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

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A short and efficient synthesis of a series of macrobicyclicaza-thioethers with pendant allyl (8, 13, 14), cyanethyl (15), 3-aminopropyl (16), 2-methoxyacetyl (17, 19), 2-methoxyethyl (18, 20), and tert-butylxycarbonyl 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 benzylic 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 features is discussed, and compared with those of the parent hexaaza-thioether macrocycles. We have obtained a series of new macrobicyclic compounds bearing olefinic, nitrile, amine, and methoxy groups in place of 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.

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, 4, 5, 6 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.
Experimental section

Materials and physical measurements

The bicyclic aza-thioethers 124 and 225, 1,2-bis(4-tert-butyl-2,6-diformylthioethane) (10), 24 bis[2-phthalimidoethyl]amine (11), and tert-butyl-bis(2-aminoethy)carbamate (21)33 were prepared according to literature. Melting points were determined with an Electrotherm 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.

Hexaallylated aza-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 triethyamine (303 mg, 3.00 mmol) in EtOH (1 mL) was added dropwise and the mixture was dissolved in EtOH (3 mL). A solution of triethylamine (404 mg, 4.00 mmol) in EtOH (1 mL) 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, 95.9 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 5.54, N 10.34; C23H21N3O4 (403.44) requires: C 68.47, H 5.25, N 10.42. IR (KBr): ν/cm−1 = 3461 w, 3091 w, 2918 w, 2855 w, 1769 s, 1711 vs, 1611 m, 1468 s, 1438 s, 1404 s, 1387 vs, 1332 m, 1306 m, 1276 w, 1191 w, 1160 w, 1142 w, 1088 m, 1018 m, 1018 s, 974 w, 939 w, 874 w, 803 w, 773 w, 726 vs, 630 w, 613 w, 567 w, 532 m, 469 w. 1H-NMR (400 MHz, CDCl3): δ = 2.74 (t, J = 6.4 Hz, 4 H, (NCH2CH2)2N), 3.15 (d, J = 6.4 Hz, 4 H, (NCH2CH2)2N), 5.67 (m, 1 H, CH = CH2), 7.50 (s, 4 H, ArH). 13C{1H}-NMR (100 MHz, CDCl3): δ = 31.60 (C(CH3)3), 34.98 (C(CH3)3), 35.82 (C(CH3)3), 50.89 (NCH2CH2)2N, 51.71 (NCH2CH2)2N, 56.88 (ArCH2NCH2CH2), 57.51 (ArCH2), 59.23 (NCH2CH2), 116.99 (ArCH2NCH2CH=CH2), 117.46 (NCH2CH2), 124, 128.18 (Ar=3’, 3”), 128.18 (Ar=2’, 2”), 136.35 (ArCH2NCH2CH=CH2), 136.34 (CH=CH2), 143.71 (Ar=1’), 151.40 (Ar=4’). This compound was additionally characterized by X-ray crystallography.

Tetraallylated aza-thioether 9. The thioether 2 (641 mg, 1.00 mmol) and allyl bromide (509 mg, 4.21 mmol) were dissolved in EtOH (3 mL). A solution of triethyamine (404 mg, 4.00 mmol) in EtOH (1 mL) was added dropwise and the mixture was allowed to stand for 2 weeks at 0 °C. HNNEt2Br crystallized, from which the reaction mixture was decanted off. The title compound precipitated from the mother liquor upon standing in air. This material was further purified by recrystallization from MeCN/CH2Cl2. Yield: 649 mg (0.46 mmol, 81%), colorless solid. Found: C 72.0, H 9.42, N 9.94, S 7.81; C49H76N10S2 (801.31) requires: C 71.95, H 9.56, N 10.49, S 8.00. m/z (ESI+, MeOH): C49H76N10S2 (800.56) [M + H]+ calc'd: 801.57; found: 801.60. IR (KBr): ν/cm−1 = 3425 w, 3072 w, 3004 w, 2962 vs, 2927 m, 2907 s, 2867 m, 2810 s, 2787 s, 2703 m, 1829 wv, 1641 w, 1594 w, 1559 wv 1477 m, 1457 1415 s, 1357 s, 1311 m, 1311 m, 1262 vs, 1126 w, 1194 w, 1154 s, 1106 vs, 1035 s, 992 s, 980 m, 914 s, 883 m, 801 vs, 741 wv, 687 w. 1H-NMR (400 MHz, CDCl3): δ = 1.23 (s, 18 H, C(CH3)3), 3.19 (3 H, H, C(CH3)3), 25.0–25.59 (m, 16 H, NCH2CH2N), 2.85 (m, 8 H, NCH2CH2), 2.87 (s, 4 H, SCH2), 3.76 (s, 8 H, ArCH2), 5.02–5.10 (m, 8 H, NCH2CH2), 5.74 (m, 4 H, CH2=CH2), 7.37 (s, 4 H, ArH). 13C{1H}-NMR (100 MHz, CDCl3): δ = 31.93 (C(CH3)3), 34.76 (C(CH3)3), 36.69 (SCH2), 42.94 (CH2), 51.16 ((NCH2CH2)2N), 55.17 ((NCH2CH2)2N), 57.91 (ArCH2), 110.0 (CH=CH2), 125.73 (Ar=3”, 3”), 129.31 (Ar=2’, 2”), 134.42 (CH=CH2), 143.78 (Ar=1”), 151.24 (Ar=4”). This compound was additionally characterized by X-ray crystallography.
D₂O): δ = 34.0 (H₂NCH₂), 49.6 ((CH₃)₂N), 56.3 (NCH₃), 124.8 (CH=CH₂), 128.2 (CH=CH₂).

N-Allyl-bis(2-aminooxy)-amine (13). A suspension of N-allyl-bis(2-aminooxy)-amine-trichlorohydride (9.76 g, 38.6 mmol) and KOC(CH₃)₃ (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 enough for the next step. IR (KBr): ν/cm⁻¹ = 3426 vs, 3054, 2951 vs, 2818 vs, 2246 vs, 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, 947 m, 887 s, 832 w, 801 vw, 774 m, 733 m, 704 vw, 681 vw, 650 w, 596 w. ¹H-NMR (300 MHz, CDCl₃): δ = 1.33 (s, 18 H, ArCH₂(CH₃)₂), 2.38 (m, 8 H, CH₂CH₂N), 2.40 (m, 4 H, CH₂CN), 2.66 (m, 8 H, (NCH₂CH₂)N), 2.67 (s, 4 H, S), 2.86 (m, 8 H, (NCH₂CH₂)N), 2.73 (m, 4 H, CH₂CH₂CN), 2.75 (s, 8 H, ArCH₂), 5.73 (s, 4 H, ArH). ¹³C(¹H)-NMR (75 MHz, CDCl₃): δ = 17.03 (CH₂CN), 17.38 (CH₂CN), 31.46 (CH₂CN), 35.00 ((CH₃)₂N), 36.16 (SCH₂), 47.5 (ArCH₂NCH₂CH₂CN), 51.82 (CH₂CH₂CN), 52.39 ((NCH₂CH₂)N), 52.96 ((NCH₂CH₂)N), 63.1 (ArCH₂N), 118.90 (ArCH₂NCH₂CH₂CN), 118.96 (CN), 125.20 (ArC=3,3'), 128.17 (ArC=2,2'), 142.71 (ArC=1), 152.26 (ArC-4). This compound was additionally characterized by X-ray crystallography.

Hexa(3-aminopropylated)aza-thioether (16). A suspension of LiBH₄ (0.48 g, 22 mmol), Me₂SiCl (4.45 g, 41 mmol), and the nitride 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): C₂₀H₄₅N₁₄S₂ (595.56) [M + H⁺]⁺ calc: 595.76; found 595.76. IR (KBr): ν/cm⁻¹ = 3360 (w, NH₂), 3063 s, 2963 s, 1593 s (w, NH₂), 1261 s, 1097 s (C-S), 1021 s, 799 s. ¹H-NMR (700 MHz, CDCl₃): δ = 1.26 (s, 18 H, (CH₃)₃C), 1.49 (tt, J = 6.7, J = 6.6 Hz, 8 H, CH₂CH₂CH₂CN), 1.56 (tt, J = 7.0, J = 6.7 Hz, 8 H, CH₂CH₂CH₂CN), 1.64 (s br, 6 H, NH₂), 2.35 (s, J = 6.6 Hz, 8 H, CH₂CH₂CH₂CN), 2.47 (s, J = 7.0 Hz, 4 H, CH₂CH₂CH₂CN), 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 (ArCH₂NCH₂CH₂CN), 30.42 (CH₂CH₂CN), 30.56 ((CH₂CH₂CN)₂), 33.77 (CH₃C), 34.32 (SCH₂), 39.48 (CH₂CN), 39.48 (CH₂CN), 50.25 (ArCH₂NCH₂CH₂CN), 53.37 ((NCH₂CH₂)N), 56.65 (ArCH₂), 123.25 (ArC=3,3'), 126.60 (ArC=2,2'), 142.45 (ArC=1), 150.12 (ArC-4).

Hexa(2-methoxycarbonylated)aza-thioether (17). Compound 1 (2.50 g, 4.08 mmol) in dry CHCl₃ (20 mL), 2-methoxycarbonyl chloride (2.86 g, 26.3 mmol), and triethylamine (2.48 g, 24.5 mmol) were reacted to give a colorless solution, which was stirred for 12 h and evaporated to dryness. The residue was suspended in THF (10 mL), filtered, and dried. The colorless solid was purified by recrystallization from EtOH. Yield: 3.38 g (79%). Found: C 49.90, H 7.35, N 7.89, S 5.88; C₂₃H₄₅N₁₄O₄S₂ (1045.36) requires: C 50.34, H 7.71, N 8.04, S 6.13. m/z (ESI⁺, MeOH):
C_{52}H_{46}N_{10}O_{12}S_{2} (1044.53) [M + H]^+ calecd: 1045.54; found 1045.5.
IR (KBr): ν/cm⁻¹ = 3483 m, 2954 s, 2824 m, 1655 vs, ν(C=O), 1560 w, 1468 s, 1433 m, 1340 m, 1291 n, 1196 s, 1125 s, 1050 w, 996 w, 966 w, 934 w, 830 vw, 801 vw, 773 vw 729 vw, 686 vw.
H-NMR (600 MHz, 400 K, DMSO-d₆): δ = 1.20 (s, 18 H, C(CH₃)₃), 3.01 (s, 4 H, S(CH₂)₃), 3.34 (s, 12 H, OCH₂), 3.40 (s, 6 H, OCH₃), 3.46 (s, 16 H, NCH₂CH₂N₂), 4.10 (s, 8 H, CH₂O), 4.18 (s, 4 H, CH₂OCH₂), 4.74 (s, 8 H, ArCH₂), 6.99 (s, 4 H, ArH).

13C{1H}-NMR (150 MHz, CDCl₃): δ = 29.81 (C(CH₃)₃), 33.56 (C(CH₃)₃), 35.29 (SCH₂), 44.89 [br, N(CH₂CH₂N₂), 48.49 (ArCH₂), 57.68 (OCH₂), 57.73 (OCH₃), 70.12 (OCH₂O), 70.21 (OCH₂O), 121.7 (Ar-C-3,3'), 125.82 (Ar-C-2,2'), 140.70 (Ar-C, 151.66 (Ar-C), 168.62 (CO), 168.69 (CO). This compound was additionally characterized by X-ray crystallography.

**Hexa(2-methoxyethylated) aza-thioether 18.** By analogy to the preparation of the 18, amide 19 (1.28 g, 1.38 mmol) in THF (20 mL), LiBH₄ (152 mg, 3.88 mmol) and Me₂SCl (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 x 10 mL). The organic fractions were combined and dried with anhydrous MgSO₄. Evaporation of the solvent gave 18 as a white solid (0.88 g, 73%). Slow evaporation of a CH₂Cl₂/MeCN (1 : 1) solution afforded colorless crystals. Found: C 64.63, H 9.26, N 9.41, S 7.34. IR (KBr): ν/cm⁻¹ = 3445 s, 2956 vs, 2871 vs, 2816 vs, 1718 m, 1654 vs, 1565 vs, 1468 s, 1434 m, 1364 s, 1301 m, 1197 s, 1125 s, 1068 m, 1019 m, 972 w, 937 m, 800 w, 750 w, 726 w, 687 w, 596 m.

4H-NMR (150 MHz, 400 K, DMSO-d₆): δ = 1.21 (s, 18 H, C(CH₃)₃), 2.43 (s, 6 H, NCH₃), 2.76 (m, 8 H, NCH₂CH₂N₃H₃), 3.03 (s, 4 H, CH₂), 3.32 (s, 12 H, OCH₃), 3.45 (s, 8 H, NCH₂CH₂N₃H₃), 4.80 (s, 8 H, ArCH₂), 7.05 (s, 4 H, ArH). 13C{1H}-NMR (150 MHz, 400 K, DMSO-d₆): δ = 29.87 (C(CH₃)₃), 33.51 (C(CH₃)₃), 35.66 (SCH₂), 41.91 (NCH₂), 44.35 (NCH₂CH₂N), 48.53 (NCH₂CH₂N₃H₃), 54.85 (ArCH₂), 57.64 (OCH₂), 70.35 (OCH₂CH₂N₃H₃), 121.59 (Ar-C, 3,3'), 126.21 (Ar-C, 2,2'), 140.79 (Ar-C, 151.44 (Ar-C), 168.25 (CO). This compound was additionally characterized by X-ray crystallography.

**Tetra(2-methoxyethylated) aza-thioether 20.** To a solution of the 18, amide 19 (1.28 g, 1.38 mmol) in THF (20 mL), LiBH₄ (152 mg, 3.88 mmol) and Me₂SCl (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 x 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 64.63, H 9.26, N 9.41, S 7.34. IR (KBr): ν/cm⁻¹ = 3445 s, 2956 vs, 2871 vs, 2816 vs, 1718 m, 1654 vs, 1565 vs, 1468 s, 1434 m, 1364 s, 1301 m, 1197 s, 1125 s, 1068 m, 1019 m, 972 w, 937 m, 800 w, 750 w, 726 w, 687 w, 596 m.

4H-NMR (600 MHz, 400 K, DMSO-d₆): δ = 1.30 (s, 18 H, C(CH₃)₃), 2.25 (s, 6 H, NCH₃), 2.50 (s, br, 8 H, NCH₂CH₂N₃H₃), 2.60 (t, J = 9.8, 8 H, NCH₂CH₂OCH₂), 2.68 (s, br, 8 H, NCH₂CH₂OCH₂), 2.79 (s, 4 H, ArCH₂), 3.28 (s, 12 H, OCH₂), 3.39 (t, J = 9.8, 8 H, NCH₂CH₂OCH₂), 3.80 (s, 8 H, ArCH₂), 7.47 (s, 4 H, ArH). 13C{1H}-NMR (100 MHz, CDCl₃): δ = 31.43 (C(CH₃)₃), 34.87 (C(CH₃)₃), 36.16 (SCH₂), 43.42 (NCH₂), 52.35 ([NCH₂CH₂N₃H], 53.37 (ArCH₂CH₂OCH₂), 58.57 (ArCH₂), 58.93 (OCH), 71.50 (CH₂CH₂OCH₂), one CH₂ signal not observed), 125.70 (Ar-C, 3,3'), 128.79 (Ar-C, 2,2'), 143.79 (Ar-C, 151.44 (Ar-C).

**Dicarbamoylated macrobicycle 22.** To a solution of tert-butylicarbamate (2-aminooctyl)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-butylicarbamate (2.51 g, 15.68 mmol) 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 x 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: 1.2 g (1.47 mmol, 21%). M.p. 136–138 °C. Found: C 64.75, H 8.58, N 9.75; C₄₁H₆₂N₈O₄S₂ 0.5 EtOH (813.21 + 23.04) requires: C 64.63, H 9.04.
N 10.05. m/z [ESI+]: 813.4 (M + H+). IR (KBr): ν/cm⁻¹ = 3443 s, 3290 m ν(NH), 2965 s, 2927 s, 2865 m, 1693 s ν(C=O), 1597 w, 1478 s, 1458 s, 1345 s, 1269 w, 1228 w, 1173 s, 1154 s, 1091 w, 1043 w, 966 w, 886 w, 858 w, 823 w, 774 w. 1H-NMR (400 MHz, CDCl3): δ = 1.29 (s, 18 H, Ar(CH3)9), 1.45 (s, 18 H, C(CH3)2) 2.96 (t, J = 6 Hz, 8 H, (NCH2CH2)2N), 3.20 (s, 4 H, SCH2), 3.49 (t, J = 6 Hz, 8 H, (NCH2CH2)2N), 3.97 (s, 8 H, ArCH2N), 7.28 (s, 4 H, ArH). 13C{¹H}-NMR (100 MHz, CDCl3): δ = 28.6 (C(CH3)3), 31.4 (Ar(CH3)3), 34.7 (Ar(CH3)3), 37.1 ([(ArSCH2)]3), 47.8 ([N(CH2CH2)2N]), 49.3 (Ar(CH3)2), 53.8 ([N(CH2CH2)2N]), 79.7 (C(CH3)3), 126.4 (Ar-C-3), 130.0 (Ar-C-2), 144.8 (Ar-C1), 152.2 (Ar-C4), 156.0 (C-O).

Methylated macrobicycle 23. 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 hydride (689 mg, 11.12 mmol). The resulting clear solution was additionally characterized by X-ray crystallography. Yield: 189 mg (0.28 mmol, 97%), colorless solid. M.p. 170–172 °C. Evaporation gave the crude product which was not purified further. Recrystallization from CH2Cl2/EtOH (1:1 v/v). Yield: 910 mg (0.29 mmol) in CH2Cl2 (0.5 mL) was added trifluoroacetic acid and its pH was brought to 13 with aqueous KOH (5 M). 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. 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. Found: C 66.32, H 9.23, N 9.59; C48H80N6O4S2 (869.32) requires: C 66.32, H 9.23, N 9.59. IR (KBr): ν/cm⁻¹ = 3441 s, 3291 m ν(NH), 2954 s, 2852 s, 2780 s, 1621 s ν(CO), 1599 m, 1458 s, 1394 w, 1364 m, 1258 m, 1227 m, 1201 s, 1175 s, 1131 s, 1107 s, 1074 w, 1048 w, 1022 m, 930 w, 890 w, 832 w, 800 m, 720 m. 1H-NMR (400 MHz, CDCl3): δ = 1.31 (s, 18 H, Ar(CH3)3), 2.07 (s, 12 H, NCH2), 2.83 (m, 8 H, (NCH2CH2)2N), 3.05 (m, 8 H, (NCH2CH2)2N), 3.53 (4 H, (SCH2)) 3.70 (s, 8 H, ArCH2N), 7.21 (s, 4 H, Ar-H).

**Crystallography**

Suitable single crystals of compounds 8, 15, 17-3DMSO, 19-2DMSO-2H2O, 20, and 23 were selected and mounted on the tip of a glass fibre using perfluoropolyether oil. The data sets for 8, 17-3DMSO, 19-2DMSO-2H2O, and 20 were collected at 183(2) K using a STOE IPDS-2 diffractometer, while those for 15 and 23 were collected on a STOE IPDS-1 diffractometer at 213(2) K. Graphite monochromated Mo-Kα radiation (λ = 0.71073 Å) was used throughout. The data were processed with the programs XAREA.32 Selected details of the data collection and refinement are given in Table 1. The structures were solved by direct methods and refined by full-matrix least-squares techniques on the basis of all data against F² using SHELX-97.24 PLATON was used to search for higher symmetry. All non-hydrogen atoms were refined anisotropically, except for those of some disordered solvate molecules. Disorder was modelled using split atom models with restrained Cl–O, O–O, C–C, and C·C distances using appropriate SADI instructions implemented in the SHELXL software package. Graphics were produced with Ortep3 for Windows and PovRAY.

In the crystal structure of 8 two allyl (N1, C18, C19, C20; C21, C22, C23) and one ethylene group (C12, C13) were found to be disordered over two sites. The site occupancies of one allyl and one ethylene group were fixed (0.74/0.26). The site occupations of the other allyl group were refined (0.55/0.45). In the crystal structure of 17-3DMSO one DMSO solvate molecule (S5, O15, C57, C58) was found to be heavily disordered and was therefore removed from the structure (and the corresponding F0) with the SQUEEZE procedure implemented in the PLATON program suite. Removing the DMSO molecule led to a solvent accessible void of 257 Å³, in good agreement with the space needed by one DMSO molecules. The solvate molecules in 19-2DMSO-2H2O were also found to be heavily disordered and were therefore removed utilizing the SQUEEZE procedure. This led to solvent accessible voids of 628 Å³, attributed to the space needed for two DMSO and two H2O molecules.

**Results and discussion**

**Synthesis**

Scheme 1 depicts the synthetic procedures for compounds 8, 9, and 15–20. The reaction of 1 with allylbromide in the presence of NEt3 in ethanol furnished the bicyclic 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]-N²-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 tetraazacycloalkanes. Thus, Michael addition of L to acrylonitrile led quantitatively to the corresponding tetraallylated system 9 (75%) as colorless needles after recrystallization from CHCl₃/EtOH. The reductive amination of tetraaldehyde 10 with N³-[3-aminopropyl]-N²-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 tetraazacycloalkanes. Thus, Michael addition of L to acrylonitrile led quantitatively to the corresponding tetraallylated product 15, which can be easily purified by recrystallization. It was reported that the nitrile functions of tetra(2-cyanoethyl)tetraazacycloalkanes can be reduced to the corresponding primary amines by reduction with LiAlH₄, diborane or H₂-RANEY®-Nickel. In our hands, the nitrile 15 failed to react in this fashion. Therefore, an alternative protocol involving reduction with LiBH₄/MesSiCl was employed. 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 N₃S₂-type macrocycles bearing “innocent” alkyl groups was employed. Key-step of this procedure is the acylation of 1 with 2-methoxycetyl chloride. Thus, in reaction with 2-methoxycetyl chloride the amide 17 was generated quantitatively and then reduced to 18 with LiBH₄/MesSiCl. As an illustration of the utility of this sequence, the N₃S₂-dimethyl derivative 2 was also quantitatively derivatized giving the bicyclic macrocycles 19 and 20, respectively.

![Scheme 1 Synthesis of compounds 8, 9, and 15–20.](image1)

![Scheme 2 Synthesis of compounds 14 and 22–24.](image2)

### 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>
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<tr>
<td><strong>Formula</strong></td>
<td>C₃₂H₄₈N₆S₂</td>
<td>C₃₂H₄₈N₁₂S₂</td>
<td>C₃₀H₂₂N₆O₁₄S₄</td>
<td>C₄₈H₇₆N₆O₈S₂</td>
<td>C₄₈H₈₄N₆O₄S₂</td>
<td>C₄₈H₈₀N₆O₄S₂</td>
</tr>
<tr>
<td><strong>Diffractometer</strong></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>
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<tr>
<td><strong>Formula weight [g mol⁻¹]</strong></td>
<td>853.34</td>
<td>1315.35</td>
<td>1201.60</td>
<td>929.27</td>
<td>873.33</td>
<td>869.30</td>
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<tr>
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<td>C2/a</td>
<td>P2₁</td>
<td>C2/c</td>
<td>C2/c</td>
<td>P2₁/c</td>
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<tr>
<td>a, Å</td>
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<td>19.48(4)</td>
<td>20.84(2)</td>
<td>19.34(3)</td>
<td>18.54(2)</td>
<td>17.95(2)</td>
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<tr>
<td>b, Å</td>
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<td>9.00(3)</td>
<td>10.20(4)</td>
<td>9.10(3)</td>
<td>9.00(3)</td>
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<tr>
<td>c, Å</td>
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<td>90.00(2)</td>
<td>105.36(2)</td>
<td>90.00(2)</td>
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<tr>
<td>Δ D(calcd-g cm⁻³)</td>
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<td>1.214</td>
<td>1.200</td>
<td>1.031</td>
<td>1.130</td>
<td>1.131</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.

² The DMSO and H₂O solvate molecules were located from the Fourier map but were heavily disordered such that they were all removed from the structure, see Experimental section.
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, the two aromatic rings are essentially coplanar, and 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 hexanitrile 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). In contrast to the hexaallylated macrocycle, molecules of 15 are connected via intermolecular CH···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 tetramethoxeylated 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-methoxycacetylated) 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-methoxycacetylated) derivative 19·2DMSO·2H₂O (Fig. 4, right). This compound crystallizes also

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Fig. 2  Molecular structure of 8 in the crystal with atomic numbering for key atoms. Thermal ellipsoids are drawn at the 50% probability level. Symmetry code used to generate equivalent atoms: 1 – x, y, 0.5 – z.

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 1 with tert-butyl-bis(2-aminoethyl)carbamate 21 was undertaken. This provided the desired macrocycle 22, albeit in low yield. Having succeeded with the preparation of 22, alkylation of the N-benzyl functions and deprotection of the carbamoyl groups could be examined. Indeed, 22 readily underwent reductive methylation with formaldehyde and NaBH₃CN 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.

Fig. 3  Left: Molecular structure of 15 in the crystal with atomic numbering for key atoms and centroids of aromatic rings. Thermal ellipsoids are set at 30% probability. Symmetry code used to generate equivalent atoms: 1/2 – x, y, 1 – z. Right: Molecular structure of 20 in the crystal. Hydrogen atoms have been omitted for clarity. Symmetry code: –x, y, 1/2 – z. CH···π interactions indicated by dashed lines.
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\_\_C\_p 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\_\_C\_p interactions. The corresponding CH\_\_C\_p 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\_\_C\_p 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\_\_C\_p interaction would be consistent with this in view.

**Acknowledgements**

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