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 macrobicyclic aza-thioethers with pendant allyl (8, 13, 14), cyanethyl (15), 3-aminopropyl (16), 2-methoxycarbonyl (17, 19), 2-methoxyethyl (18, 20), and tert-butylxoycarbonyl 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 benzylid 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 monomeric 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 N,S2 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 aza-thioethers 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 4,30 5,31 and 632 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, nitrite, 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.

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† 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 225, 1,2-bis(4-tert-butyl-2,6- diformylthioethane) (10),24 bis(2-phenalimidoethylene)amine6 (11), and tert-butyl-bis(2-aminooethyl)carbamate (21)31 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.

Hexaallylatedaza-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 precipitated from the mother liquor upon standing in air. Yield: 392 mg (0.46 mmol, 92%), colorless solid. M.p. 170–172 °C. Yield: 392 mg (0.46 mmol, 92%), colorless solid. M.p.

N-Allyl-bis(2-phenalimidoethylyl)-amine (12). A mixture of bis(2-phenalimidoethylyl)-amine 11 (25.0 g, 68.8 mmol), K2CO3 (9.51 g, 68.8 mmol), and allyl bromide (11.6 g, 9.59 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 68.18, H 5.54, N 10.34; C15H13NO2 (403.44) requires: C 68.47, H 5.25, N 10.42. IR (KBr): ν/cm−1 = 3461 w, 2931 w, 2895 w, 2576 w, 2116 w, 1765 s, 1711 vs, 1611 m, 1485 s, 1418 s, 1391 w, 1387 vs, 1332 m, 1306 m, 1276 s, 1191 vs, 1160 w, 1142 w, 1088 m, 1018 m, 974 w, 939 w, 874 w, 803 w, 773 vs, 713 w, 687 w. 1H-NMR (400 MHz, CDCl3): δ = 3.24 (t, J = 6.4 Hz, 4 H, (CH2)2), 7.50–7.67 (m, 8 H, ArH). 13C{1H}-NMR (100 MHz, CDCl3): δ = 31.60 (C(CH3)3), 34.98 (C(CH3)2), 38.52 (C(CH3)2), 50.89 ((NCH2CH2)2N), 51.71 ((NCH2CH2)2N), 56.88 (ArCH2NCH2CH2), 57.51 (ArCH2), 59.23 (NCH2CH2CH2), 116.99 (ArCH2NCH2CH=CH2), 117.46 (NCH2CH=CH2), 124.86 (Ar-C=3,3′), 128.18 (Ar-C=2,2′), 136.35 (ArCH2NCH2CH=CH2), 136.34 (CH=CH2), 143.71 (Ar-C=1), 151.40 (Ar-C=3). This compound was additionally characterized by X-ray crystallography.

Tetraallylatedaza-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 triethylamine (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. HNEt3Br 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 9.84, S 7.81; C46H78N6S2 (801.30) requires: C 71.95, H 9.56, N 10.49, S 8.00. m/z (ESI+, MeOH): C46H78N6S2 (800.56 [M + H]+) calcld: 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 vw, 1641 w, 1594 w, 1559 w 1477 m, 1459 s, 1415 m, 1357 w, 1330 m, 1311 m, 1262 vs, 1216 w, 1194 w, 1154 s, 1106 vs, 1035 vs, 992 s, 980 s, 914 s, 883 m, 801 vs, 741 w, 687 w. 1H-NMR (400 MHz, CDCl3): δ = 1.21 (s, 18 H, C(CH3)3), 2.12 (s, 6 H, CH3), 2.50–2.59 (m, 16 H, NCH2CH2N), 2.85 (m, 8 H, NCH2CH2CH2), 2.87 (s, 4 H, SCH2), 3.76 (s, 8 H, ArCH3), 5.02–5.10 (m, 10 H, NCH2CH2CH2), 5.74 (m, 4 H, CH=CH2), 7.37 (s, 4 H, ArH). 13C{1H}-NMR (100 MHz, CDCl3): δ = 31.39 (C(CH3)3), 34.76 (C(CH3)2), 36.69 (CH2)3, 42.94 (CH2), 51.16 ((NCH2CH2)2N), 55.17 ((NCH2CH2)2N), 56.58 (NCH2CH=CH2), 57.91 (ArCH2), 117.50 (CH=CH2), 125.73 (Ar-C=3,3′), 129.31 (Ar-C=2,2′), 135.42 (CH=CH2), 143.78 (Ar-C=1), 151.24 (Ar-C=4). This compound was additionally characterized by X-ray crystallography.

N-Allyl-bis(2-aminooethyl)amine trihydrochloride (13·3HCl). A suspension of N-allyl-bis(2-phenalimidoethyl)-amine (15.6 g, 38.7 mmol) was dissolved in 200 mL of concentrated HCl and refluxed for 2 days. The clear solution was cooked 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 m, 2963 vs, 2039 w, 1602 m, 1471 s, 1372 m, 1262 s, 1099 vs, 1019 vs, 959 s, 869 w, 801 vs, 662 vw, 603 w, 461 w. 1H-NMR (400 MHz, D2O): δ = 3.45 (m, J = 6.4 Hz, 4 H, (H2NCH2)2), 3.52 (t, J = 6.4 Hz, 4 H, (CH2)2N), 3.89 (d, J = 7.2 Hz, 2 H, NCH2CH=CH2), 5.67 (m, 1 H, CH=CH2), 5.93 (m, 2 H, CH=CH2). 13C{1H}-NMR (100 MHz,
N-Allyl-bis(2-amino-ethyl)-amine (13). A suspension of N-allyl-bis(2-amino-ethyl)-amine-trihydrochloride (9.76 g, 38.6 mmol) and KOCl(CH$_2$I)$_3$ (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 to be unstable for the next step. IR (KBr): ν/cm$^{-1}$ = 3426 vw, 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 s, 987 m, 961 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, CDCl$_3$): δ = 1.33 (8 s, 18 H, Ar(CH$_2$CH$_2$N)$_3$), 2.38 (m, 8 H, CH$_2$CN), 2.40 (m, 4 H, CH$_2$CN), 2.66 (m, 8 H, (NCH$_2$CH$_2$N)$_2$), 2.67 (m, 4 H, SCHR$_2$), 2.68 (m, 8 H, (NCH$_2$CH$_2$N)$_3$), 2.73 (m, 4 H, CH$_2$CH$_2$CN), 3.76 (s, 8 H, ArCH$_2$), 7.53 (s, 4 H, ArH). 13C{1H}-NMR (75 MHz, CDCl$_3$): δ = 17.03 (CH-CN), 17.38 (CH-CN), 31.46 (CH$_2$N), 35.00 ([C(CH$_3$)$_3$]), 36.16 ([SCHR$_2$]), 47.3 ([ArCH$_2$NCH$_2$CH$_2$CN]), 51.82 ([CH$_2$CH$_2$CN]), 52.39 ([NCH$_2$CH$_2$N]$_2$), 52.96 ([NCH$_2$CH$_2$N]), 63.1 ([ArCH$_3$N]), 118.90 ([ArCH$_2$NCH$_2$CH$_2$CN]), 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 LiBH$_4$ (0.48 g, 22 mmol), Me$_2$SiCl (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 CH$_2$Cl$_2$ (4 × 20 mL). The organic fractions were combined and dried with anhydrous K$_2$CO$_3$. 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): C$_{42}$H$_{80}$N$_{6}$O$_{12}$S$_{2}$ (955.56) [M + H$^+$] calc'd: 955.76; found 955.76. IR (KBr): ν/cm$^{-1}$ = 3360 (w, NH$_2$), 3063 s, 1593 s (w, NH$_2$), 1593 s (w, NH$_2$), 1021 s, 799 s. 1H-NMR (700 MHz, CDCl$_3$): δ = 1.26 (8 s, 18 H, C(CH$_3$)$_3$), 1.49 (tt, $j_y$ = 6.7, $j_y$ = 6.6 Hz, 8 H, CH$_2$CH$_2$CN), 1.56 (tt, $j_y$ = 7.0, $j_y$ = 6.7 Hz, 8 H, CH$_2$CH$_2$CN), 1.64 (s br, 6 H, NH$_2$), 2.35 (tt, $j_y$ = 6.6 Hz, 8 H, CH$_2$CH$_2$NH$_2$), 2.47 (tt, $j_y$ = 7.0, 4 H, CH$_2$CH$_2$CH$_2$NH), 2.53 (m, 16 H, NC(CH$_2$N)$_2$), 2.55 (s 4 H, SCHR$_2$), 3.51 (s, 8 H, ArCH$_2$), 7.41 (s, 4 H, ArH). 13C{1H}-NMR (100 MHz, CDCl$_3$): δ = 30.25 ([ArCH$_2$NCH$_2$CH$_2$CN]$_2$), 30.42 ([C(CH$_3$)$_3$]), 30.56 ([CH$_2$CH$_2$CN]), 33.77 ([C(CH$_3$)$_3$]), 34.32 ([SCHR$_2$]), 39.48 ([CH$_2$NH$_2$]), 39.48 ([CH$_2$NH$_2$]), 50.25 ([ArCH$_2$NCH$_2$CH$_2$N]), 53.37 ([NCH$_2$CH$_2$NH]), 56.65 ([ArCH$_3$]), 123.25 ([ArC-3,3']), 126.60 ([ArC-2,2']), 142.45 ([ArC-1]), 150.12 ([ArC-4]).

Hexa(2-methoxyacetylated) aza-thioether 17. Compound 1 (2.5 g, 4.08 mmol) in dry CHCl$_3$ (20 mL), 2-methoxycetyl 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 59.40, H 7.71, N 8.04, S 6.13. m/z (ESI+, MeOH):
C_{22}H_{31}N_{2}O_{12}S_{2} (1044.53) [M + H]^{+} calculated: 1045.54; found: 1045.5. IR (KBr): ν/cm\(^{-1}\) = 3483 m, 2954 s, 2824 m, 1655 vs, ν(CO), 1560 w, 1468 s, 1433 s, 1340 m, 1191 s, 1196 s, 1125 s, 1050 w, 996 w, 966 w, 934 w, 830 wV, 801 wV, 773 wV, 729 wV, 686 wV.

\(^{1}\)H-NMR (600 MHz, 400 K, DMSO-d\(_{6}\)): δ = 1.20 (s, 18 H, C(CH\(_{3}\))\(_{3}\)), 3.01 (s, 4 H, SCH\(_{2}\)), 3.34 (s, 12 H, OCH\(_{2}\)), 3.40 (s, 6 H, OCH\(_{3}\)), 3.46 (s, 16 H, NCH\(_{2}\)CH\(_{2}\)N\(_{2}\)), 4.10 (s, 8 H, CH\(_{2}\)O), 4.18 (s, 4 H, CH\(_{2}\)OCH\(_{3}\)), 4.74 (s, 8 H, ArCH\(_{2}\)), 6.99 (s, 4 H, Ar-H).

\(^{13}\)C-NMR (150 MHz, 400 K, DMSO-d\(_{6}\)): δ = 29.81 ([C(CH\(_{3}\)]\(_{3}\)), 33.56 ([C(CH\(_{3}\)])), 35.29 ([SCH\(_{2}\])], 44.89 [br, N(CH\(_{2}\)CH\(_{2}\)N\(_{2}\)], 48.49 [ArCH\(_{2}\)], 57.68 ([OCH\(_{3}\)], 57.73 ([OCH\(_{2}\)]), 70.12 ([OCH\(_{2}\)O]), 70.21 ([OCH\(_{2}\)O]), 121.17 ([Ar-C-3,3]), 125.82 ([Ar-C-2,2]), 140.70 ([Ar-C-1]), 151.66 ([Ar-C-4]), 168.62 ([CO]), 168.69 ([CO]). This compound was also characterized by X-ray crystallography.

**Hexa(2-methoxymethylated)aza-thioether 18.** Compound 17 (3.0 g, 2.90 mmol) in THF (20 mL), LiBH\(_{4}\) (872 mg, 38.0 mmol) and Me\(_{2}\)SiCl (8.10 g, 74.6 mmol) in THF (20 mL) were reacted under N\(_{2}\) to give a colorless solution which was stirred for 12 h, quenched with MeOH and evaporated to dryness. The residue was triturated with aqueous lithium hydroxide solution (3 M, 20 mL) and CH\(_{2}\)Cl\(_{2}\) (50 mL). The layers were separated and the aqueous phase was extracted with CH\(_{2}\)Cl\(_{2}\) (3 \× 10 mL). The organic fractions were combined and dried with anhydrous MgSO\(_{4}\). Evaporation of the solvents gave 18 as a white solid (2.03 g, 73%). Slow evaporation of a CH\(_{2}\)Cl\(_{2}/MeCN\) (1 : 1) solution afforded colorless crystals. Found: C 61.80, H 8.25, N 8.89, S 6.65; calculated for C\(_{44}\)H\(_{83}\)N\(_{10}\)O\(_{11}\)S\(_{2}\): C 62.02, H 8.24, N 9.04, S 6.90.

\(^{1}\)H-NMR (600 MHz, 400 K, DMSO-d\(_{6}\)): δ = 1.32 (s, 18 H, C(CH\(_{3}\))\(_{3}\)), 2.64 (t, J = 5.3, 8 H, NCH\(_{2}\)CH\(_{2}\)OCH\(_{3}\)), 2.73 (m, 4 H, NCH\(_{2}\)CH\(_{2}\)OCH\(_{3}\)), 2.75 (s, 4 H, SCH\(_{2}\)), 2.85 (m, 16 H, NCH\(_{2}\)CH\(_{2}\)N\(_{2}\)), 3.28 (s, 12 H, OCH\(_{3}\)), 3.31 (s, 6 H, OCH\(_{3}\)), 3.41 (t, J = 5.3, 8 H, CH\(_{2}\)OCH\(_{3}\)), 3.60 (m, 4 H, CH\(_{2}\)OCH\(_{3}\)), 3.78 (s, 8 H, ArCH\(_{2}\)), 7.53 (s, 4 H, ArH).

\(^{13}\)C-NMR (100 MHz, DMSO-d\(_{6}\)): δ = 31.32 ([C(CH\(_{3}\)])), 34.68 ([C(CH\(_{3}\)]), 35.57 ([SCH\(_{2}\])], 50.82 ([NCH\(_{2}\)CH\(_{2}\)N\(_{2}\)]), 50.92 ([N(CH\(_{2}\)CH\(_{2}\)N\(_{2}\)])], 52.74 ([Ar CH\(_{2}\)NCH\(_{2}\)CH\(_{2}\)OCH\(_{3}\)]), 54.68 ([NCH\(_{2}\)CH\(_{2}\)N\(_{2}\)]), 58.17 ([ArCH\(_{2}\)]), 58.92 ([OCH\(_{3}\)]), 58.97 ([OCH\(_{3}\)]), 70.50 ([OCH\(_{2}\)]), 70.82 ([OCH\(_{2}\)])].

**Tetra(2-methoxycarbonylated)aza-thioether 19.** By analogy to the preparation of 18, amide 19 (1.28 g, 1.38 mmol) in THF (20 mL), LiBH\(_{4}\) (152 mg, 6.98 mmol) and Me\(_{2}\)SiCl (1.49 g, 13.7 mmol) in THF (20 mL) were reacted under N\(_{2}\) 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 CH\(_{2}\)Cl\(_{2}\) (50 mL), the layers were separated and the aqueous phase was extracted with CH\(_{2}\)Cl\(_{2}\) (3 \× 10 mL). The organic fractions were combined and dried with anhydrous MgSO\(_{4}\). Evaporation of the solvents gave 19 as a white solid (0.88 g, 73%). Slow evaporation of a CH\(_{2}\)Cl\(_{2}/MeCN\) (1 : 1) solution afforded colorless crystals. Found: C 46.63, H 9.78, N 9.41, S 7.22; calculated for C\(_{44}\)H\(_{84}\)N\(_{10}\)O\(_{4}\)S\(_{2}\): C 46.61, H 9.69, N 9.62, S 7.34.

\(^{1}\)H-NMR (600 MHz, 400 K, DMSO-d\(_{6}\)): δ = 1.30 (s, 18 H, C(CH\(_{3}\))\(_{3}\)), 2.25 (s, 6 H, NCH\(_{3}\)), 2.50 (s, 8 H, CH\(_{2}\)NCH\(_{2}\)N\(_{2}\)), 2.60 (t, J = 9.8, 8 H, NCH\(_{2}\)CH\(_{2}\)OCH\(_{3}\)), 2.68 (s, 8 H, NCH\(_{2}\)CH\(_{2}\)OCH\(_{3}\)), 2.79 (s, 4, 8 H, SCH\(_{2}\)), 3.28 (s, 12 H, OCH\(_{3}\)), 3.30 (t, J = 9.8, 8 H, NCH\(_{2}\)CH\(_{2}\)OCH\(_{3}\)), 3.80 (s, 8 H, ArCH\(_{2}\)), 7.47 (s, 4 H, ArH).

**Dicarbamoylated macrocycle 22.** To a solution of tert-butyldiazene (2-aminomethyl)carbamate (2.89 g, 14.22 mmol) in EtOH/CHCl\(_{3}\) (800 mL, 3 : 1 v/v) at 0°C was added a solution of 1,2-bis(4-tert-butyldimethylsilyl)ethene (3.34 g, 7.11 mmol) in CHCl\(_{3}\) (500 mL) over the course of 8 h. After the resulting mixture was stirred for further 2 h, the CHCl\(_{3}\) 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 CH\(_{2}\)Cl\(_{2}/H\(_{2}\)O (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 CH\(_{2}\)Cl\(_{2}\) (4 × 50 mL). The organic fractions were combined and dried with anhydrous MgSO\(_{4}\). 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 64.75, H 8.58, N 9.75; calculated for C\(_{44}\)H\(_{84}\)N\(_{10}\)O\(_{4}\)S\(_{2}\): 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, 1365 s, 1249 m, 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)3)], 1.45 [s (18 H, C(CH3)3)], 2.96 (t, 3J = 6 Hz, 8 H, (NCCH2CH2)2N), 3.20 [s (4 H, SCH2)], 3.49 (t, 3J = 6 Hz, 8 H, (NCCH2CH2)2N), 3.97 [s (8 H, ArCH2N)], 7.28 [s (4 H, ArH)]. 13C{1H}-NMR (100 MHz, DMSO-d6): δ = 28.6 (C(CH3)3), 34.7 (Ar(CH3)3), 37.1 [(ArSCH2)], 47.8 [(NCH2CH2)2N], 49.3 (ArCH2N), 53.8 [(NCCH2CH2)N], 79.7 (C(CH3)3), 83.8 w, 814 w, 804 w, 772 w, 701 w, 685 w, 635 w, 546 w. 1H-NMR (400 MHz, CDCl3); δ = 1.31 (s, 18 H, Ar(CH3)3), 2.07 (s, 12 H, NCH3), 2.83 [m (8 H, (NCH2CH2)2N), 3.05 [m (8 H, (NCH2CH2)2N), 3.53 [s (4 H, SCH2)], 3.70 [s (8 H, ArCH2N)], 7.21 [s (4 H, Ar-H)]. 13C{1H}-NMR (150 MHz, 400 K, DMSO-d6): δ = 31.3 (C(CH3)3), 34.5 (C(CH3)3), 38.0 (SCH2), 40.8 (NCH3), 47.3 [(NCH2CH2)2N], 56.2 [(NCCH2CH2)N], 63.1 (ArCH2N), 117.8 (q, 3J = 291 Hz, CF3), 129.2 (Ar-C), 133.4 (Ar-C), 143.3 (Ar-C), 150.8 (Ar-C), 162.1 (CF3). 19F-NMR (376 MHz, CDCl3): δ = 75.9 (s, CF3).

**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. 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 SHELXL-97. 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 (C12, C13) were found to be disordered over two sites. The site occupancies of one allyl and one ethyl group were fixed (0.74/0.26). The site occupancies 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 Fw) 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 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 tetraazacycloalkanes.36 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 nitrile functions of tetra(2-cyanoethyl)tetraazacycloalkanes can be reduced to the corresponding primary amines by reduction with LiAlH₄, diborane or H₂-RANEY®-Nickel.37–39 In our hands, the nitrile 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 N₆ dimethyl derivative 2 was also quantitatively derivatized giving the bicyclic macrocycles 19 and 20, respectively.
Crystal structures

Fig. 2 displays the molecular structure of the hexaaallylated macrocycle 8. The molecule has crystallographically imposed C$_2$ symmetry, and adopts a folded conformation. Unlike in the permethylated derivative 3, 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 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 tetramethoxycetylated 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-methoxyacetylated) 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-methoxyacetylated) derivative 19-2DMSO-2H$_2$O (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 CH3•••π interaction would be consistent with this in view.

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References

4 F. A. Cotton, G. Wilkinson, C. A. Murillo and M. Bochmann, 


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


