone*, *partial cone* and *1,2-alternate* conformations functionalised at the lower rim with an amide fragment by treating the thiacalixarene **1** with *N*-(*p*-nitrophenyl)-α-bromoacetamide in the presence of M_2CO_3 (M = Na, K and Cs). We have found that the formation of two different disubstituted compounds, distal disubstituted thiacalixarene in the *cone* conformation and proximal disubstituted thiacalixarene in the *1,2-alternate* conformation, is possible depending on the nature of the base. Moreover, we found that increasing the amount of the base leads to higher yields when using sodium carbonate, while lower yields were observed for potassium and caesium carbonates. Finally, we found that changing the solvent from acetone to acetonitrile results in significant decrease in the reaction time (from 72 to 20 h). The obtained compounds are promising supramolecular building blocks.

Experimental section

General

The ^{1}H NMR spectra were recorded at room temperature using a Varian VXR-Unity spectrometer at 300 MHz using $CDCl_3$ as a solvent; chemical shifts are reported in ppm. The NMR signals were assigned with the aid of 2D NOESY spectra. The IR spectra were recorded in KBr pellets using a Bruker Vector 22 FT-IR spectrometer with the resolution of 1 cm^{-1} with 64 accumulated scans in the range of 400–4000 cm^{-1}. The mass spectra were obtained using MALDI-TOF Dynamo Finnigan and Kratos Kompact MALDI-II mass spectrometers (with 1,8,9-trihydroxyanthracene or 4-nitroaniline matrices). Melting points were recorded using a Kofler hot block and are uncorrected. The reactions were monitored by ^{1}H NMR spectroscopy and TLC (Silufol UV-254 plates, visualisation by iodine vapour). Where necessary, solvents were purified prior to use. Acetone and acetonitrile were distilled from P_2O_5 before use. Unless stated otherwise, commercial grade chemicals were used without further purification. 5,11,17,23-Tetra-*tert*-butyl-2,8,14,20-tetrathiacalix[4]arene-25,26,27,28-tetrol (TCA) was synthesised as described earlier (*1*). All reagents purchased were of reagent grade and used as purchased unless otherwise noted.

N-(p-*nitrophenyl)-α-bromoacetamide (NPNBA)*

A solution of the bromoacetyl bromide (10.0 mmol) in dry benzene (10 ml) was added dropwise to the suspension of *p*-nitroaniline (14.6 mmol) in dry benzene (30 ml). The mixture was heated to reflux for 8 h. After cooling, the solid residue was removed by filtration. Yields 3.59 g (94%); mp 174°C. IR (KBr) ν = 493 (C—Br); 3226, 3166, 3105 (NH); 1568 (C(O)—NH); 1683 (C═O); 1506, 1338 (NO_2) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 25°C): δ = 2.06 (s, 1H, NH), 3.97 (s, 2H, CH—), 7.81 (m, $3J^{ortho}_{AX} = {}^3J^{ortho}_{A'X'} = 9.0$ Hz, ${}^5J^{para}_{A'X} = {}^5J^{para}_{AX'} = 0.3$ Hz, ${}^4J^{meta}_{AA'} = {}^4J^{meta}_{XX'} = 5.0$ Hz, 2H, Ar-H_A, Ar-$H_{A'}$), 8.13 (m, ${}^3J^{ortho}_{AX} = {}^3J^{ortho}_{A'X'} = 9.0$ Hz, ${}^5J^{para}_{A'X} = {}^5J^{para}_{AX'} = 0.3$ Hz, ${}^4J^{meta}_{AA'} = {}^4J^{meta}_{XX'} = 5.0$ Hz, 2H, Ar-H_X, Ar-$H_{X'}$), 8.37 (s, 1H, NH) ppm. MS (EI): m/z = 260 (M^+). $C_8H_7BrN_2O_3$ (259.06): calcd C 37.09; H 2.72; Br 30.84; N 10.81; found: C 36.81; H 2.72; Br 30.04; N 10.21.

General procedure for the preparation of thiacalix[4]arenes **2–6**

TCA (1 g, 1.39 mmol) was suspended in 50 ml of dry acetone or acetonitrile containing 4-fold (or 6-fold) excess of an anhydrous alkali carbonate. The mixture was heated under argon for 2 h. Then, the suspension of 2-fold excess of NPNBA in 20 ml of dry acetone or acetonitrile was added. The mixture was refluxed under argon for several hours (Tables 1–3). The reaction was monitored by TLC. After cooling, the solid residue was removed by filtration. The filtrate was evaporated to dryness. Then, both solids were treated separately using the same procedure. The solid was dissolved in 50 ml of chloroform and was washed with 50 ml of 2 M HCl. The organic layer was dried over $MgSO_4$, filtered and evaporated under reduced pressure. Crystallisation of the resulting solid from chloroform/ethanol mixture gave pure samples of **2–6**. Single crystals of monosubstituted compound **3** were obtained by recrystallisation from acetonitrile.

*5,11,17,23-Tetra-*tert*-butyl-25,27-bis-hydroxy-26,28-[N-(p-nitrophenyl)aminocarbonylmethoxy]-thiacalix[4] arene (2) (11)*

Yield 52%; mp 315°C. IR (KBr) ν = 3648 (OH); 3341 (NH); 1709 (C═O); 1599 (C(O)—NH); 1546, 1512

(NO_2) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25°C): $\delta = 1.17$ (s, 18H, $(CH_3)_3C$); 1.30 (s, 18H, $(CH_3)_3C$); 4.74 (s, 4H, OCH_2); 7.63 (s, 4H, Ar-H); 7.64 (d, $^3J_{HH} = 9.3$ Hz, 4H, Ar′-H); 7.76 (s, 4H, Ar-H); 8.17 (d, $^3J_{HH} = 9.3$ Hz, 4H, Ar′-H); 8.93 (s, 2H, NH); 10.69 (s, 2H, OH) ppm. $^1H—^1H$ NOESY: H_3/H_4, H_7/H_8, H_1/H_{10}, H_1/H_{11}. MS (EI): $m/z = 1076$ (M^+). $C_{56}H_{60}N_4O_{10}S_4$ (1077.35): calcd C 62.4; H 5.6; S 11.9; N 5; found: C 62.6; H 5.7; N 5.4; S 11.7.

5,11,17,23-Tetra-tert-*butyl-25,26,27-trihydroxy-28-[*N-*(*p*-nitrophenyl)aminocarbonylmethoxy]-thiacalix[4]arene (3)*

Yield 51% as a colourless powder; mp 157°C (CH_3CN). IR (KBr) $\nu = 3326$ (OH); 3375 (NH); 1708 (C═O); 1549 (C(O)—NH); 1514, 1341 (NO_2) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25°C): $\delta = 0.86$ (s, 9H, $(CH_3)_3C$), 1.11 (s, 18H, $(CH_3)_3C$), 1.20 (s, 9H, $(CH_3)_3C$), 4.85 (s, 2H, O—CH_2), 7.66 (d, $^4J_{HH} = 2.5$ Hz, 2H, Ar-H), 7.67 (s, 2H, Ar-H), 7.69 (s, 2H, Ar-H), 7.73 (d, $^4J_{HH} = 2.5$ Hz, 2H, Ar-H), 8.11 (m, $^3J_{HH}^{ortho} + {}^5J_{HH}^{para} = 9.3$ Hz, 2H, Ar′-H), 8.28 (m, $^3J_{HH}^{ortho} + {}^5J_{HH}^{para} = 9.3$ Hz, 2H, Ar′-H), 9.26 (s, 2H, OH), 9.55 (s, 1H, OH), 11.11 (s, 1H, NH) ppm. $^1H—^1H$ NOESY: H_3/H_8, H_7/H_8, H_7/H_4, H_3/H_4, H_1/H_9, H_9/H_{10}, H_3/H_{10}, H_1/H_3, H_3/H_{11}, H_1/H_{10}, H_7/H_{10}, H_{11}/H_{14}, H_1/H_{11}. MS (EI): $m/z = 899$ (M^+). MALDI-TOF: $m/z = 900$ $[M + H]^+$, 922 $[M + Na]^+$, 938 $[M + K]^+$. $C_{48}H_{54}N_2O_7S_4$ (899.21): calcd C 64.3; H 6.3; N 3.3; S 14.1; found: C 64.1; H 6.1; N 3.1; S 14.3.

X-ray crystallography of 3

$C_{48}H_{54}N_2O_7S_4 \cdot C_2H_3N$, MW = 940.27, monoclinic, space group *Ia*, $a = 12.3572(8)$, $b = 31.803(3)$, $c = 13.058(2)$ Å, $\beta = 99.345(8)°$, $V = 5063.7(1)$ Å, $Z = 4$, $\rho_c = 1.23\ g\,m^{-3}$. Cell parameters and intensities of 5375 independent reflections (4517 with $I \geq 2\sigma$) were measured on an Enraf–Nonius CAD-4 diffractometer, $\omega/2\theta$-scan mode, $\theta \leq 74.21°$, using Cu K_α radiation with graphite monochromator. The intensity falling was not observed at three control measurements. The empirical absorption correction was applied (μCu Kα 21.38 cm^{-1}). The structure was solved by a direct method using the SIR program (*19*) and refined by the full-matrix least squares using the SHELX-97 (*20*) program package. All non-hydrogen atoms were refined anisotropically. The hydrogens at oxygen and nitrogen atoms were located from difference Fourier calculations, and other hydrogens calculated and refined as riding atoms. The final divergence factors are $R = 0.037$ and $Rw = 0.099$ based on 4517 reflections with $F^2 \geq 2\sigma^2$. All calculations were performed on PC using the WinGX (*21*) program. Cell parameters, data collection and data reduction were performed on Alpha Station 200 computer using the MoLEN (*22*) program package. Figures of molecules were performed with the program PLATON (*23*). Atomic coordinates, bond lengths, bond angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre CCDC (Reference No. 646022).

5,11,17,23-Tetra-tert-*butyl-25,26-bis-hydroxy-27,28-bis-[*N-*(*p*-nitrophenyl)aminocarbonylmethoxy]-thiacalix[4]arene (4)*

Yield 53% as a colourless powder; mp 265°C. IR (KBr) $\nu = 3336$ (OH); 3385 (NH); 1712 (C═O); 1541 (C(O)—NH); 1342, 1513 (NO_2) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25°C): $\delta = 0.87$ (s, 18H, $(CH_3)_3C$), 1.12 (s, 18H, $(CH_3)_3C$), 4.58 (d, $^2J_{HH} = 14.5$ Hz, 2H, O—CH_2), 4.86 (d, $^2J_{HH} = 14.5$ Hz, 2H, O—CH_2), 6.75 (s, 2H, —OH), 7.09 (m, $^3J_{HH}^{ortho} + {}^5J_{HH}^{para} = 8.9$ Hz, 4H, Ar′-H), 7.36 (d, $^4J_{HH} = 2.4$ Hz, 2H, Ar-H), 7.42 (d, $^4J_{HH} = 1.9$ Hz, 2H, Ar-H), 7.51 (d, $^4J_{HH} = 2.4$ Hz, 2H, Ar-H), 7.63 (d, $^4J_{HH} = 1.9$ Hz, 2H, Ar-H), 7.97 (m, $^3J_{HH}^{ortho} + {}^5J_{HH}^{para} = 8.9$ Hz, 4H, Ar'-H), 8.49 (s, 2H, NH) ppm. $^1H–^1H$ NOESY: H_{11}/H_{10a}, H_{11}/H_{10b}, H_1/H_{13}, H_{13}/H_{12}, H_{13}/H_1, H_1/H_{10b}, H_1/H_{11}, H_1/H_{12}, H_1/H_7, H_1/H_{7*}, H_1/H_{3*}; $H_{13}/H_{12} \gg H_{13}/H_7$, H_{13}/H_3, H_{13}/H_{7*}, H_{13}/H_{3*}; $H_1/H_{12} \gg H_1/H_7$; H_{10a}/H_{11}, H_{10b}/H_{11}, H_{13}/H_{12}, H_{13}/H_3, H_{13}/H_{3*}, H_{10a}/H_3, H_{10b}/H_{3*}, H_7/H_{7*}, H_3/H_7, H_{10b}/H_1. MS (EI): $m/z = 1077$ (M^+). MALDI-TOF: $m/z = 1078$ $[M + H]^+$, 1100 $[M + Na]^+$, 1116 $[M + K]^+$. $C_{56}H_{60}N_4O_{10}S_4$ (1077.35): calcd C 62.4; H 5.6; N 5.2; S 11.9; found: C 61.9; H 5.5; N 5.2; S 11.6.

5,11,17,23-Tetra-tert-*butyl-25-hydroxy-26,27,28-tris-[*N-*(*p*-nitrophenyl)aminocarbonylmethoxy]-thiacalix[4]arene (5)*

Yield 26% as a colourless powder; mp 201°C. IR (KBr) $\nu = 3316$(OH); 3369(NH); 1707(C═O); 1542(C(O)—NH); 1513, 1342 (NO_2) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25°C): $\delta = 0.94$ (s, 18H, $(CH_3)_3C$), 1.33 (s, 9H, $(CH_3)_3C$), 1.38 (s, 9H, $(CH_3)_3C$), 4.69 (d, $^2J_{HH} = 14.9$ Hz, 2H, O—OH_2), 4.95 (s, 2H, O—OH_2), 4.95 (d, $^2J_{HH} = 14.9$ Hz, 2H, O—OH_2), 7.18 (d, $^4J_{HH} = 2.4$ Hz, 2H, Ar-H), 7.20 (d, $^4J_{HH} = 2.4$ Hz, 2H, Ar-H), 7.61 (m, $^3J_{HH}^{ortho} + {}^5J_{HH}^{para} = 9.3$ Hz, 4H, Ar′-H), 7.75 (s, 2H, Ar-H), 7.79 (s, 2H, Ar-H), 7.93 (m, $^3J_{HH}^{ortho} + {}^5J_{HH}^{ortho} = 9.1$ Hz, 2H, Ar′-H), 8.11 (m, $^3J_{HH}^{ortho} + {}^5J_{HH}^{para} = 9.3$ Hz, 4H, Ar′-H), 8.21 (m, $^3J_{HH}^{ortho} + {}^5J_{HH}^{para} = 9.1$ Hz, 2H, Ar′-H), 9.32 (s, 1H, NH), 9.64 (s, 2H, NH) ppm. $^1H–^1H$ NOESY: H_8/H_7, H_{7*}/H_8, H_{12}/H_{13}, H_3/H_4, H_{9a}/H_{14}, H_{9a}/H_{9b}, H_{9b}/H_{14}, H_8/H_3, H_8/H_{12}, H_{17}/H_{18}, H_{13}/H_3, H_4/H_{12}, H_{18}/H_{11}, H_7/H_3. MS (EI): $m/z = 1255$ (M^+). MALDI-TOF: $m/z = 1256$ $[M + H]^+$, 1278 $[M + Na]^+$, 1294 $[M + K]^+$. $C_{64}H_{66}N_6O_{13}S_4$ (1255.50): calcd C 61.2; H 5.3; N 6.6; S 10.2; found: C 61.2; H 4.9; N 5.9; S 10.0.

5,11,17,23-Tetra-tert-*butyl-25-hydroxy-26,27,28-tris-[N-(*p-*nitrophenyl)aminocarbonylmethoxy]-thiacalix[4]arene (6)*

Yield 6% as a colourless powder; mp 211°C. IR (KBr) $\nu = 3319$ (OH); 3380 (NH); 1708 (C═O); 1595 (C(O)—NH); 1514, 1340 (NO_2) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25°C): $\delta = 0.74$ (s, 18H, $(CH_3)_3C$), 1.04 (s, 9H, $(CH_3)_3C$), 1.51 (s, 9H, $(CH_3)_3C$), 4.46 (d, $^2J_{HH} = 15.1$ Hz, 2H, O—OH_2—), 4.60 (s, 2H, —O—OH_2—),5.13 (d, $^2J_{HH} = 15.1$ Hz, 2H, —O—OH_2—), 5.95 (s, 1H, NH), 6.29 (m, $^3J_{HH}^{ortho} + {}^5J_{HH}^{para} = 9.4$ Hz, 2H, Ar′-H), 7.27 (d, $^4J_{HH} = 2.5$ Hz, 2H, Ar-H), 7.51 (d, $^4J_{HH} = 2.5$ Hz, 2H, Ar-H), 7.50 (s, 2H, Ar-H), 7.90 (s, 2H, Ar-H), 7.28 (m, $^3J_{HH}^{ortho} + {}^5J_{HH}^{para} = 9.0$ Hz, 4H, Ar′-H), 7.51 (m, $^3J_{HH}^{ortho} + {}^5J_{HH}^{para} = 9.3$ Hz, 2H, Ar′-H), 7.72 (m, $^3J_{HH}^{ortho} + {}^5J_{HH}^{para} = 9.4$ Hz, 2H, Ar'-H), 7.98 (m, $^3J_{HH}^{ortho} + {}^5J_{HH}^{para} = 9.4$ Hz, 4H, Ar′-H), 8.55 (s, 1H, —OH), 8.98 (s, 2H, NH) ppm. $^1H-{}^1H$ NOESY: H_{17}/H_{18}, H_7/H_{7*}, H_9/H_{13}, H_{12}/H_{11}, H_8/H_4, $H_8/H_{15} \approx H_8/H_7$, H_8/H_{7*}, H_{7*}/H_8, H_{10}/H_{12}, H_{13}/H_{14}, H_{17}/H_4, H_3/H_4, H_{15}/H_7. MS (EI): $m/z = 1255$ (M^+). MALDI-TOF: $m/z = 1256$ $[M + H]^+$, 1278 $[M + Na]^+$, 1294 $[M + K]^+$. $C_{64}H_{66}N_6O_{13}S_4$ (1255.50): calcd C 61.2; H 5.3; N 6.6; S 10.2; found: C 60.9; H 5.1; N 5.9; S 10.1.

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