Synthesis and structural chemistry of bicyclic hexaaza-dithia macrocycles containing pendant donor groups†

Mathias Gressenbuch, Ulrike Lehmann and Berthold Kersting*

A short and efficient synthesis of a series of macrobicyclic aza-thioethers with pendant allyl (8, 13, 14), cyanethyl (15), 3-aminopropyl (16), 2-methoxycarbonyl (17, 19), 2-methoxyethyl (18, 20), and tert-butylcarbonyl substituents (22, 23) has been achieved. The parent macrobicycles 1 and 2 are readily alkylated without overalkylation and without affecting the masked thiolate functions. The protocol is also feasible for the synthesis of macrobicycles with different alkyl groups on the benzyl and central nitrogen atoms of the linking diethylene triamine units. The identity of the compounds was substantiated using ESI MS, FT-IR, 1H-NMR, and 13C-NMR spectroscopy. The crystal and molecular structures of six compounds (8, 15, 17 3DMSO, 19 2DMSO-2H2O, 20 and 23) were additionally solved. The macrocycles are rather flexible and can adopt folded or stepped conformations. The ability of the compounds to form inclusion complexes with DMSO is also demonstrated. The crystal structures are governed by extensive inter- and intramolecular CH⋯π interactions.

Introduction

The synthesis of macrocyclic ligands with pendant donor arms is highly desirable in view of a range of potential applications such as catalysis, selective cation binding, biomimetic chemistry, and radionuclide therapy.1–5 Thus, the chemistry of aliphatic polyaza-macrocycles has been well investigated as has the chemistry of their corresponding thia analogs. Many monocyclic macrocycles with side arms terminated with N, O, S, or P donor groups have been prepared and their coordination chemistry investigated.6–7 Surprisingly, the chemistry of multidentate macrocycles with mixed N and S donor functions has received much less attention.8–10 This is true in particular for the families of amine-thioether ligands containing aromatic thioether groups.11–13 An early example is the 14-membered aromatic N8S2 macrocycle, which was described by Lindoy and co-workers.14,15 Until now only few more ligands of this sort have been reported in the literature.16–23

Our group has reported the synthesis of the macrobicyclic azathioethers 124 and 225 and of some alkylated derivatives 3–5 (Fig. 1).26,27 More recently, we have reported the first examples of bicyclic aminothioethers bearing pendant hydroxyethyl groups (6, 7).28 The structures of the free macrocycles 3,29 4,25 5,27 and 630 have been determined. The macrocycles adopt a folded conformation in which the two aryl rings and the alkyl residues forming a cavity. However, none of these structures are clathrate, nor inclusion, complexes. As part of this program, we sought to extend our exploration to other variants of this versatile ligand system. To our knowledge, there are no systematic investigations on such hexaaza-thioether macrocycles. We have obtained a series of new macrobicyclic compounds bearing olefinic, nitrile, amine, and methoxy groups in place of the alkyl functions. Herein, we describe their synthesis and solid state structures. The effect of the pendant groups on the structural features is discussed, and compared with those of the parent ligand systems 1–3.

---

† Electronic supplementary information (ESI) available: 1H, 13C, IR and MS spectra for new compounds. Crystallographic data in CIF format for 8, 15, 17 3DMSO, 19 2DMSO-2H2O, 20 and 23. CCDC 1436363–1436368. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c5nj03197d

Fig. 1 Formula of macrobicyclic aza-thioethers 1–7.
Experimental section

Materials and physical measurements

The bicyclicaza-thioethers 124 and 2,25 1,2-bis(4-tert-butyl-2,6-diformylthioethane) (10),24 bis[2-phthalimidoethyl]amine20 (11), and tert-butyl-bis[2-aminoethoxy]carbamate (21) were prepared according to literature. Melting points were determined with an Electrothermal IA9000 series instrument using open glass capillaries and are uncorrected. Mass spectra were obtained using the positive ion electrospray ionization modus (ESI) on a FT-ICR-MS Bruker Daltonics APEX II instrument. NMR spectra were recorded on a Bruker DRX-600, Bruker DRX-400 or Varian Mercury plus 400 spectrometer. Chemical shifts refer to solvent signals. The atom labels used to assign the NMR signals are not identical with those used in the X-ray structures. Elemental analyses were carried out with a VARIO EL– elemental analyzer.

Synthesis and analysis of compounds

The corresponding spectra for the IR, 1H-NMR, 13C-NMR are included in the ESI,† for each of the synthesized compounds. A summary of the obtained results are shown here.

Hexasubstitutedaza-thioether. 8. The thioether 1 (307 mg, 0.50 mmol) and allyl bromide (372 mg, 3.07 mmol) were dissolved in EtOH (3 mL). A solution of triethylamine (303 mg, 3.00 mmol) in EtOH (1 mL) was added dropwise and the mixture was allowed to stand for 2 weeks at 0 °C. The mixture was decanted off from the resulting HNEt3Br. Crystals of the title compound crystallized from the mother liquor upon standing in air. Yield: 392 mg (0.46 mmol, 92%), colorless solid. M.p. 85.39 (ArCH2NCH2Q = 31.60 (C(CH3)3), 2.60 (m, 16 H, NCH2CH2N), 2.74 (s, 4 H, SCH2), 2.97 (d, 8 H, CH2), 3.00 (d, 4 H, CH2), 5.82 (m, 6 H, CH=CH2), 7.50 (s, 4 H, ArH). 13C{1}H-NMR (100 MHz, CDCl3): δ = 31.60 (C(CH3)3), 34.98 (C(CH3)2), 38.52 (C(CH3)2), 50.89 [(NCH2CH2)N], 51.71 [(NCH2CH2)N], 56.88 [ArCH2NCH2CH2], 57.51 (ArCH2), 59.23 [(NCH2CH2)N], 116.99 (ArCH2NCH2CH=CH2), 117.46 [(NCH2CH2)N], 124.86 (Ar=O, 3), 128.18 (Ar=O, 3), 136.35 [ArCH2NCH2CH=CH2], 136.34 (CH=CH2), 143.71 (Ar=O), 151.40 (Ar=O). This compound was additionally characterized by X-ray crystallography.

N-Allyl-bis[2-phthalimidoethyl]-amine (12). A mixture of bis[2-phthalimidoethyl]-amine 11 (25.0 g, 68.8 mmol), K2CO3 (9.51 g, 68.8 mmol), and allyl bromide (11.6 g, 959 mmol) in 700 mL of THF was stirred for 30 min at room temperature and for 12 h at 50 °C. The resulting mixture was filtered, and concentrated in vacuum to one fourth of its original volume. The resulting crystals were collected and dried under vacuum. Yield: 15.5 g, 56%, mp 132 °C. Found: C 68.19, H 5.14, N 10.34; C22H23N3O2 (403.44) requires: C 68.47, H 5.25, N 10.42. IR (KBr): ν/cm−1 = 3461 w, 3091 w, 2985 w, 2925 m, 2855 m, 1769 s, 1711 vs, 1611 m, 1548 s, 1510 m, 1468 s, 1415 m, 1387 vs, 1332 m, 1306 m, 1276 w, 1191 w, 1160 w, 1142 w, 1091 m, 1018 s, 974 w, 874 w, 803 w, 773 vs, 726 w, 630 w, 613 w, 567 w, 532 w, 469 w. 1H-NMR (400 MHz, CDCl3): δ = 2.74 (t, J = 6.4 Hz, 4 H, NCH2CH2N), 3.15 (d, J = 6.4 Hz, 2 H, CH2CH2=CH2), 3.67 (t, J = 6.4 Hz, 4 H, NCH2CH2N), 4.98–5.08 (dd, 1 H, 3Q), 5.56–5.63 (m, 2 H, Ar=CH=CH2), 7.60–7.67 (m, 8 H, ArH).

11C[1H]-NMR (100 MHz, CDCl3): δ = 36.30 [(NCH2CH2)N], 51.90 [(NCH2CH2)N], 57.03 [(CH=CH2), 118.47 (CH=CH2), 123.59 (Ar=O, 3), 137.23 (Ar=O, 3), 139.86 (Ar=O, 3), 143.36 (CH=CH2), 168.74 (CO).

N-Allyl-bis[2-aminoethoxy]-amine trihydrochloride (13·3HCl). A suspension of N-allyl-bis[2-phthalimidoethyl]-amine (15.6 g, 38.7 mmol) was dissolved in 200 mL of concentrated HCl and refluxed for 2 days. The clear solution was cooled and filtered. The clear solution was concentrated in vacuum, to give a brown oil, which was washed with THF. The oil was separated and dried under vacuum to give a colorless, hygroscopic solid. The compound could not be obtained in analytically pure form but was found pure enough for the next step. Yield: 8.16 g (83%). IR (KBr): ν/cm−1 = 3415 w, 2963 vs, 2039 w, 1602 m, 1471 s, 1372 m, 1262 s, 1099 vs, 1019 vs, 959 s, 869 w, 801 s, 662 vv, 603 vv, 461 w. 1H-NMR (400 MHz, D2O): δ = 3.45 (m, J = 6.4 Hz, 4 H, H3NCH2), 3.52 (t, J = 6.4 Hz, 4 H, CH2(NH2)2N), 3.89 (d, J = 7.2 Hz, 2 H, NCH2CH=CH2), 5.67 (m, 1 H, CH=CH2), 5.93 (m, 2 H, CH2CH2). 13C{1}H-NMR (100 MHz,
D₂O): δ = 34.0 (H₂NCH₂), 49.6 ((CH₃)₂N), 56.3 (NCH₂), 124.8 (CH=), 128.2 (CH=CH₂).

N-Allyl-bis(2-aminothio)-amin (13). A suspension of N-allyl-bis(2-aminothio)-amine-trihydrochloride (9.76 g, 38.6 mmol) and KOC(CH₃)₂ (13.0 g, 116 mmol) in 50 mL of THF was stirred at 55 °C for 3 d and filtered. The THF was removed in vacuum to give an oil, which was purified by distillation in vacuum. Yield: 5.25 g (89%). The compound is hygroscopic and could not be obtained in analytically pure form. The compound was found pure enough for the next step. IR (KBr): ν/cm⁻¹ = 3405 vs, 3072 s, 2933 vs, 2360 m, 2343 m, 1572 vs, 1479 vs, 1384 m, 1309 s, 1147 w, 1090 w, 1038 w, 997 w, 920 m, 859 m, 679 s. 1H-NMR (400 MHz, CD₂OD): δ = 2.54 (t, 3J = 6.6 Hz, 4 H, H₂NCCH₂), 2.69 (t, 3J = 6.4 Hz, 2 H, NCH₂CH=CH₂), 5.17 (m, 1 H, CH=CH₂), 5.89 (m, 2 H, CH=CH₂).

13C{1H}-NMR (100 MHz, CD₂OD): δ = 38.57 (HC₃N), 55.96 ((CH₃)₂N), 116.70 (CH=CH₂), 135.27 (CH=CH₂).

Bisallylated aza-thioether 14. A solution of N-allyl-bis(2-aminothio)-amine 13 (702 mg, 4.61 mmol) in EtOH (150 mL, 3:1, v:v) and a solution of 1,2-bis(4-tert-butyl-2,6-dimethylphenyl)ethane 10 (1.08 g, 2.30 mmol) in CH₂Cl₂ (500 mL) were added simultaneously over the course of 3 h into a EtOH/CH₂Cl₂ (600 mL, 1:3 v:v) solution mixture. After the resulting mixture was stirred for further 2 d, the CH₂Cl₂ solvent was removed under reduced pressure. Sodium borohydride (690 mg, 18.24 mmol) was added and the mixture was stirred at r.t. for another 2 h. The excess reducing agent was destroyed by adding HCl cone (final pH = 1). The mixture was subsequently evaporated to dryness, re-dissolved in CH₂Cl₂/H₂O (100 mL, 1:1 v:v), and the pH was adjusted to ~13 with aqueous KOH (5 M). After stirring for 2 h, the layers were separated and the aqueous phase was extracted with dichloromethane (4 × 150 mL). The organic fractions were combined and dried with anhydrous K₂CO₃. Evaporation of the solvent gave a foam, which was recrystallized from EtOH to give 1.41 g (88%) of the title compound. Found: C 68.90, H 9.29, N 12.29, S 9.11; C₄₀H₇₀N₆S₂ (693.11) requires: C 69.32, H 9.31, N 12.13, S 9.25.

1H-NMR (300 MHz, CDCl₃): δ = 1.30 (s, 18 H, C(CH₃)₃), 2.81 (s, 4 H, SCH₂), 2.96 (m, 8 H, N(CH₂CH₂N(CH₃)₂), 3.14 (m, 8 H, N(CH₂CH₂N(CH₃)₂), 3.30 (d, 3J = 6.6 Hz, 4 H, CH₂CH=CH₂), 4.12 (s, 8 H, ArCH₂), 4.12 (m, 2 H, CH=CH₂), 5.23 (m, 2 H, CH=CH₂), 5.90 (m, 2 H, CH=CH₂), 6.32 (s [br], 4 H, NH), 7.72 (s, 4 H, ArH).

13C{1H}-NMR (75 MHz, CDCl₃): δ = 31.36 (C(CH₃)₃), 35.20 (C(CH₃)₂), 37.58 (SC₂H₂), 49.02 ((CH₂CH₂N(CH₃)₂), 50.31 ((CH₂CH₂N(CH₃)₂), 51.41 (ArCH₂), 60.20 (NCH₂CH=CH₂), 119.32 (CH=CH₂), 128.34 (ArC=3,3'), 130.07 (ArC=2,2'), 134.56 (CH=CH₂), 140.16 (ArC=1), 154.18 (ArC=4).

Hexa-(cyanoethylated) aza-thioether 15. The thioether 1 (1.67 g, 7.62 mmol) was dissolved in acetonitrile (3 mL) and the resulting mixture was stirred for 3 d at 80 °C. The excess acetonitrile was evaporated, and the yellow solid was dissolved in 100 mL of a 2:1 CH₂Cl₂/CH₃CN solvent mixture. Evaporation of the CH₂Cl₂ provided a colorless solid, which was filtered and dried in air.

Yield: 7.08 g (7.6 mol%, 99%), colorless solid. M.p. 170–172 °C. Found: C 66.83, H 7.92, N 17.82; C₅₂H₇₀N₆S₂ (931.37) requires: C 67.06, H 8.01, N 18.05. m/z (ESI+, MeOH): C₅₂H₇₀N₆S₂ (930.56) [M + H⁺] calculated: 931.57; found 931.56. IR (KBr): ν/cm⁻¹ = 3426 wv, 3054 m, 2951 vs, 2818 vs, 2246 vs (ν(CN)), 1593 m, 1556 vw, 1477 m, 1464 s, 1434 s, 1424 s, 1405 m, 1381 m, 1356 s, 1328 m, 1292 m, 1276 s, 1248 m, 1215 m, 1171 w, 1139 s, 1110 vs, 1047 s, 1005 m, 987 m, 961 m, 947 s, 887 s, 832 w, 801 vw, 774 m, 733 m, 704 vw, 681 vw, 650 w, 596 w.

Hexa(3-aminopropylated) aza-thioether 16. A suspension of LiBH₄ (0.48 g, 22 mmol), Me₅SiCl (4.45 g, 41 mmol), and the nitrile 15 (0.50 g, 0.54 mmol) in 300 mL of dry THF was stirred for 10 h at 50 °C. The mixture was refluxed for further 12 h, cooled to r.t., and quenched with MeOH to give a clear solution. The solution was stirred for 1 h, evaporated to dryness, and suspended in 40 mL of 3 M NaOH solution. The aqueous phase was extracted with CH₂Cl₂ (4 × 20 mL). The organic fractions were combined and dried with anhydrous K₂CO₃. Evaporation of the solvent gave 16 as a colorless solid (376 mg, 73%). The compound is hygroscopic and could not be obtained in analytically pure form, but the spectroscopic data (see ESI†) prove the formulation of this compound. m/z (ESI+, MeOH): C₅₂H₇₀N₆O₁₂S₂ (1045.36) [M + H⁺] calculated: 1045.76; found 1045.76. IR (KBr): ν/cm⁻¹ = 3360 (w, NH₂), 3051 m, 2963 s, 1153 (w, NH₂), 1261 s, 1097 (s, C–S), 1021 s, 799 s. 1H-NMR (700 MHz, CDCl₃): δ = 1.26 (s, 18 H, C(CH₃)₁), 1.49 (tt, 3J = 6.7, 7.6 Hz, 8 H, CH₂CH₂CH₂CH₂N), 1.56 (tt, 3J = 7.0, 6.7 Hz, 4 H, CH₂CH₂CH₂NH), 1.64 (s [br], 6 H, NH₃), 2.35 (t, 3J = 6.6 Hz, 8 H, CH₂CH₂CH₂NH₂), 2.47 (tt, 3J = 7.0, 4 Hz, CH₂CH₂CH₂NH₂), 2.53 (m, 16 H, NCH₂CH₂N), 2.55 (s, 4 H, SCH₂), 3.51 (s, 8 H, ArCH₂), 7.41 (s, 4 H, ArH).

13C{1H}-NMR (100 MHz, CDCl₃): δ = 30.25 (ArCH₂NCH₂CH₂NH₂), 30.42 (C(CH₃)₃), 30.56 (CH₂CH₂NH₂), 33.77 (C(CH₃)₂), 34.32 (SC₂H₂), 39.48 (CH₂NH₂), 39.48 (CH₂NH₂), 50.25 (ArCH₂NCH₂CH₂NH₂), 53.37 (NCH₂CH₂NH₂), 56.65 (ArCH₂), 123.25 (ArC=3,3'), 126.60 (ArC=2,2'), 142.45 (ArC=1), 150.12 (ArC=4).
C₂₅H₂₇N₂O₁₂S₂ (1044.53) \([\text{M + H}^+\text{]}\) calecd: 1045.54; found 1045.5.
IR (KBr): \(\nu/C=1 = 3483 \text{ m}, 2954 \text{ s}, 2824 \text{ m}, 1655 \text{ [v, }\nu/\text{CO}],\)
1560 w, 1468 s, 1433 s, 1364 m, 1194 s, 1125 s, 1050 w, 996 w, 966 w, 934 w, 830 vw, 773 vw 729 vw, 686 vw.
\(^1\)H-NMR (600 MHz, 400 K, DMSO-d₆): \(\delta = 1.12 \text{ (s, 18 H, C(CH₃)₃)},\)
2.43 (s, 6 H, NCH₃), 2.76 (m, 8 H, (NCH₂CH₂)₂NCH₃), 3.03 (s, 4 H, SCH₃),
3.32 (s, 12 H, OCH₃), 3.45 (s, 8 H, (NCH₂CH₂)₂NCH₃), 4.80 (s, 8 H, ArCH₂), 7.05 (s, 4 H, ArH).
\(^1\)C\(^{13}\)(H)-NMR (150 MHz, 400 K, DMSO-d₆): \(\delta = 29.87 \text{ ([C(CH₃)])},\)
33.51 ([C(CH₃)]), 35.66 ([SCH₃]), 41.91 (NCH₃), 44.35 ([NCH₂CH₃N]),
48.53 ([NCH₂CH₂)₂NCH₃], 54.85 ([ArCH₃]), 57.64 ([OCH₃]), 70.12 ([NCOOCH₃CH₃]),
121.59 ([Ar-3,3'), 126.21 ([Ar-2,2'], 140.79 ([Ar-1], 151.44 ([Ar-4]), 168.25 ([CO]).
This compound was additionally characterized by X-ray crystallography.

**Tetra(2-methoxyethylated) aza-thioether 20.** By analogy to the preparation of 18, amide 19 (1.28 g, 1.38 mmol) in THF (20 mL), LiBH₄ (152 mg, 6.98 mmol) and Me₂SiCl (1.49 g, 13.7 mmol) in THF (20 mL) were reacted under N₂ to give a colorless solution which was stirred for 12 h, quenched with MeOH and evaporated to dryness. The residue was triturated with aqueous LiOH (3 M, 20 mL) and CH₂Cl₂ (50 mL), the layers were separated and the aqueous phase was extracted with CH₂Cl₂ (3 × 10 mL). The organic fractions were combined and dried with anhydrous MgSO₄. Evaporation of the solvent gave 20 as a white solid (0.88 g, 73%). Slow evaporation of a CH₂Cl₂/MeCN (1:1) solution afforded colorless crystals. Found: C 66.13, H 9.78, N 9.41, S 7.22, C₂₆H₄₂N₆O₈S₂ (873.6) requires: C 64.96, H 9.65, N 9.62, S 7.34.

**Dicarbamoylated macrocycle 22.** To a solution of tert-butyl benzo[2(2-aminoethyl)]carbamate (2.89 g, 14.22 mmol) in EtOH/CHCl₃ (800 mL, 3:1 v/v) at 0 °C was added a solution of 1,2-bis-[4-tert-butyl-2,6-diformylphenyl]ethane (3.34 g, 7.11 mmol) in CHCl₃ (500 mL) over the course of 8 h. After the resulting mixture was stirred for further 2 d, the CHCl₃ solvent was removed under reduced pressure. Sodium borohydride (2.15 g, 56.88 mmol) was added and the mixture was stirred at r.t. for 18 h. The mixture was evaporated to dryness, then redissolved in CH₂Cl₂/H₂O (100 mL, 1:1, v/v), and the pH was adjusted to ~13 with aqueous KOH (5 M). After stirring for 2 h, the layers were separated and the aqueous phase was extracted with CH₂Cl₂ (4 × 50 mL). The organic fractions were combined and dried with anhydrous MgSO₄. Evaporation of the solvent gave an oil, which crystallized from EtOH (10 mL) after standing for 4 weeks. Yield: 1.20 g (1.47 mmol, 21%). M.p. 136–138 °C. Found: C 54.75, H 9.25, C₂₆H₂₅N₈O₂S₂ 0.5 EtOH (813.21 + 23.04) requires: C 64.63, H 9.04,
To a suspension of 22 (1.13 g, 1.39 mmol) in MeOH (55 mL) was added acetic acid (4 mL) followed by formaldehyde (4 mL), and sodium cyanoborohydride (689 mg, 11.12 mmol). The resulting clear solution was stirred for 3 h at r.t., and its pH was brought to 13 with aqueous KOH (5 M). The MeOH was removed under reduced pressure, and 50 mL CH2Cl2/H2O (1:1 v/v) was added. After stirring for 2 h, the layers were separated and the aqueous phase was extracted with CH2Cl2 (4 × 5 mL). The organic fractions were combined and dried with anhydrous MgSO4. Evaporation gave the crude product, which was purified by recrystallization from CH2Cl2/EtOH (1:1 v/v). Yield: 910 mg (1.05 mmol, 75%), colorless crystals. Mp 217–219 °C.

Compound 23. To a suspension of 22 (250 mg, 0.29 mmol) in CH2Cl2 (0.5 mL) was added trifluoroacetic acid (1 mL). The resulting clear solution was stirred for 2 h at r.t., and its pH was brought to 13 with aqueous KOH (5 M). The aqueous phase was extracted with CH2Cl2 (4 × 5 mL). The organic fractions were combined and dried with anhydrous MgSO4. Evaporation gave the crude product which was not purified further. Yield: 189 mg (0.28 mmol, 97%), colorless solid. M.p. 170–172 °C.

**Results and discussion**

**Synthesis**

Scheme 1 depicts the synthetic procedures for compounds 8, 9, 15, and 19–20. The reaction of 1 with allylbromide in the presence of NEt3 in ethanol furnished the bicycle 8 in good yields (> 81%). To prevent overalkylation the reaction was carried out at 0 °C. Under similar conditions, the dimethylated precursor 2 reacted preferentially in the benzylic position providing the...
corresponding tetraallylated system 9 (75%) as colorless needles after recrystallization from CHCl₃/EtOH. The reductive amination of tetraaldehyde 10 with N³-(3-aminopropyl)-N³-methylpropane-1,3-diamine 13 under medium-dilution conditions provided the bis-allylated macrocycle 14 in excellent yield (Scheme 2).

The second ligand system was prepared according to a protocol used for the cyanethylation of tetraazaacycloalkanes.⁶ Thus, Michael addition of 1 to acrylonitrile led quantitatively to the hexacyanethylated product 15, which can be easily purified by recrystallization. It was reported that the nitrite functions of tetra(2-cyanoethyl)tetraazaacycloalkanes can be reduced to the corresponding primary amines by reduction with LiAlH₄, diborane or H₂-RANEY-Ni.⁷⁻⁹ In our hands, the nitrite 15 failed to react in this fashion. Therefore, an alternative protocol involving reduction with LiBH₄/Me₃SiCl was employed.⁴⁰ This sequence provided the hexa(3-aminopropylated) macrocycle 16 in moderate to good yields.

The route used for the synthesis of the amino-thioethers with methoxymethyl substituent is depicted in Scheme 1. A reaction sequence similar to that developed for similar N₆S₂-type macrocycles bearing “innocent” alkyl groups was employed. Key-step of this procedure is the acylation of 1 with 2-methoxyacetyl chloride. Thus, in reaction with 2-methoxyacetyl chloride the amide 17 was generated quantitatively and then reduced to 18 with LiBH₄/Me₃SiCl. As an illustration of the utility of this sequence, the N₆N₂-dimethyl derivative 2 was also quantitatively derivatized giving the bicyclic macrocycles 19 and 20, respectively.

Table 1 Selected crystallographic data for compounds 8, 15, 17-3DMSO, 19-2DMSO-2H₂O, 20, and 23

<table>
<thead>
<tr>
<th>Compound</th>
<th>8</th>
<th>15</th>
<th>17-3DMSO</th>
<th>19-2DMSO-2H₂O</th>
<th>20</th>
<th>23</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formula</td>
<td>C₃₂H₄₈N₆S₂ &amp; C₃₂H₄₂N₁₂S₂ &amp; C₁₆H₁₀₂N₆O₄S₂ &amp; C₄₈H₈₂N₆O₄S₂ &amp; C₄₈H₈₀N₆O₄S₂ &amp; C₄₈H₉₀N₆O₄S₂</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diffractometer</td>
<td>IPDS-2</td>
<td>IPDS-1</td>
<td>IPDS-2</td>
<td>IPDS-2</td>
<td>IPDS-2</td>
<td>IPDS-1</td>
</tr>
<tr>
<td>7/K</td>
<td>180(2)</td>
<td>213(2)</td>
<td>180(2)</td>
<td>180(2)</td>
<td>213(2)</td>
<td>213(2)</td>
</tr>
<tr>
<td>Formula weight [g mol⁻¹]</td>
<td>853.34</td>
<td>931.35</td>
<td>1201.60</td>
<td>929.27</td>
<td>873.33</td>
<td>869.30</td>
</tr>
<tr>
<td>Space group</td>
<td>C2/c</td>
<td>I2/a</td>
<td>P1</td>
<td>I2/a</td>
<td>C2/c</td>
<td>P2₁/c</td>
</tr>
<tr>
<td>α, Å</td>
<td>27.300(2)</td>
<td>19.481(4)</td>
<td>12.894(2)</td>
<td>18.943(3)</td>
<td>19.845(3)</td>
<td>19.285(4)</td>
</tr>
<tr>
<td>γ, deg</td>
<td>90.00</td>
<td>91.86(2)</td>
<td>90.00</td>
<td>90.00</td>
<td>90.00</td>
<td>90.00</td>
</tr>
<tr>
<td>V, Å³</td>
<td>5243.9(5)</td>
<td>5095(2)</td>
<td>6476(2)</td>
<td>5987(2)</td>
<td>5132(2)</td>
<td>2553.7(9)</td>
</tr>
<tr>
<td>Z</td>
<td>4</td>
<td>4</td>
<td>2</td>
<td>4</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Dcalcd, g cm⁻³</td>
<td>1.081</td>
<td>1.214</td>
<td>1.200</td>
<td>1.031</td>
<td>1.130</td>
<td>1.131</td>
</tr>
<tr>
<td>Cryst. size, mm</td>
<td>3</td>
<td>0.25 x 0.20 x 0.15</td>
<td>0.15 x 0.15 x 0.15</td>
<td>0.23 x 0.23 x 0.10</td>
<td>0.39 x 0.23 x 0.18</td>
<td>0.15 x 0.27 x 0.18</td>
</tr>
<tr>
<td>µ(Mo Kα), mm⁻¹</td>
<td>0.140</td>
<td>0.153</td>
<td>0.205</td>
<td>0.136</td>
<td>0.149</td>
<td>0.150</td>
</tr>
<tr>
<td>R₁, R₂ (R₁ all data)</td>
<td>0.0547 (0.0754)</td>
<td>0.0427 (0.0618)</td>
<td>0.0506 (0.0951)</td>
<td>0.0458 (0.0566)</td>
<td>0.0677 (0.0875)</td>
<td>0.0360 (0.1038)</td>
</tr>
<tr>
<td>wR₂ (R₁ all data)</td>
<td>0.1458 (0.1552)</td>
<td>0.1029 (0.1078)</td>
<td>0.1019 (0.1127)</td>
<td>0.1321 (0.1387)</td>
<td>0.2012 (0.2136)</td>
<td>0.0446 (0.0519)</td>
</tr>
<tr>
<td>Max, min peaks, e Å⁻³</td>
<td>0.654/-0.394</td>
<td>0.505/-0.264</td>
<td>0.260/-0.426</td>
<td>0.431/-0.228</td>
<td>1.598/-0.519</td>
<td>0.147/-0.132</td>
</tr>
<tr>
<td>CCDC</td>
<td>1436363</td>
<td>1436364</td>
<td>1436365</td>
<td>1436366</td>
<td>1436367</td>
<td>1436368</td>
</tr>
</tbody>
</table>

* Three DMSO solvate molecules were located from the Fourier map but one was heavily disordered such that it was removed from the structure.

# Scheme 1 Synthetic of compounds 8, 9, and 15-20.

# Scheme 2 Synthetic of compounds 14 and 22-24.
So far only the precursors 1 and 2 had been utilized for functionalization. In reactions with 1 all six NH donors are derivatized, while modifications of 2 involved only the benzylic NH donors. We decided to develop a method that allows the selective functionalization of the two central NH donors. In an orienting experiment, the reductive amination of the tetraaldehyde with tert-butyl-bis(2-aminooethyl)carbamate was undertaken. This provided the desired macrocycle, albeit in low yield. Having succeeded with the preparation of 22, allylation of the N-benzyl functions and deprotection of the carbamoyl groups could be examined. Indeed, 22 readily underwent reductive methylation with formaldehyde and NaBH₄CN to give the tetramethylated derivative 23 in 75% yields, which was fully characterized including IR, ¹H and ¹³C NMR spectroscopy. Some compounds were further characterized by X-ray crystallography, in order to study their host-guest chemistry.

### Crystal structures

Fig. 2 displays the molecular structure of the hexaallylated macrocycle 8. The molecule has crystallographically imposed C₂ symmetry, and adopts a folded conformation. Unlike in the permethylated derivative 3,²⁹ the two aromatic rings are essentially coplanar, but are twisted about the S₁–S₁' vector (torsional angle C₁–S₁–S₁’–C₁a = 37.8°), attributed to steric interactions between the tert-butyl groups. The allyl residues are all oriented away from the cavity. There are no specific intermolecular interactions in 8. The C–S bonds are of length 1.783(1) Å (S₁–C₁, S₁’–C₁'). Virtually the same distances are seen in 3.

Fig. 3 displays the molecular structure of the hexanitrite 15. The macrobicycle adopts a folded conformation, which is similar but not identical to that seen in 8. Here, the two phenyl rings plane are bent into the cleft formed by the macrocycle, at an interplanar angle of 19°. The structure is stabilised by two intermolecular CH···π interactions as indicated by relatively short distances between the methylene groups and the aromatic rings (C₁₁···centroid(aromatic ring) = 3.823 Å).¹¹ In contrast to the hexaallylated macrocycle, molecules of 15 are connected via intermolecular CH₂···NC interactions (N₄···H₁₇b'' = 3.013, N₅···H₂₅b'' 2.517, N₆···H₁₉b'' 2.735 Å). These interactions lead to a three-dimensional network. The structure of the tetramethoxycarboxyethylated aza-thioether 20 is very similar to that of 15 (when neglecting the different N-substituents). However, the tilting of the two aryl rings is not so pronounced (5°) and the C₁₁···centroid distances are longer at 3.875 Å.

Hexa(2-methoxycetylated) macrobicycle 17 crystallizes from DMSO with three solvate molecules. Fig. 4 shows the structure of the macrobicycle, which forms an inclusion complex with a DMSO molecule. The guest molecule is held in place by a CH···π interaction of length 3.823 Å (C₁₁···centroid(aromatic ring)). The other two DMSO molecules are enclathrated in the voids of the structure. The structure of 17·3DMSO should be compared with that of the tetra(2-methoxacytalyzed) derivative 19·2DMSO·2H₂O (Fig. 4, right). This compound crystallizes also...
with solvate molecules, but does not form an inclusion complex. The two phenyl rings in 19 are coplanar as in the hexanitrile 15. However, the distance between the two best planes through the benzene rings is much larger at 5.087 Å. As a consequence, the phenyl rings are not involved in intermolecular CH⋯π interactions with the adjacent benzyl group (C11⋯centroid(aromatic ring) = 4.802 Å). Clearly, removal of two methoxyacetyl residues exerts more conformational flexibility on the macrocycle.

Fig. 5 displays the structure of the protected macrobicycle 23, which has crystallographically imposed inversion symmetry. Unlike in the above structures, the thioether adopts a stepped conformation, presumably a consequence of the steric requirements of the N-carbamate groups. As a consequence, the macrocycles are engaged in intermolecular CH⋯π interactions. The corresponding CH⋯π distances at 3.428 Å (C11⋯centroid(aromatic ring)) are significantly shorter than in 15 or 20. This compound crystallizes without guest molecules.

Conclusion
Overall, a short and efficient protocol for the functionalization of bicyclic aza-thioethers has been described. All six secondary amine functions of the parent macrobicycles 1 and 2 are readily alkylated without overalkylation and without affecting the masked thiolate functions. The protocol is also feasible for the synthesis of macrobicycles with different alkyl groups on the benzylic and central nitrogen atoms of the linking diethylene triamine units, such that these derivatives are also now available. Six of the twelve new compounds were obtained in crystalline form, such that their molecular structures could be determined. In the solid state the macrobicycles can adopt a stepped or a folded conformation. The structures appear to be primarily governed by inter- and intramolecular CH⋯π interactions (involving the benzylic methylene groups and the aromatic rings) rather due to steric effects played by the N alkyl functions. The observation that DMSO, which is a good CH donor, can form an inclusion complex held in place by a CH⋯π interaction would be consistent with this in view.

Acknowledgements
We are thankful to Prof. Dr H. Krautscheid for providing facilities for X-ray crystallographic measurements. This work was supported by the Deutsche Forschungsgemeinschaft (DFG Research unit 1154, “Towards Molecular Spintronics”).

References


34 G. M. Sheldrick, *SHELXL-97, Computer program for crystal structure refinement*, University of Göttingen, Göttingen, Germany, 1997.


