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Synthesis of conformationally diverse tetrathiacalix[4]arene(amido)crowns and tetrathiacalix[4]arene amides with pendant amine functions

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Abstract—A series of conformationally diverse novel tetrathiacalix[4]arene(amido)crowns and amides from tetrakis((ethoxycarbonyl)-methoxy)*p-tert*-butyl tetrathiacalix[4]arene and its debutylated analog have been prepared by their reaction with diamines [$H_2N(CH_2)_nNH_2$; n=2,3,4, and 6] and polyamines. It has been determined that the length of the alkyl spacer in diamines is pivotal for the formation of either the tetrathiacalix[4]arene bis(amido)crowns or tetrathiacalix[4]arene amides with pendant amine functions. The synthesized compounds represent potential building blocks for achieving sophisticated molecular assemblies for molecular organization and recognition. Single crystal X-ray analysis of tetrathiacalix[4]arene bis(amido)crown **6a** revealed that it has a 1,3-alternate conformation, which forms supramolecular complexes with chloroform.

1. Introduction

Calixamidocrowns represent a new class of synthetic molecular receptors, which combine the structure and properties of calixarenes[1] and amidocrown[2] compounds. The first 1,3-calix[4]arene(amido)crown[3] was synthesized and evaluated by Reinhoudt et al. in 1991 while Bitter et al.[4] reported the synthesis of doubly bridged proximal calix[4]arene(amido)-crown compounds through intramolecular ring closure of chloroalkylamide precursors in 1998. Recently Samanta et al.[5] have reported *N*-(4-aminophthalimidoethyl)calix[4]-amidocrown as a fluorescent sensor for iron(III) and copper(II).

It was envisaged that similar analogs of tetrathiacalix[4]-arenes,[6] which contain sulfur atoms in lieu of methylene bridges in calixarenes could provide conformationally diverse receptors with enhanced potential for interaction with a variety of guests. The new molecular receptors, in principle, would offer immense possibilities for further exploration. While our work in this area was in progress, a report[7] describing the low yield synthesis of proximally bridged tetrathiacalix[4]arene(amido)crown appeared, which has prompted us to report our initial work on tetrathiacalix[4]arene(amido)-crown derivatives with variable ring size and conformations for possible applications in nuclear-waste remediation, sensing, and radiopharmacy.

2. Results and discussion

2.1. Synthesis

Tetrathiacalix[4]arenes **1a**[8] and **1b**[9,10] were obtained by the base catalyzed condensation of *p-tert*-butylphenol and sulfur as reported previously by us and others.[8–11] They were esterified[12] by reaction with bromoethylacetate in the presence of sodium carbonate and cesium carbonate in separate reactions to give tetrathiacalix[4]arene esters **2**, **3**, and **4**. Compounds **2**, **3**, and **4** were further reacted with alkyl diamines of varying chain lengths [$NH_2(CH_2)_nNH_2$; n=2, 3,4, and 6] and a polyamine by refluxing in toluene/methanol (1:1) in the case of **2** and **4**; and THF/methanol (1:1) in the case of **3** (Schemes 1–3) to yield tetrathiacalix[4]arene-(amido)crowns and tetrathiacalix[4]arene amides with pendant amine function as described in this paper.

2.2. Characterization of products

It was observed that the reaction of **2** with 1,2-diamino-ethane and 1,3-diaminopropane resulted in the formation of products designated as **5a** and **5b**. Molecular mass determination and absence of free amino group in their spectra (IR and NMR) revealed that both **5a** and **5b** were cyclic (amido)crown compounds. The molecular ion peaks at

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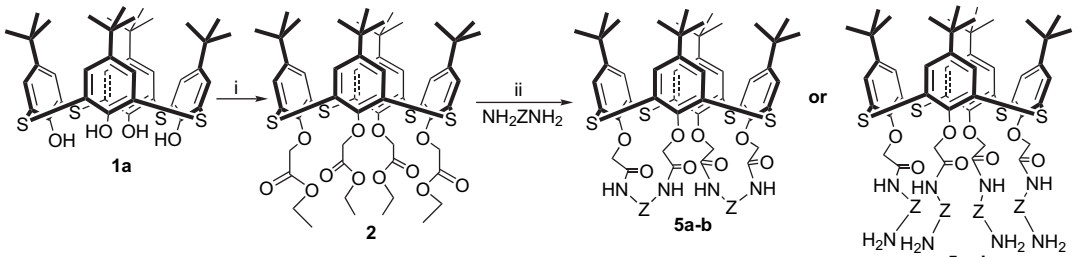
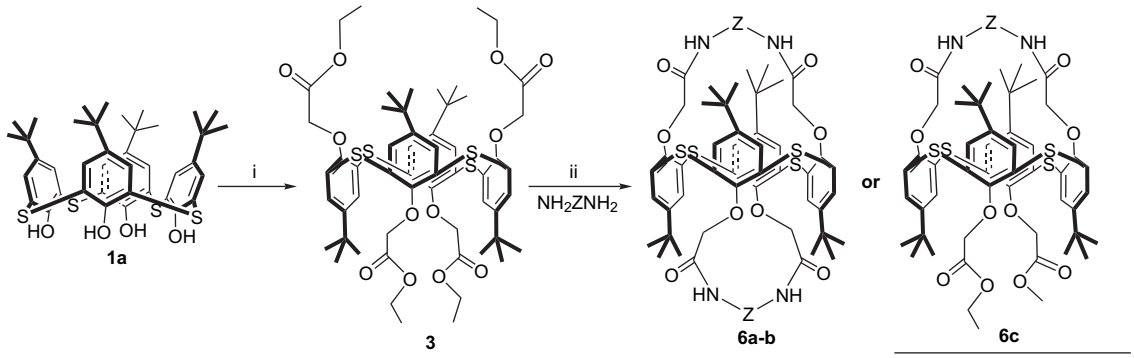


	Z
5a	CH_2CH_2
5b	$CH_2CH_2CH_2$

	Z
5c	$CH_2CH_2CH_2CH_2$
5d	$CH_2CH_2CH_2CH_2CH_2CH_2$

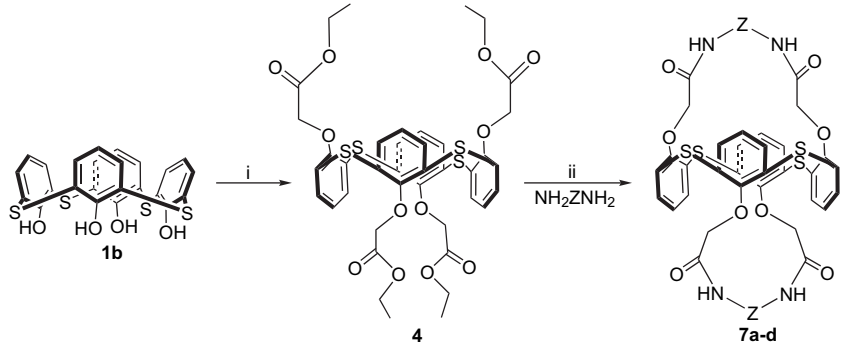
Scheme 1. (i) $Na_2CO_3/BrCH_2COOC_2H_5$, acetone; (ii) toluene/methanol (1:1).



	Z
6a	$-CH_2CH_2-$
6b	$-CH_2CH_2CH_2-$

	Z
6c	$-CH_2CH_2CH_2CH_2-$

Scheme 2. (i) $Cs_2CO_3/BrCH_2COOC_2H_5$, acetone; (ii) THF/methanol (1:1).



	Z
7a	$-CH_2CH_2-$
7b	$-CH_2CH_2CH_2-$
7c	$-CH_2CH_2CH_2CH_2-$
7d	$-CH_2CH_2NHCH_2CH_2-$

Scheme 3. (i) $Cs_2CO_3/BrCH_2COOC_2H_5$, acetone; (ii) toluene/methanol (1:1).

1001 [M^+] and 1029 [M^+] for **5a** and **5b**, respectively, in the FABMS spectrum confirmed the formation of tetrathiacalix[4]arene bis(amido)crowns. Since the formation of tetrathiacalix[4]arene(amido)crowns could in principle encompass the ester functionalities at either the proximal positions (a,b and c,d) or the distal positions (a,c and b,d) (Fig. 1), the issue was resolved by NMR experiments. For instance, the ^{1}H NMR spectrum of **5a** exhibited a pair of doublets for the ArOCH_2 protons at δ 3.97 and 5.09 to reveal the non-equivalence of the geminal protons attached to the phenolic function of tetrathiacalix[4]arene. A similar pattern

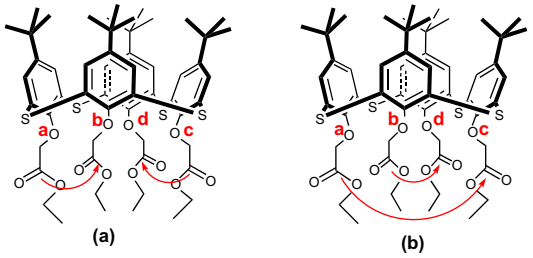


Figure 1. Possibility of (amido)crown formation by utilizing ester groups at (a) a, b and c, d and (b) a, b and c, d.

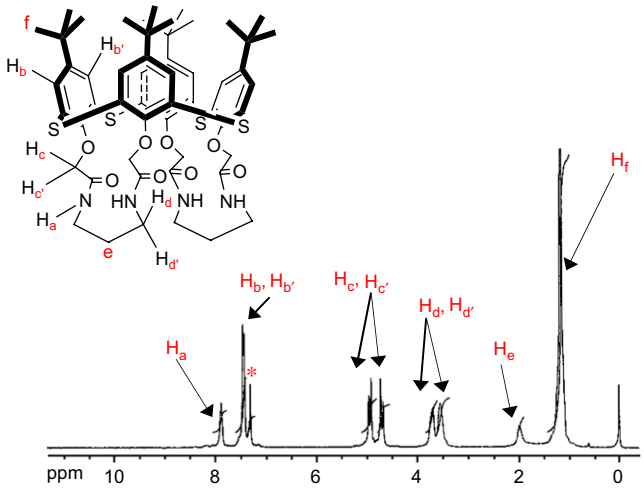


Figure 2. ^{1}H NMR spectrum of **5b**.

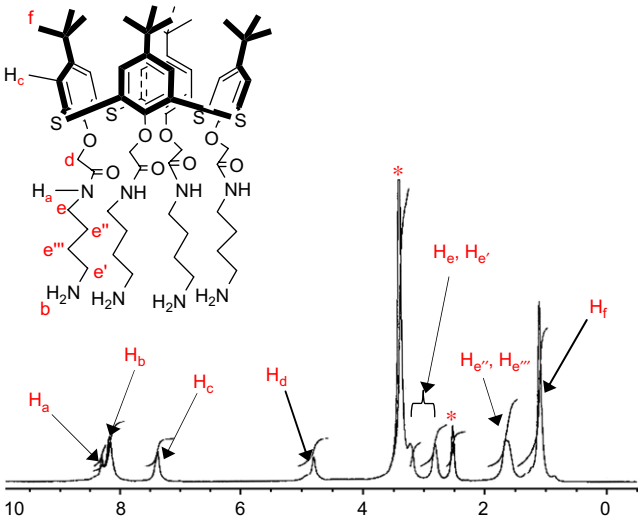


Figure 3. ^{1}H NMR spectrum of **5c**.

for ArOCH_2 protons was observed for **5b** with a pair of doublets at δ 4.69 and 4.93 (Fig. 2). It was evident that the ArOCH_2 protons would be non-equivalent only if the tetrathiacalix[4]arene(amido)crown formation takes place by condensation with the ester groups present at proximal positions. In the event that the tetrathiacalix[4]arene(amido)crown formation had involved the distal groups, the ArOCH_2 protons would appear as a singlet due to magnetic equivalence.

The appearance of one signal for the *tert*-butyl groups and two singlets in the aromatic region at 7.29 and 7.32 ppm in the case of **5a** and at 7.38 and 7.40 ppm for **5b** suggested that the synthesized compounds might possibly exist as proximally substituted cyclic amides with a cone or 1,2-alternate conformation of the tetrathiacalixarene core. The possibility of a 1,2-alternate conformation of tetrathiacalix[4]arene was excluded with the help of a NOESY spectrum. No correlation was found between the *tert*-butyl groups and the amide function. When **2** was reacted with higher diamines (1,4-diaminobutane and 1,6-diaminohexane), it gave new compounds **5c** and **5d**. The ^{1}H NMR spectrum of **5c** (Fig. 3) revealed the appearance of a broad singlet for the ArOCH_2 protons at 4.79 ppm along with singlets at δ 7.36, 8.16, and 8.29 as depicted in Figure 3. The broad singlets at δ 8.16 and 8.29 exchanged with deuterium when shaken with D_2O. This indicated the presence of two types of NH protons, which could be attributed to the –$CH_2CH_2CH_2CH_2NH_2$ and ArOCH_2-CON*H*CH_2 protons, respectively. Thus, **5c** could be identified as tetrathiacalix[4]arene amide with pendant amine functions. This was further supported by the [M^+] peak at 1233 observed in its FABMS spectrum. Compound **5d** also revealed similar ^{1}H NMR and mass spectral patterns.

When tetraester **3** was subjected to aminolysis with diamines containing varying spacer lengths, it yielded a series of compounds **6a–c**. The products **6a** and **6b** exhibited rather simple ^{1}H NMR spectra with one singlet each for the ArOCH_2, the aromatic, and the *tert*-butyl protons (Fig. 4). This could be attributed to the highly symmetric nature of the tetrathiacalix[4]arene bis(amido)crown compounds. The 1,3-alternate conformation of **6a** was unequivocally proved by its single crystal X-ray diffraction analysis (see Section 2.3).

The ^{1}H NMR spectrum of **6c** exhibited a deuterium exchangeable broad triplet for the ArOCH_2CON*H*CH_2 protons at δ 5.83, which integrated for two protons suggesting the formation of two amide linkages. Absence of signals for

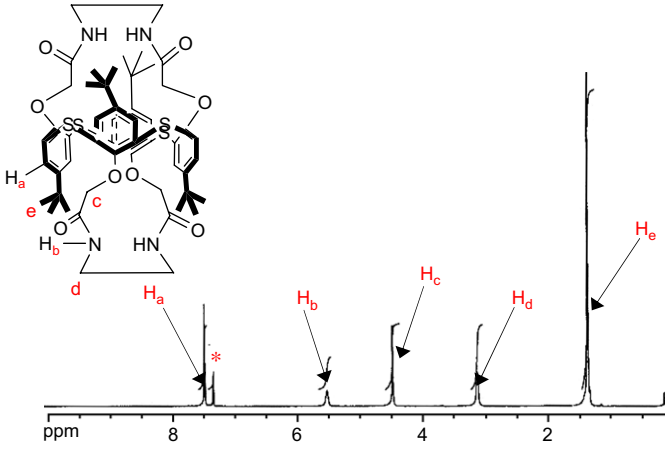


Figure 4. ^{1}H NMR spectrum of **6a**.

the –NH_2 protons suggested the possibility of formation of tetrathiacalix[4]arene mono(amido)crown derivative. Two broad signals at δ 3.19 and 1.09 for the CONHCH_2CH$_2$ and the CONHCH$_2$CH_2 protons, respectively, indicated the formation of tetrathiacalix[4]arene mono(amido)crown with the possibility of two uncondensed ester groups in **6c**. A quartet at δ 4.11 for the OCH_2CH$_3$ protons integrating for two protons and a triplet for three protons at δ 1.19 for the OCH$_2$CH_3 protons suggested the presence of only one ethyl ester group. However, a singlet at δ 3.65 integrating for three protons in its ^{1}H NMR spectrum and a signal at δ 51 for OCH_3 carbon in DEPT-135 spectrum suggested that one methyl ester function was present in **6c**. This was confirmed by the appearance of three signals for the ArOCH_2 protons at δ 4.45, 4.43, and 4.39 in the ratio of 2:1:1 in the ^{1}H NMR spectrum of **6c** (Fig. 5).

Though the products obtained in the reaction of **3** with 1,6-diaminohexane and diethylene triamine could not be fully characterized due to their insolubility in common solvents, it could be inferred on the basis of solubility characteristics and R_f values that bis(amido)crowns were not present in the reaction mixture.

When the debutylated tetraester **4** was subjected to aminolysis with diamines with varying spacer lengths, it yielded a series of compounds **7a**–**d**. All these compounds exhibited a rather simple pattern of ^{1}H NMR spectra with one doublet and one triplet for the aromatic protons and one singlet for the ArOCH_2 protons (Fig. 6), suggesting a highly symmetric nature for **7a**–**d**. A deuterium exchangeable broad triplet integrating for four N*H* protons suggested the presence of four amide linkages in the tetrathiacalix[4]arene core. Absence of signals for the NH_2 protons, the proton integration for the methylene groups present in the corresponding spacer chain as well as FAB mass spectrometric analysis confirmed that the compounds in hand were tetrathiacalix[4]arene bis(amido)crowns.

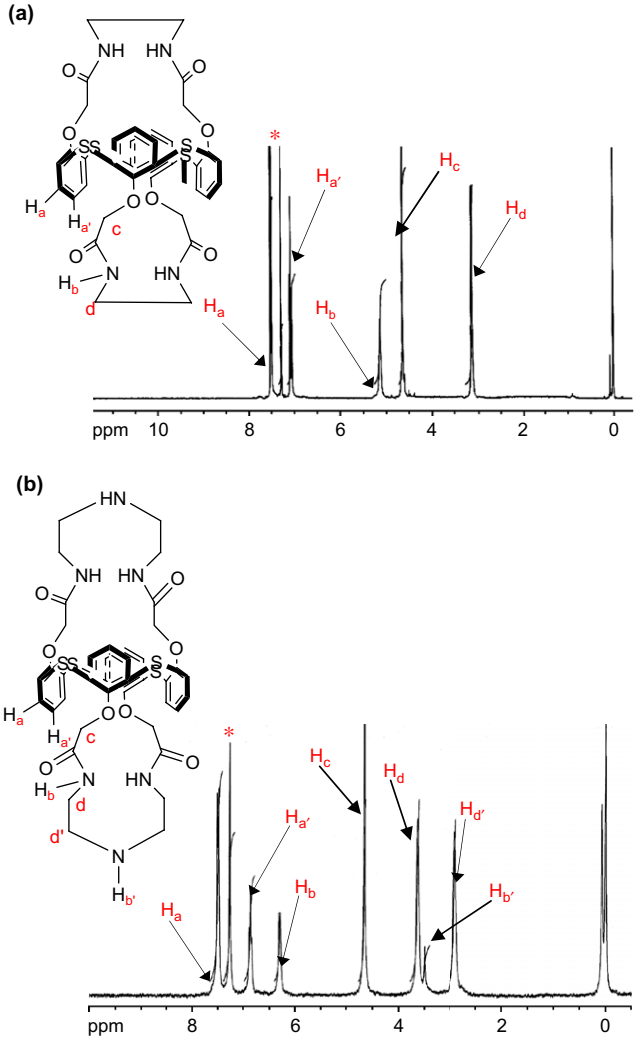


Figure 6. ^{1}H NMR spectra of (a) **7a** and (b) **7e**. * Indicates residual solvent peak or water peak.

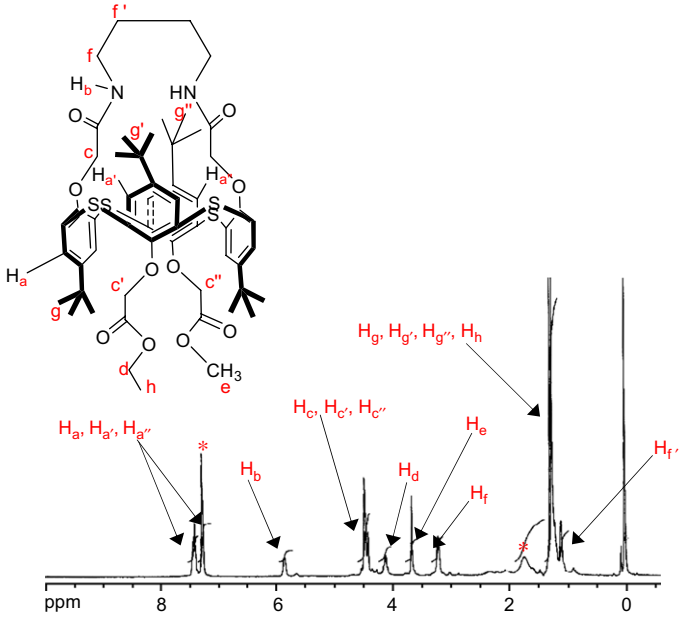


Figure 5. ^{1}H NMR spectrum of **6c**.

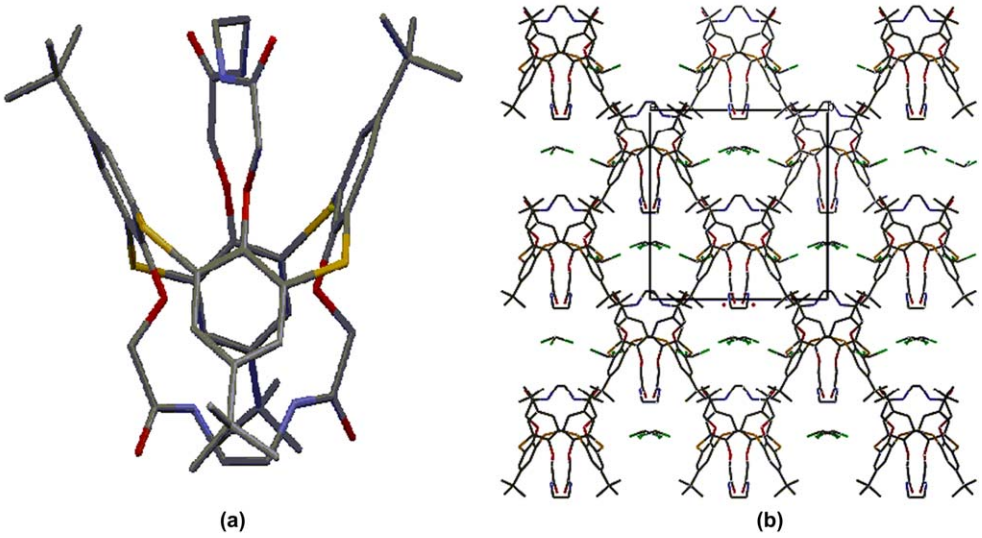


Figure 7. (a) X-ray structure of **6a** and (b) crystal packing of **6a** along *a* axis showing unit cell having four tetrathiacalix[4]arene molecules (hydrogen atoms have been omitted for clarity).

2.3. X-ray crystallographic analysis of 6a

A definitive proof for the geometry of **6a** was obtained by single crystal X-ray analysis (Fig. 7a). Colorless crystals of **6a** with space group I-4 were obtained by slow evaporation of a chloroform solution. The torsion angles at the sulfur bridges revealed a sequence of ++, −−, ++, −− that is consistent with the 1,3-alternate conformation found in calix[4]arene[13] and tetrathiacalix[4]arene derivatives.[14] The average distances between two adjacent and two opposite sulfur atoms are 5.58 and 7.76 Å, respectively, while the typical distances between the corresponding CH_2 groups in 1,3-alternate calix[4]arene are 5.0 and 7.1 Å. This indicated that the cavity of tetra-*tert*-butyl tetrathiacalix[4]arenes is bigger than the classical tetra-*tert*-butylcalix[4]arenes. The unit cell of **6a** consists of four thiacalix[4]arene molecules, eight chloroform, and eight water molecules (Fig. 7b). The distance of the two distal rings ranges from 5.28 Å (lower rim) to 7.94 Å (upper rim) with an inclination angle of around 54°. All the four amido chains have their carbonyl groups *exo* with respect to the thiacalix[4]arene cavity. The hydrogen of the amide group is *endo* to the thiacalix[4]arene cavity and is not involved in intra or intermolecular hydrogen bonding. Each chloroform molecule is intermolecularly hydrogen bonded to the bridging sulfur atom of one thiacalix[4]arene molecule and the carbonyl oxygen of the other thiacalix[4]-arene molecule. These intermolecular interactions between tetrathiacalix[4]arene and chloroform molecules lead to the formation of supramolecular aggregates with large cavities as depicted in Figure 7b.

2.4. Discussion

It has been observed that the reaction of **2** with ethylene and propylene diamines proceeds smoothly to result in the formation of proximally bridged tetrathiacalix[4]arene(amido)-crowns, **5a** and **5b**. When the reaction is carried out with 1,4-diaminobutane, it does not provide proximally bridged (amido)crown compounds as expected but instead provides a tetrathiacalix[4]arene amide with pendant primary amine functionality. This implies that the length of the alkyl chain of the condensing diamines plays an important role in their reaction with tetrathiacalix[4]arene esters. Accordingly, the reaction when carried out with a diamine with a larger spacer unit (e.g., 1,6-diaminohexane) gives the 5,11,17,23-tetra-*tert*-butyl-25,26,27,28-tetrakis[((*N*-6-aminohexyl)aminocarbonyl)-methoxy]tetrathiacalix[4]arene in appreciable yields.

It is known that tetrathiacalix[4]arene tetraesters in their 1,3-alternate conformation[1] possess larger annuli (i.e., a greater distance between the distal ester moieties) than their cone counterparts. They are therefore expected to require larger diamino components to curtail mobility as compared to the cone conformers and should therefore yield different results on their condensation with diamines of varying spacer lengths. Thus, the 1,3-alternate conformation of *p-tert*-butyl thiacalix[4]arene tetraethylester **3** when reacted with 1,2-diaminoethane and 1,3-diaminopropane, yields bis(amido)-crowns in good yields. However, the reaction with 1,4-diaminobutane, even when refluxing is continued for seven days, provides a mixture, which on purification by column chromatography gives *p-tert*-butyl tetrathiacalix[4]arene mono(amido)crown (**6c**) with two unreacted ester moieties.

The formation of **6c** is interesting in this reaction as it indicates that there is a competition between the solvent and the diamines used. The basic diamine promotes the methanolysis of one of the ester functions in tetra-*tert*-butyl tetrathiacalix[4]arene to yield **6c**. This point is currently being investigated in our laboratories. This presumably leads to a change in the 1,3-alternate conformation in such a way that further reaction is hindered.

The aminolysis reaction of the debutylated analog of tetrathiacalix[4]arene, **4**, with 1,2-diaminoethane and 1,3-diaminopropane yielded the tetrathiacalix[4]arene bis-(amido)crowns in good yields (81–85%) while its reaction with 1,4-diaminobutane and diethylene triamine gave tetrathiacalix[4]arene bis(amido)crowns in low yields (8–15%). The better yields of the cyclized tetrathiacalix[4]arene 1,3-bis(amido)crowns (**7a**, **7b**) in comparison to their *p-tert*-butyl tetrathiacalix[4]arene analogs could be attributed to

steric crowding due to the neighboring *tert*-butyl groups and the aromatic rings in the latter series of compounds. It has been observed that the absence of *p*-*tert*-butyl groups in the tetrathiacalix[4]arenes allows them to enjoy greater conformational mobility to react with larger diamines to provide tetrathiacalix[4]arene bis(amido) crowns even with 1,4-diaminobutane and diethylene triamine (**7c**, **7e**) but the same has not been observed in the case of *p*-*tert*-butyl tetrathiacalix[4]arene esters.

It is worth mentioning that Lhotak et al.[7] have recently synthesized bis(amido)crowns with ethylene, propylene, and butylene spacer groups under different reaction conditions (refluxing in ethanol, 16 h) in 36, 19, and 9% yields, respectively, as against our conditions, which involve refluxing of reactants in a mixture of toluene and methanol for 24 h, which gave significantly different results. In our experiments, toluene was used to solubilize **2** and **4** while methanol under basic conditions leads to trans esterification of ethyl ester group to provide a more reactive methyl ester, which apparently facilitates the aminolysis reaction to allow isolation of tetrathiacalix[4]arene bis(amido)crown compounds **5a** and **5b** in 71 and 69% yields, respectively. Tetrathiacalix[4]arene bis(amido)crowns with a butylene spacer group could not be obtained under these conditions, which allowed the isolation of 5,11,17,23-tetra-*tert*-butyl-25,26,27,28-tetrakis[((*N*-4-aminobutyl)aminocarbonyl)-methoxy]tetrathiacalix[4]arene (**5c**) in 83% yield. Since **3** was not completely soluble in toluene/methanol, an alternative solvent system (THF/methanol) was used in this case.

It has been observed that the alkyl spacer group of the diamine plays a greater role in the aminolysis reaction of tetrathiacalix[4]arene tetraesters as compared to that of their calix[4]arene analogs, which provide the proximally bridged calix[4]arene amidocrown compounds even with larger spacer units (1,4-diaminobutane, diethylene triamine, and triethylene tetramine). The aminolysis reaction of the cone conformers of tetrathiacalix[4]arene esters with higher diamines (1,4-diaminobutane and 1,6-diaminohexane) gave tetrakis[(alkyl)aminocarbonyl-methoxy]tetrathiacalix[4]-arene amides with pendant amine functionality. The 1,3-alternate conformer of tetrathiacalix[4]arene tetraethylacetate, however, gave tetrathiacalix[4]arene bis(amido)crown derivatives in their 1,3-alternate conformation to pave the way for obtaining molecular capsules.

In conclusion, a new strategy has enabled the synthesis of conformationally diverse tetrathiacalix[4]arene(amido)-crown compounds of different sizes. These could serve as building blocks for the synthesis of larger and more sophisticated molecular assemblies and molecular capsules of tetrathiacalix[4]arene(amido)crowns in the 1,3-alternate conformation thereby opening up a new dimension to tetrathiacalix[4]arene(amido)crown chemistry.

3. Experimental

3.1. General

All the reagents used in the study were purchased from Sigma–Aldrich or Merck and were considered chemically pure to be used without further purification. The solvents used were distilled. Melting points were recorded on an electric melting point apparatus (Toshniwal, India) and are uncorrected. IR spectra were recorded on a Nicolet Protégé 460 spectrometer in KBr discs while CHN analyses were obtained by using a Perkin–Elmer 240C elemental analyzer. ^{1}H NMR spectra were recorded on a 300 MHz Bruker DPX 300 instrument at room temperature using tetramethylsilane (TMS) as an internal standard. The FAB mass spectra were recorded on a JEOL SX 102/DA-6000 Mass spectrometer/Data System using Argon/Xenon (6 kV, 10 mA) as the FAB gas.

3.2. Preparation of the starting materials

p-*tert*-Butyl tetrathiacalix[4]arene[8] (**1a**) and tetrathiacalix[4]arene[9] (**1b**) were synthesized by methods reported earlier. The tetra acetates **2**, **3**, and **4** were synthesized by the method[10] reported in the literature, which involved the use of ethylbromoacetate and acetone/M_2CO_3 system (M=Na and Cs) for effecting the condensation reactions.

3.3. General procedure for the synthesis of tetrathiacalix[4]arene amides

A mixture of tetrathiacalix[4]arene tetraethylacetate (0.5 g, 0.493 mmol) and diamine (9.86 mmol) was refluxed in toluene/methanol (1:1) (30 mL) or THF/methanol (1:1) (30 mL). After removing the solvents, the crude mixture was precipitated with methanol to provide compounds, which were purified either by crystallization from appropriate solvents or by column chromatography.

3.3.1. (a,b;c,d)-5,11,17,23-Tetra-*tert*-butyl tetrathiacalix[4]arene(ethyleneamido)biscrown, 5a. White solid recrystallized from $CHCl_3$/MeOH (0.35 g, 71%), mp 240 °C (dec). IR (KBr, ν/cm^{-1}): 3335, 1677. Anal. Calcd for $C_{52}H_{64}N_4O_8S_4$: C, 62.37; H, 6.44; N, 5.60. Found: C, 62.48; H, 6.40; N, 5.58. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.34 (br s, 4H, CON*H*), 7.32 (s, 4H, Ar*H*), 7.29 (s, 4H, Ar*H*), 5.09 (d, J=13.8 Hz, 4H, ArOCH_2), 3.97 (d, J=13.8 Hz, 4H, ArOCH_2), 3.63 (br s, 4H, CONHCH_2), 3.51 (br s, 4H, CONHCH_2), 1.05 (s, 36H, C(CH_3)$_3$), FABMS: calcd for $C_{52}H_{64}N_4O_8S_4$: m/z=1001.35 [M$^+$]; found: m/z=1001 [M$^+$, 100%].

3.3.2. (a,b;c,d)-5,11,17,23-Tetra-*tert*-butyl tetrathiacalix[4]arene(propyleneamido)biscrown, 5b. White solid recrystallized from $CHCl_3$/MeOH (0.35 g, 69%), mp 266 °C (dec). IR (KBr, ν/cm^{-1}): 3334, 1676. Anal. Calcd for $C_{54}H_{68}N_4O_8S_4$: C, 63.01; H, 6.66; N, 5.44. Found: C, 62.91; H, 6.72; N, 5.48. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.84 (br s, 4H, CON*H*), 7.40 (s, 4H, Ar*H*), 7.38 (s, 4H, Ar*H*), 4.93 (d, J=14.6 Hz, 4H, ArOCH_2), 4.69 (d, J=14.6 Hz, 4H, ArOCH_2), 3.67 (br s, 4H, CONHCH_2), 3.52 (br s, 4H, CONHCH_2), 1.96 (m, 4H, CONHCH$_2$CH_2), 1.12 (s, 36H, C(CH_3)$_3$), FABMS: calcd for $C_{54}H_{68}N_4O_8S_4$: m/z=1029.40 [M$^+$]; found: m/z=1029 [M$^+$, 100%].

3.3.3. 5,11,17,23-Tetra-*tert*-butyl-25,26,27,28-tetrakis[((*N*-4-aminobutyl)aminocarbonyl)-methoxy]tetrathiacalix[4]arene, 5c. White solid recrystallized from MeOH/H_2O (0.51 g, 83%), mp 268 °C. IR (KBr, ν/cm^{-1}): 3414,

1676. Anal. Calcd for $C_{64}H_{96}N_8O_8S_4$: C, 62.30; H, 7.84; N, 9.08. Found: C, 62.42; H, 7.76; N, 9.10. ^{1}H NMR (300 MHz, DMSO-d_6[†]) δ_H 8.29 (br s, 4H, CON*H*), 8.16 (br s, 8H, CH_2NH_2), 7.36 (s, 8H, Ar*H*), 4.79 (s, 8H, ArOCH_2), 3.21 (m, 8H, CONHCH_2), 2.80 (m, 8H, CH_2NH_2), 1.64 (m, 16H, NHCH_2CH_2CH_2), 1.08 (s, 36H, C(CH_3)$_3$), FABMS: calcd for $C_{64}H_{96}N_8O_8S_4$: *m*/*z*=1233.76 [M$^+$]; found: *m*/*z*=1233 [M$^+$, 100%].

3.3.4. 5,11,17,23-Tetra-*tert*-butyl-25,26,27,28-tetrakis [((*N*-6-aminohexyl)aminocarbonyl)-methoxy]tetrathiacalix[4]arene, 5d. White solid recrystallized from MeOH/H_2O (0.53 g, 81%), mp 130 °C. IR (KBr, ν/cm^{-1}): 3339, 1642. Anal. Calcd for $C_{72}H_{112}N_8O_8S_4$: C, 64.25; H, 8.39; N, 8.33. Found: C, 64.36; H, 8.36; N, 8.38. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.34 (s, 8H, Ar*H*), 5.83 (br s, 4H, CON*H*), 5.30 (br s, 8H, CH_2NH_2), 4.82 (s, 8H, ArOCH_2), 3.36 (br s, 8H, CONHCH_2), 2.69 (br s, 8H, CH_2NH_2), 1.60–1.33 (m, 32H, NHCH_2(CH_2)$_4$), 1.11 (s, 36H, C(CH_3)$_3$), FABMS: calcd for $C_{72}H_{112}N_8O_8S_4$: *m*/*z*=1345.97 [M$^+$]; found: *m*/*z*=1346 [M$^+$, 100%].

3.3.5. (a,c;b,d)-5,11,17,23-Tetra-*tert*-butyl tetrathiacalix[4]arene(ethyleneamido)biscrown, 6a. White solid recrystallized from $CHCl_3$/MeOH (0.32 g, 65%), mp 297 °C (dec). IR (KBr, ν/cm^{-1}): 3410, 1688. Anal. Calcd for $C_{52}H_{64}N_4O_8S_4$: C, 62.37; H, 6.44; N, 5.61. Found: C, 62.26; H, 6.52; N, 5.58. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.40 (s, 8H, Ar*H*), 5.44 (br s, 4H, CON*H*), 4.40 (s, 8H, ArOCH_2), 3.05 (br s, 8H, CONHCH_2), 1.28 (s, 36H, C(CH_3)$_3$), FABMS: calcd for $C_{52}H_{64}N_4O_8S_4$: *m*/*z*=1001.35 [M$^+$]; found: *m*/*z*=1001 [M$^+$, 100%].

3.3.6. (a,c;b,d)-5,11,17,23-Tetra-*tert*-butyl tetrathiacalix[4]arene (propyleneamido)biscrown, 6b. White solid recrystallized from $CHCl_3$/MeOH (0.30 g, 61%), mp 307 °C (dec). IR (KBr, ν/cm^{-1}): 3415, 1685. Anal. Calcd for $C_{54}H_{68}N_4O_8S_4$: C, 63.01; H, 6.66; N, 5.44. Found: C, 63.09; H, 6.69; N, 5.51. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.39 (s, 8H, Ar*H*), 5.46 (s, 4H, CON*H*), 4.33 (s, 8H, ArOCH_2), 3.11 (br s, 8H, CONHCH_2), 1.66 (br s, 4H, CONHCH$_2$CH_2), 1.28 (s, 36H, C(CH_3)$_3$), FABMS: calcd for $C_{54}H_{68}N_4O_8S_4$: *m*/*z*=1029.40 [M$^+$]; found: *m*/*z*=1029 [M$^+$, 100%].

3.3.7. (a,c)-5,11,17,23-Tetra-*tert*-butyl tetrathiacalix[4]-arene(butyleneamido)monocrown, 6c. White solid purified by column chromatography (9.6:0.4 chloroform/ethyl actetate, R_f=0.46) (0.17 g, 33%), mp 210 °C (dec). IR (KBr, ν/cm^{-1}): 3403, 1769, 1737, 1682. Anal. Calcd for $C_{55}H_{70}N_2O_{10}S_4$: C, 63.07; H, 6.74; N, 2.67. Found: C, 63.19; H, 6.78; N, 2.61. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.41 (d, *J*=5.2 Hz, 2H, Ar*H*), 7.39 (d, *J*=5.8 Hz, 2H, Ar*H*), 7.25 (s, 4H, Ar*H*), 5.83 (s, 2H, CON*H*), 4.45 (s, 4H, ArOCH_2), 4.44 (s, 2H, ArOCH_2), 4.39 (s, 2H, ArOCH_2), 4.11 (q, *J*=21.2 Hz, 2H, OCH_2CH$_3$), 3.65 (s, 3H, OCH_3), 3.19 (br s, 4H, NHCH_2CH$_2$), 1.24 (s, 36H, C(CH_3)$_3$), 1.19 (t, *J*=13.9 Hz, 3H, OCH$_2$CH_3), 1.09 (br s, 4H, CONHCH$_2$CH_2). DEPT-135 (75 MHz, $CDCl_3$) δ 131.2, 130.9, 125.5 (aromatic *C*H), 69.2, 64.8, 64.4, 64.2 (Ar-OCH_2 & –CO(O)CH_2CH$_3$), 51.2 (–OCH_3), 37.1 (–CONHCH_2), 31.1, 30.8 (Ar-C-CH_3), 25.8 (–CONHCH$_2$CH_2), 14.1 (–CO(O)CH$_2$CH_3), FABMS: calcd for $C_{55}H_{70}N_2O_{10}S_4$: *m*/*z*=1047.41 [M$^+$]; found: *m*/*z*=1047 [M$^+$, 100%].

3.3.8. (a,c;b,d)-Tetrathiacalix[4]arene(ethyleneamido)-biscrown, 7a. White solid recrystallized from $CHCl_3$/MeOH (0.393 g, 85%), mp 307 °C (dec). IR (KBr, ν/cm^{-1}): 3414, 1686. Anal. Calcd for $C_{36}H_{32}N_4O_8S_4$: C, 55.65; H, 4.15; N, 7.21. Found: C, 55.59; H, 4.09; N, 7.26. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.49 (d, *J*=7.7 Hz, 8H, Ar*H*), 7.07 (t, *J*=15.5 Hz, 4H, Ar*H*), 5.11 (s, 4H, CON*H*), 4.65 (s, 8H, ArOCH_2), 3.12 (s, 8H, CONHCH_2), FABMS: calcd for $C_{36}H_{32}N_4O_8S_4$: *m*/*z*=776.92 [M$^+$]; found: *m*/*z*=777 [M$^+$, 100%].

3.3.9. (a,c;b,d)-Tetrathiacalix[4]arene(propyleneamido)-biscrown, 7b. White solid recrystallized from $CHCl_3$/MeOH (0.388 g, 81%), mp 308 °C (dec). IR (KBr, ν/cm^{-1}): 3415, 1688. Anal. Calcd for $C_{38}H_{36}N_4O_8S_4$: C, 56.70; H, 4.61; N, 6.96. Found: C, 56.58; H, 4.68; N, 6.91. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.47 (d, *J*=7.7 Hz, 8H, Ar*H*), 7.05 (t, *J*=15.4 Hz, 4H, Ar*H*), 5.09 (br s, 4H, CON*H*), 4.62 (s, 8H, ArOCH_2), 3.24 (m, 8H, CONHCH_2), 1.71 (br s, 4H, NHCH$_2$CH_2), FABMS: calcd for $C_{38}H_{36}N_4O_8S_4$: *m*/*z*=804.97 [M$^+$]; found: *m*/*z*=805 [M$^+$, 95%].

3.3.10. (a,c;b,d)-Tetrathiacalix[4]arene(butyleneamido)-biscrown, 7c. White solid recrystallized from $CHCl_3$/MeOH (0.039 g, 8%), mp 310 °C (dec). IR (KBr, ν/cm^{-1}): 3418, 1686. Anal. Calcd for $C_{41}H_{42}N_4O_7S_4$: C, 59.25; H, 5.09; N, 6.74. Found: C, 59.38; H, 5.11; N, 6.79. ^{1}H NMR (300 MHz, DMSO-d_6[†]) δ_H 7.48 (d, *J*=7.7 Hz, 8H, Ar*H*), 7.04 (t, *J*=15.4 Hz, 4H, Ar*H*), 5.04 (s, 4H, CON*H*), 4.60 (s, 8H, ArOCH_2), 3.24 (m, 8H, CONHCH_2), 1.71 (br s, 4H, NHCH$_2$CH_2), FABMS: calcd for $C_{41}H_{42}N_4O_7S_4$: *m*/*z*=831.05 [M$^+$]; found: *m*/*z*=831 [M$^+$, 95%].

3.3.11. (a,c;b,d)-Tetrathiacalix[4]arene(diethylenetriaminoamido)biscrown, 7d. White solid recrystallized from $CHCl_3$/MeOH (0.077 g, 15%), mp 315 °C (dec). IR (KBr, ν/cm^{-1}): 3409, 3272, 1657. Anal. Calcd for $C_{40}H_{42}N_6O_8S_4$: C, 53.58; H, 4.25; N, 10.41. Found: C, 53.42; H, 4.36; N, 10.28. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.50 (d, *J*=7.3 Hz, 8H, Ar*H*), 6.88 (t, *J*=14.7 Hz, 4H, Ar*H*), 6.29 (s, 4H, CON*H*), 4.64 (s, 8H, ArOCH_2), 3.62 (br s, 8H, CONHCH_2CH$_2$), 3.49 (br s, 2H, CH$_2$N*H*CH$_2$), 2.89 (br s, 8H, CONHCH$_2$CH_2), FABMS: calcd for $C_{40}H_{42}N_6O_8S_4$: *m*/*z*=863.06 [M$^+$]; found: *m*/*z*=863 [M$^+$, 100%].

3.4. X-ray crystallography

Crystals suitable for single crystal X-ray diffraction were obtained by slow cooling of a warm solution of **6a**, in chloroform, having molecular formula $C_{56}H_{64}Cl_{12}N_4O_{12}S_4$, M=1538.75, tetragonal, space group I-4 with *a*=15.251(3), *b*=15.251(3), *c*=16.342(4), α=90.0, β=90.0, γ=90.0°, and D_c=1.344 g/cm^3 for *Z*=2. Intensity diffraction data were calculated up to θ=20.50° by using 2ω step scanning mode with Mo K$_\alpha$ radiation (λ=0.71073 Å) at 298 K. A total of 3343 reflections were calculated and used in structure analysis and refinement. All the non-hydrogen atoms were

[†] **5c** and **7c** were not completely soluble even in DMSO-d_6, hence they were solubilized by heating with NaCl.

refined anisotropically using restraints on the bond lengths and thermal parameters. All hydrogen atoms were placed in their geometrical positions and were not refined. Using observed data and refinement of 203 parameters with no restraints, the final R index was R_{all}=0.0924, R_{gt}=0.0824, wR_{ref}=0.2384, and wR_{gt}=0.2254. All calculations and structure solution was accomplished by using SHELXTL-PC VERSION of software. Crystallographic data for the structure have been deposited with Cambridge Crystallographic Database as supplementary publication number CCDC (295846).

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