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

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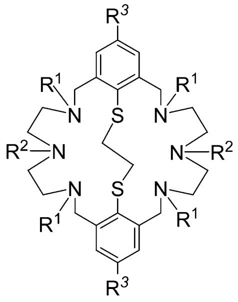
A short and efficient synthesis of a series of macrobicyclic aza-thioethers with pendant allyl (**8**, **13**, **14**), cyanethyl (**15**), 3-aminopropyl (**16**), 2-methoxyacetyl (**17**, **19**), 2-methoxyethyl (**18**, **20**), and *tert*-butyloxycarbonyl substituents (**22**, **23**) has been achieved. 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, ^{1}H-NMR, and ^{13}C-NMR spectroscopy. The crystal and molecular structures of six compounds (**8**, **15**, **17**·3DMSO, **19**·2DMSO·2H$_2$O, **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 N$_2$S$_2$ 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 **1**[24] and **2**[25] 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 **6**[28] 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**.



1 (R^1 = R^2 = H, R^3 = *t*Bu)
2 (R^1 = H, R^2 = CH$_3$, R^3 = *t*Bu)
3 (R^1 = R^2 = CH$_3$, R^3 = *t*Bu)
4 (R^1 = CH$_2$CH$_3$, R^2 = CH$_3$, R^3 = *t*Bu)
5 (R^1 = R^2 = CH$_3$, R^3 = C$_6$H$_4$-*t*Bu)
6 (R^1 = CH$_2$CH$_2$OH, R^2 = CH$_3$, R^3 = *t*Bu)
7 (R^1 = R^2 = CH$_2$CH$_2$OH, R^3 = *t*Bu)

Fig. 1 Formula of macrobicyclic aza-thioethers **1–7**.

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† Electronic supplementary information (ESI) available: ^{1}H, ^{13}C, IR and MS spectra for new compounds. Crystallographic data in CIF format for **8**, **15**, **17**·3DMSO, **19**·2DMSO·2H$_2$O, **20** and **23**. CCDC 1436363–1436368. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c5nj03197d

Experimental section

Materials and physical measurements

The bicyclic aza-thioethers **1**[24] and **2**,[25] 1,2-bis(4-*tert*-butyl-2,6-diformylthioethane) (**10**),[24] bis(2-phthalimidoethyl)amine[30] (**11**), and *tert*-butyl-bis(2-aminoethyl)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 Daltronics 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, ^{1}H-NMR, ^{13}C-NMR are included in the ESI,† for each of the synthetized 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 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 $HNEt_3Br$. 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. 170–172 °C. Found: C 72.90, H 9.32, N 9.84, S 7.21; $C_{52}H_{80}N_6S_2$ (853.37) requires: C 73.19, H 9.45, N 9.85, S 7.51. *m*/*z* (ESI+, MeOH): $C_{52}H_{80}N_6S_2$ (852.59) $[M + H^+]^+$ calcd: 853.60; found 853.60. IR (KBr): ν/cm^{-1} = 3443 w, 3078 w, 3004 w, 2962 vs, 2927 m, 2904 m, 2867 m, 2810 vs, 2712 vw, 1843 vw, 1643 w, 1593 w, 1559 vw 1477 w, 1459 w, 1442 w, 1418 w, 1404 w, 1358 m, 1260 m, 1242 w, 1229 w, 1153 w, 1100 s, 1023 vw, 993 m, 963 w, 917 vs, 900 vw, 863 vw, 801 vw, 734 vw, 690 vw, 639 vw, 600 vw, 573 vw. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.31 (s, 18 H, $C(CH_3)_3$), 2.60 (m, 16 H, (NCH_2CH_2N)), 2.74 (s, 4 H, SCH_2), 2.97 (d, 8 H, ^3J = 6.4 Hz, NCH_2CHCH_2), 3.10 (d, 4 H, ^3J = 6.4 Hz, NCH_2CHCH_2), 3.70 (s, 8 H, $ArCH_2$), 5.05–5.18 (m, 12 H, CH = CH_2), 5.82 (m, 6 H, $CH{=}CH_2$), 7.50 (s, 4 H, Ar*H*). $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$): δ = 31.60 ($C(CH_3)_3$), 34.98 ($C(CH_3)_3$), 35.82 ($(SCH_2)_2$), 50.89 ($(NCH_2CH_2)_2N$), 51.71 ($(NCH_2CH_2)_2N$), 56.88 ($ArCH_2NCH_2CHCH_2$), 57.51 ($ArCH_2$), 59.23 (NCH_2CHCH_2), 116.99 ($ArCH_2NCH_2CH{=}CH_2$), 117.46 ($NCH_2CH{=}CH_2$), 124.86 (Ar*C*-3,3′), 128.18 (Ar*C*-2,2′), 136.35 ($ArCH_2NCH_2CH{=}CH_2$), 136.34 ($CH{=}CH_2$), 143.71 (Ar*C*-1), 151.40 (Ar*C*-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 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. $HNEt_3Br$ 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 $MeCN/CH_2Cl_2$. Yield: 649 mg (0.46 mmol, 81%), colorless solid. Found: C 72.0, H 9.42, N 9.94, S 7.81; $C_{48}H_{76}N_6S_2$ (801.30) requires: C 71.95, H 9.56, N 10.49, S 8.00. *m*/*z* (ESI+, MeOH): $C_{48}H_{76}N_6S_2$ (800.56) $[M + H^+]^+$ calcd: 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 vw 1477 m, 1459 s, 1415 m, 1357 s, 1330 m, 1311 m, 1262 vs, 1216 w, 1194 w, 1154 s, 1106 vs, 1035 vs, 992 s, 980 m, 914 s, 883 m, 801 vs, 741 vw, 687 w. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.21 (s, 18 H, $C(CH_3)_3$), 2.21 (s. 6 H, CH_3), 2.50–2.59 (m, 16 H, NCH_2CH_2N), 2.85 (m, 8 H, NCH_2CHCH_2), 2.87 (s, 4 H, SCH_2), 3.76 (s, 8 H, $ArCH_2$), 5.02–5.10 (m, 8 H, NCH_2CHCH_2), 5.74 (m, 4 H, $CH{=}CH_2$), 7.37 (s, 4 H, Ar*H*). $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$): δ = 31.39 ($C(CH_3)_3$), 34.76 ($C(CH_3)_3$), 36.69 ($(SCH_2)_2$), 42.94 (CH_3), 51.16 ($(NCH_2CH_2)_2N$), 55.17 ($(NCH_2CH_2)_2N$), 56.58 ($NCH_2CH{=}CH_2$), 57.91 ($ArCH_2$), 117.50 ($CH{=}CH_2$), 125.73 (Ar*C*-3,3′), 129.31 (Ar*C*-2,2′), 135.42 ($CH{=}CH_2$), 143.78 (Ar*C*-1), 151.24 (Ar*C*-4). 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), K_2CO_3 (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 68.19, H 5.54, N 10.34; $C_{23}H_{21}N_3O_4$ (403.44) requires: C 68.47, H 5.25, N 10.42. IR (KBr): ν/cm^{-1} = 3461 w, 3091 vw, 3018 vw, 2955 w, 2835 w, 1769 s, 1711 vs, 1611 m, 1468 s, 1438 s, 1404 s, 1387 vs, 1332 m, 1306 m, 1276 w, 1191 w, 1160 vw, 1142 w, 1088 m,1041 m, 1018 s, 974 w, 939 w, 874 w, 803 w, 773 vw, 726 vs, 630 w, 613 w, 567 vw, 532 m, 469 vw. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.74 (t, ^3J = 6.4 Hz, 4 H, ($NCH_2CH_2)_2N$, 3.15 (d, ^3J = 6.4 Hz, 2 H, $CH_2CH{=}CH_2$), 3.67 (t, ^3J = 6.4 Hz, 4 H, ($NCH_2CH_2)_2N$, 4.98–5.08 (dd, 1 H, ^3J = 16.4 Hz, ^3J = 10.4 Hz, $CH{=}CH_2$), 5.56–5.63 (m, 2 H, $CH{=}CH_2$), 7.60–7.67 (m, 8 H, ArH). $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$): δ = 36.30 ($NCH_2CH_2)_2N$), 51.90 ($NCH_2CH_2)_2N$, 57.03 ($CH_2CH{=}CH_2$), 118.47 ($CH{=}CH_2$), 123.59 (ArC-2,2′), 132.73 (ArC-1,1′), 133.96 (ArC-3,3′), 135.56 ($CH{=}CH_2$), 168.74 (*C*O).

***N*-Allyl-bis(2-aminoethyl)-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 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 vw, 461 w. ^{1}H-NMR (400 MHz, D_2O): δ = 3.45 (m, ^3J = 6.4 Hz, 4 H, (H_2NCH_2), 3.52 (t, ^3J = 6.4 Hz, 4 H, $(CH_2)_2N$), 3.89 (d, ^3J = 7.2 Hz, 2 H, $NCH_2CH{=}CH_2$), 5.67 (m, 1 H, $CH{=}CH_2$), 5.93 (m, 2 H, $CH{=}CH_2$). $^{13}C\{^1H\}$-NMR (100 MHz,

D_2O): δ = 34.0 (H_2NCH_2), 49.6 ($(CH_2)_2N$), 56.3 (NCH_2), 124.8 ($CH{=}CH_2$), 128.2 ($CH{=}CH_2$).

***N*-Allyl-bis(2-aminoethyl)-amin (13).** A suspension of *N*-allyl-bis(2-aminoethyl)-amine-trihydrochloride (9.76 g, 38.6 mmol) and $KOC(CH_3)_3$ (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 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. ^{1}H-NMR (400 MHz, CD_3OD): δ = 2.54 (t, ^3J = 6.0 Hz, 4 H, (H_2NCH_2), 2.69 (t, ^3J = 6.0 Hz, 4 H, ($(CH_2)_2N$), 3.14 (d, ^3J = 6.4 Hz, 2 H, $NCH_2CH{=}CH_2$), 5.17 (m, 1 H, $CH{=}CH_2$), 5.89 (m, 2 H, $CH{=}CH_2$). $^{13}C\{^1H\}$-NMR (100 MHz, CD_3OD): δ = 38.57 (H_2NCH_2), 55.96 ($(CH_2)_2N$), 57.12 (NCH_2), 116.70 ($CH{=}CH_2$), 135.27 ($CH{=}CH_2$).

Bisallylated aza-thioether 14. A solution of *N*-allyl-bis(2-aminoethyl)-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-diformylphenylthio)ethane **10** (1.08 g, 2.30 mmol) in CH_2Cl_2 (500 mL) were added simultaneously over the course of 3 h into a EtOH/CH_2Cl_2 (600 mL, 1 : 3 v : v) solvent mixture. After the resulting mixture was stirred for further 2 d, the CH_2Cl_2 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 conc (final pH = 1). The mixture was subsequently evaporated to dryness, re-dissolved in CH_2Cl_2/H_2O (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 K_2CO_3. 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; $C_{40}H_{64}N_6S_2$ (693.11) requires: C 69.32, H 9.31, N 12.13, S 9.25. IR (KBr): ν/cm^{-1} = 3424 m, 3261 m, 2955 vs, 2902 s, 2867 s, 2803 vs, 1599 m, 1577 m, 1451 vs, 1417 s, 1366 s, 1330 w, 1293 w, 1262 m, 1230 w, 1205 m, 1149 s, 1094 s, 1054 s, 1029 s, 921 m, 897 w, 804 s. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.30 (s, 18 H, $C(CH_3)_3$), 2.81 (s, 4 H, SCH_2), 2.96 (m, 8 H, $(NCH_2CH_2)_2N$), 3.14 (m, 8 H, $(NCH_2CH_2)_2N$), 3.30 (d, J = 6.6 Hz, 4 H, $CH_2CH{=}CH_2$), 4.12 (s, 8 H, $ArCH_2$), 5.21 (m, 2 H, $CH{=}CHH$), 5.23 (m, 2 H, $CH{=}CHH$), 5.90 (m, 2 H, $CH{=}CH_2$), 6.32 (s (br), 4 H, NH), 7.72 (s, 4 H, ArH). $^{13}C\{^1H\}$-NMR (75 MHz, $CDCl_3$): δ = 31.36 ($C(CH_3)_3$), 35.20 ($C(CH_3)_3$), 37.58 $(SCH_2)_2$, 49.02 ($(NCH_2CH_2)_2N$), 50.31 ($(NCH_2CH_2)_2N$), 51.41 ($ArCH_2$), 60.20 ($NCH_2CH{=}CH_2$), 119.32 ($CH{=}CH_2$), 128.34 (Ar*C*-3,3′), 130.07 (Ar*C*-2,2′), 134.56 ($CH{=}CH_2$), 140.16 (Ar*C*-1), 154.18 (Ar*C*-4).

Hexa-(cyanoethylated) azathioether 15. The thioether **1** (4.67 g, 7.62 mmol) was dissolved in acrylonitrile (3 mL) and the resulting mixture was stirred for 3 d at 80 °C. The excess acrylonitrile was evaporated, and the yellow solid was dissolved in 100 mL of a 2 : 1 CH_2Cl_2/CH_3CN solvent mixture. Evaporation of the CH_2Cl_2 provided a colorless solid, which was filtered and dried in air. Yield: 7.08 g (7.6 mmol, 99%), colorless solid. M.p. 170–172 °C. Found: C 66.83, H 7.92, N 17.82; $C_{52}H_{74}N_{12}S_2$ (931.37) requires: C 67.06, H 8.01, N 18.05. *m*/*z* (ESI+, MeOH): $C_{52}H_{74}N_{12}S_2$ (930.56) $[M + H^+]^+$ calcd: 931.57; found 931.56. 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 m, 987 m, 961 m, 947 m, 887 s, 832 w, 801 vw, 774 m, 733 m, 704 vw, 681 vw, 650 w, 596 w. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.33 (s, 18 H, $ArC(CH_3)_3$), 2.38 (m, 8 H, CH_2CN),2.40 (m, 4 H, CH_2CN), 2.66 (m, 8 H, $(NCH_2CH_2)_2N$), 2.67 (s, 4 H, SCH_2), 2.68 (m, 8 H, $(NCH_2CH_2)_2N$), 2.73 (m, 8 H, CH_2CH_2CN), 2.78 (m, 4 H, CH_2CH_2CN), 3.76 (s, 8 H, $ArCH_2$), 7.53 (s, 4 H, ArH). $^{13}C\{^1H\}$-NMR (75 MHz, $CDCl_3$): δ = 17.03 (CH_2CN), 17.38 (CH_2CN), 31.46 ($C(CH_3)_3$), 35.00 ($C(CH_3)_3$), 36.16 (SCH_2), 47.3 ($ArCH_2NCH_2CH_2CN$), 51.82 (CH_2CH_2CN), 52.39 ($(NCH_2CH_2)_2N$), 52.96 ($(NCH_2CH_2)_2N$), 63.1 ($ArCH_2N$), 118.90 ($ArCH_2NCH_2CH_2CN$), 118.96 (CN), 125.20 (Ar*C*-3,3′), 128.17 (Ar*C*-2,2′), 142.71 (Ar*C*-1), 152.26 (Ar*C*-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_3SiCl (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 CH_2Cl_2 (4 × 20 mL). The organic fractions were combined and dried with anhydrous K_2CO_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): $C_{52}H_{98}N_{12}S_2$ (955.56) $[M + H^+]^+$ calcd: 955.76; found 955.76. IR (KBr): ν/cm^{-1} = 3360 (w, NH_2), 3051 m, 2963 s, 1593 (w, NH_2), 1261 s, 1097 (s, C–S), 1021 s, 799 s. ^{1}H-NMR (700 MHz, $CDCl_3$): δ = 1.26 (s, 18 H, $C(CH_3)_3$), 1.49 (tt, ^3J = 6.7, ^3J = 6.6 Hz, 8 H, $CH_2CH_2CH_2NH_2$), 1.56 (tt, ^3J = 7.0, ^3J = 6.7 Hz, 4 H, $CH_2CH_2CH_2NH_2$), 1.64 (s br, 6 H, NH_2), 2.35 (t, ^3J = 6.6 Hz, 8 H, $CH_2CH_2CH_2NH_2$), 2.47 (t, ^3J = 7.0 Hz, 4 H, $CH_2CH_2CH_2NH_2$), 2.53 (m, 16 H, NCH_2CH_2N), 2.55 (s, 4 H, SCH_2), 3.51 (s, 8 H, $ArCH_2$), 7.41 (s, 4 H, ArH). $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$): δ = 30.25 ($ArCH_2NCH_2CH_2CH_2NH_2$), 30.42 ($C(CH_3)_3$), 30.56 ($CH_2CH_2NH_2$), 33.77 ($C(CH_3)_3$), 34.32 (SCH_2), 39.48 (CH_2NH_2), 39.48 (CH_2NH_2), 50.25 ($ArCH_2NCH_2CH_2CH_2N$), 53.37 (NCH_2CH_2-CH_2NH_2), 56.65 ($ArCH_2$), 123.25 (Ar*C*-3,3′), 126.60 (Ar*C*-2,2′), 142.45 (Ar*C*-1), 150.12 (Ar*C*-4).

Hexa(2-methoxyacetylated) aza-thioether 17. Compound **1** (2.50 g, 4.08 mmol) in dry $CHCl_3$ (20 mL), 2-methoxyacetyl 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 7.35, N 7.89, S 5.88; $C_{52}H_{80}N_6O_{12}S_2$ (1045.36) requires: C 59.75, H 7.71, N 8.04, S 6.13. *m*/*z* (ESI+, MeOH):

$C_{52}H_{80}N_6O_{12}S_2$ (1044.53) $[M + H^+]^+$ calcd: 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, 1364 m, 1301 m, 1196 s, 1125 s, 1050 w, 996 w, 966 w, 934 w, 830 vw, 801 vw, 773 vw 729 vw, 686 vw. ^{1}H-NMR (600 MHz, 400 K, DMSO-d$_6$): δ = 1.20 (s, 18 H, C(C*H*$_3$)), 3.01 (s, 4 H, SC*H*$_2$), 3.34 (s, 12 H, OC*H*$_3$), 3.40 (s, 6 H, OC*H*$_3$), 3.46 (s, 16 H, NC*H*$_2$C*H*$_2$N), 4.10 (s, 8 H, C*H*$_2$O), 4.18 (s, 4 H, C*H*$_2$OCH$_3$), 4.74 (s, 8 H, ArC*H*$_2$), 6.99 (s, 4 H, Ar-H). ^{13}C{^{1}H}-NMR (150 MHz, 400 K, DMSO-d$_6$): δ = 29.81 (C(CH$_3$)$_3$), 33.56 (C(C*H*$_3$)$_3$), 35.29 (SCH$_2$), 44.89 (br, NCH$_2$CH$_2$N), 48.49 (Ar*C*H$_2$), 57.68 (O*C*H$_3$), 57.73 (O*C*H$_3$), 70.12 (O*C*H$_2$O), 70.21 (O*C*H$_2$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 additionally characterized by X-ray crystallography.

Hexa(2-methoxyethylated) aza-thioether 18. Compound **17** (3.03 g, 2.90 mmol) in THF (20 mL), LiBH$_4$ (827 mg, 38.0 mmol) and Me$_3$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 (2 mL) 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 solvent 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 64.76, H 9.89, N 8.65, S 6.50; $C_{52}H_{92}N_6O_6S_2$ (961.46) requires: C 64.96, H 9.65, N 8.74, S 6.67. *m*/*z* (ESI+, MeOH): $C_{52}H_{92}N_6O_6S_2$ (960.55) $[M + H^+]^+$ calcd: 961.66; found 961.7. IR (KBr): ν/cm^{-1} = 3425 s, 2953 vs, 2871 vs, 2816 vs, 2336 vw, 1954 vw, 1667 m, 1594 m,1559 w, 1451 vs, 1404 s, 1362 vs, 1297 s, 1261 m, 1199 s, 1119 vs, 1080 vs, 1018 s, 958 m, 927 m, 894 m, 781 w, 733 w, 704 w, 647 w, 558 w. ^{1}H-NMR (600 MHz, 400 K, DMSO-d$_6$): δ = 1.32 (s, 18 H, C(C*H*$_3$)), 2.64 (t, ^3J = 5.3, 8 H, NC*H*$_2$CH$_2$OCH$_3$), 2.73 (m, 4 H, NC*H*$_2$CH$_2$OCH$_3$)), 2.75 (s, 4 H, SC*H*$_2$), 2.85 (m, 16 H, NC*H*$_2$-C*H*$_2$N), 3.28 (s, 12 H, OC*H*$_3$), 3.31 (s, 6 H, OC*H*$_3$), 3.41 (t, ^3J = 5.3, 8 H, C*H*$_2$OCH$_3$), 3.60 (m, 4 H, C*H*$_2$OCH$_3$), 3.78 (s, 8 H, ArC*H*$_2$), 7.53 (s, 4 H, Ar*H*). ^{13}C{^{1}H}-NMR (100 MHz, CDCl$_3$): δ = 31.32 (C(*C*H$_3$)$_3$), 34.68 (*C*(CH$_3$)$_3$), 35.57 (S*C*H$_2$), 50.82 (N*C*H$_2$CH$_2$OCH$_3$), 50.92 ((N*C*H$_2$CH$_2$)$_2$N), 52.74 (ArCH$_2$N*C*H$_2$CH$_2$OCH$_3$), 54.68 ((NCH$_2$*C*H$_2$)$_2$N), 58.17 (Ar*C*H$_2$N), 58.92 (O*C*H$_3$), 58.97 (O*C*H$_3$), 70.50 (*C*H$_2$OCH$_3$), 70.82 (*C*H$_2$OCH$_3$), 125.72 (Ar*C*-3,3′), 128.55 (Ar*C*-2,2′), 142.30 (Ar*C*-1), 151.87 (Ar*C*-4).

Tetra(2-methoxyacetylated) aza-thioether 19. By analogy to the preparation of **17**, compound **2** (1.60 g, 2.50 mmol) in dry chloroform (20 mL), 2-methoxyacetyl chloride (1.14 g, 10.5 mmol), and triethylamine (1.10 g, 10.0 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: 2.00 g (86%). Found: C 61.80, H 8.25, N 8.89, S 6.65; $C_{48}H_{76}N_6O_8S_2$ (929.29) requires: C 62.04, H 8.24, N 9.04, S 6.90. *m*/*z* (ESI+, MeOH): $C_{48}H_{76}N_6O_8S_2$ (928.52) $[M + H^+]^+$ calcd: 929.52; found 929.52. IR (KBr): ν/cm^{-1} = 3449 s, 2958 vs, 2822 m, 1655 vs νCO, 1469 vs, 1430 vs, 1361 m, 1296 m, 1197 s, 1125 vs, 1068 m, 1019 m, 972 w, 937 m, 800 w, 750 w, 726 w, 687 w, 596 m. ^{1}H-NMR (600 MHz, 400 K, DMSO-d$_6$): δ = 1.21 (s, 18 H, C(C*H*$_3$)$_3$), 2.43 (s, 6 H, NC*H*$_3$), 2.76 (m, 8 H, (NCH$_2$C*H*$_2$)$_2$NCH$_3$), 3.03 (s, 4 H, SC*H*$_2$), 3.32 (s, 12 H, OC*H*$_3$), 3.45 (s, 8 H, (NC*H*$_2$CH$_2$)$_2$NCH$_3$), 4.80 (s, 8 H, ArC*H*$_2$), 7.05 (s, 4 H, ArH). ^{13}C{^{1}H}-NMR (150 MHz, 400 K, DMSO-d$_6$): δ = 29.87 (C(*C*H$_3$)$_3$), 33.51 (*C*(CH$_3$)$_3$), 35.66 (S*C*H$_2$), 41.91 (NCH$_3$), 44.35 (N*C*H$_2$CH$_2$N), 48.53 (NCH$_2$*C*H$_2$)$_2$NCH$_3$), 54.85 (Ar*C*H$_2$), 57.64 (O*C*H$_3$), 70.35 (NCO*C*H$_2$OCH$_3$), 121.59 (Ar*C*-3,3′), 126.21 (Ar*C*-2,2′), 140.79 (Ar*C*-1), 151.44 (Ar*C*-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), LiBH$_4$ (152 mg, 6.98 mmol) and Me$_3$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 solvent gave **20** 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 66.13, H 9.78, N 9.41, S 7.22; $C_{48}H_{84}N_6O_4S_2$ (873.36) requires: C 66.01, H 9.69, N 9.62, S 7.34. *m*/*z* (ESI+, MeOH): $C_{48}H_{84}N_6O_4S_2$ (872.60) $[M + H^+]^+$ calcd: 873.61; found 873.60. IR (KBr): ν/cm^{-1} = 3425 s, 2953 vs, 2871 vs, 2816 vs, 2336 vw, 1954 vw, 1667 m, 1594 m, 1559 w, 1451 vs, 1404 s, 1362 vs, 1297 s, 1261 m, 1199 s, 1119 vs, 1080 vs, 1018 s, 958 m, 927 m, 894 m, 781 w, 733 w, 704 w, 647 w, 558 w. ^{1}H-NMR (600 MHz, 400 K, DMSO-d$_6$): δ = 1.30 (s, 18 H, C(C*H*$_3$)$_3$), 2.25 (s, 6 H, NCH$_3$), 2.50 (s(br), 8 H, (NCH$_2$C*H*$_2$)$_2$NCH$_3$), 2.60 (t, ^3J = 9.8, 8 H, NC*H*$_2$CH$_2$OCH$_3$), 2.68 (s (br), 8 H, (NC*H*$_2$CH$_2$)$_2$NCH$_3$), 2.79 (s, 4 H, SC*H*$_2$), 3.28 (s, 12 H, OC*H*$_3$), 3.39 (t, ^3J = 9.8, 8 H, NCH$_2$-C*H*$_2$OCH$_3$), 3.80 (s, 8 H, ArC*H*$_2$), 7.47 (s, 4 H, Ar*H*). ^{13}C{^{1}H}-NMR (100 MHz, CDCl$_3$): δ = 31.43 (C(*C*H$_3$)$_3$), 34.87 (*C*(CH$_3$)$_3$), 36.16 (S*C*H$_2$), 43.42 (NCH$_3$), 52.35 ((N*C*H$_2$CH$_2$)$_2$N), 53.37 (ArCH$_2$-N*C*H$_2$CH$_2$OCH$_3$), 58.57 (Ar*C*H$_2$N), 58.93 (O*C*H$_3$), 71.50 (*C*H$_2$OCH$_3$), (one CH$_2$ signal not observed), 125.70 (Ar*C*-3,3′), 128.79 (Ar*C*-2,2′), 143.79 (Ar*C*-1), 151.44 (Ar*C*-4).

Dicarbamoylated macrobicycle 22. To a solution of *tert*-butyl bis(2-aminoethyl)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*-butyl-2,6-diformylphenylthio)ethane (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 d, 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; $C_{44}H_{72}N_6O_4S_2$ 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, 1411 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. ^{1}H-NMR (400 MHz, CDCl$_3$): δ = 1.29 (s, 18 H, ArC(C*H*$_3$)$_3$), 1.45 (s, 18 H, C(C*H*$_3$)$_3$), 2.96 (t, ^3J = 6 Hz, 8 H, (NC*H*$_2$CH$_2$)$_2$N), 3.20 (s, 4 H, SC*H*$_2$), 3.49 (t, ^3J = 6 Hz, 8 H, (NCH$_2$C*H*$_2$)$_2$N), 3.97 (s, 8 H, ArC*H*$_2$N), 7.28 (s, 4 H, Ar*H*). ^{13}C{^{1}H}-NMR (100 MHz, CDCl$_3$): δ = 28.6 (C(*C*H$_3$)$_3$), 31.4 (ArC(*C*H$_3$)$_3$), 34.7 (Ar*C*(CH$_3$)$_3$), 37.1 ((ArS*C*H$_2$)$_2$), 47.8 ((NCH$_2$*C*H$_2$)$_2$N), 49.3 (Ar*C*H$_2$N), 53.8 ((N*C*H$_2$CH$_2$)$_2$N), 79.7 (*C*(CH$_3$)$_3$), 126.4 (Ar*C*-3,3), 130.0 (Ar*C*-2,2), 144.8 (Ar*C*-1), 152.2 (Ar*C*-4), 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 d 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 CH$_2$Cl$_2$/H$_2$O (1 : 1 v/v) was added. After stirring for 2 h, the layers were separated and the aqueous phase was extracted with CH$_2$Cl$_2$ (4 × 25 mL). The organic fractions were combined and dried with anhydrous MgSO$_4$. Evaporation gave the crude product, which was purified by recrystallization from CH$_2$Cl$_2$/EtOH (1 : 1 v/v). Yield: 910 mg (1.05 mmol, 75%), colorless crystals. Mp 217–219 °C. Found: C 65.93, H 9.23, N 9.59; C$_{48}$H$_{80}$N$_6$O$_4$S$_2$ (869.32) requires: C 66.32, H 9.28, N 9.67. *m*/*z* (ESI+, MeOH): C$_{48}$H$_{80}$N$_6$O$_4$S$_2$ (868.57) [M + H$^+$]$^+$ calcd: 869.58; found 869.50. IR (KBr): ν/cm^{-1} = 3444 m, 2965 s, 2857 m, 2802 s, 2716 w, 1688 s (ν(C═O)), 1569 w, 1557 w, 1479 s, 1456 s, 1416 s, 1393 m, 1365 s, 1293 m, 1273 m, 1249 m, 1227 m, 1209 m, 1161 s, 1125 m, 1109 m, 1046 m, 1035 m, 1019 m, 984 w, 970 w, 953 w, 912 w, 905 w, 891 m, 864 w, 838 w, 814 w, 804 w, 772 w, 701 w, 685 w, 635 w, 546 w. ^{1}H-NMR (400 MHz, CDCl$_3$): δ = 1.30 (s, 18 H, ArC(C*H*$_3$)$_3$), 1.48 (s, 18 H, C(C*H*$_3$)$_3$), 2.08 (m, 12 H, NC*H*$_3$), 2.69 (m, 8 H, (NC*H*$_2$CH$_2$)$_2$N), 3.20 (s, 4 H, SC*H*$_2$), 3.40 (m, 8 H, (NCH$_2$C*H*$_2$)$_2$N), 3.71 (s, 8 H, ArC*H*$_2$N), 7.28 (s, 4 H, Ar*H*). ^{13}C{^{1}H}-NMR (100 MHz, CDCl$_3$): δ = 28.6 (C(*C*H$_3$)$_3$), 31.4 (ArC(*C*H$_3$)$_3$), 34.7 (Ar*C*(CH$_3$)$_3$), 37.1 (S*C*H$_2$), 41.3 (N*C*H$_3$), 45.6 ((NCH$_2$*C*H$_2$)$_2$N), 56.7 ((N*C*H$_2$CH$_2$)$_2$N), 61.9 (Ar*C*H$_2$N), 79.5 (*C*(CH$_3$)$_3$), 126.8 (Ar*C*-3,3), 131.4 (Ar*C*-2,2)), 143.8 (Ar*C*-1), 150.9 (Ar*C*-4), 155.7 (*C*═O). This compound was additionally characterized by X-ray crystallography.

Compound 24·CF$_3$COOH. To a suspension of **23** (250 mg, 0.29 mmol) in CH$_2$Cl$_2$ (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 CH$_2$Cl$_2$ (4 × 5 mL). The organic fractions were combined and dried with anhydrous MgSO$_4$. 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 63.09, H 8.82, N 11.43; C$_{38}$H$_{64}$N$_6$S$_2$ CF$_3$CO$_2$H (783.12) requires: C 61.35, H 8.37, N 10.73. *m*/*z* (ESI+, MeOH): C$_{38}$H$_{64}$N$_6$S$_2$ (668.46) [M + H$^+$]$^+$ calcd: 669.47; found 669.47. IR (KBr): ν/cm^{-1} = 3441 s, 3291 m ν(NH), 2954 s, 2852 m, 2780 s, 1681 s ν(CO), 1599 m, 1458 s, 1394 w, 1364 m, 1258 m, 1227 m, 1201 s, 1175 s, 1131 s, 1074 w, 1048 m, 1022 m, 930 w, 890 w, 832 w, 800 m, 720 m. ^{1}H-NMR (400 MHz, CDCl$_3$): δ = 1.31 (s, 18 H, ArC(C*H*$_3$)$_3$), 2.07 (s, 12 H, NC*H*$_3$), 2.83 (m, 8 H, (NC*H*$_2$CH$_2$)$_2$N), 3.05 (m, 8 H, (NCH$_2$C*H*$_2$)$_2$N), 3.53 (s, 4 H, (SC*H*$_2$)), 3.70 (s, 8 H, ArC*H*$_2$N), 7.21 (s, 4 H, Ar-*H*). ^{13}C{^{1}H}-NMR (150 MHz, 400 K, DMSO-d$_6$): δ = 31.3 (C(*C*H$_3$)$_3$), 34.5 (*C*(CH$_3$)$_3$), 38.0 (S*C*H$_2$), 40.8 (N*C*H$_3$), 47.3 ((NCH$_2$*C*H$_2$)$_2$N), 56.2 ((N*C*H$_2$CH$_2$)$_2$N), 63.1 (Ar*C*H$_2$N), 117.8 (q, ^1J = 291 Hz, *C*F$_3$), 129.2 (Ar*C*-3,3), 133.4 (Ar*C*-2,2), 143.3 (Ar*C*-1), 150.8 (Ar*C*-4), 162.1 (CF$_3$*C*OO). ^{19}F-NMR (376 MHz, CDCl$_3$): −75.9 (s, C*F*$_3$).

Crystallography

Suitable single crystals of compounds **8**, **15**, **17**·3DMSO, **19**·2DMSO·2H$_2$O, **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·2H$_2$O, 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-K_α 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[33] and refined by full-matrix least-squares techniques on the basis of all data against F^2 using SHELXL-97.[34] PLATON was used to search for higher symmetry.[35] 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 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 F_o) with the SQUEEZE procedure implemented in the PLATON program suite. Removing the DMSO molecule led to a solvent accessible void of 257 Å^3, in good agreement with the space needed by one DMSO molecules. The solvate molecules in **19**·2DMSO·2H$_2$O were also found to be heavily disordered and were therefore removed utilizing the SQUEEZE procedure. This led to solvent accessible voids of 628 Å^3, attributed to the space needed for two DMSO and two H$_2$O molecules.

Results and discussion

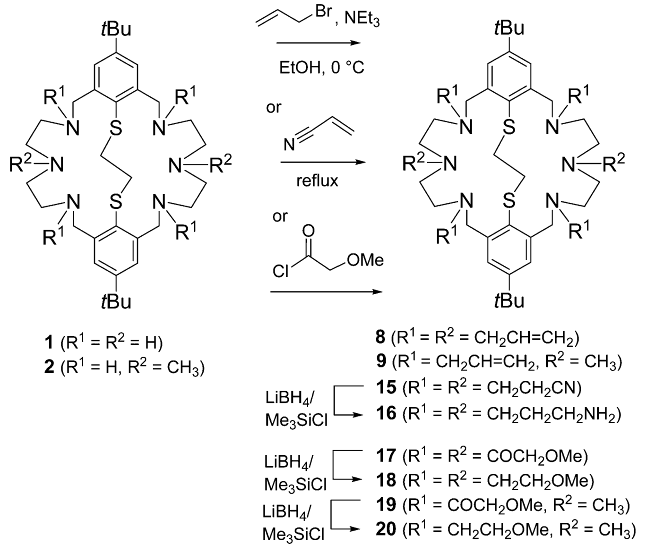
Synthesis

Scheme 1 depicts the synthetic procedures for compounds **8**, **9**, and **15–20**. The reaction of **1** with allylbromide in the presence of NEt$_3$ 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

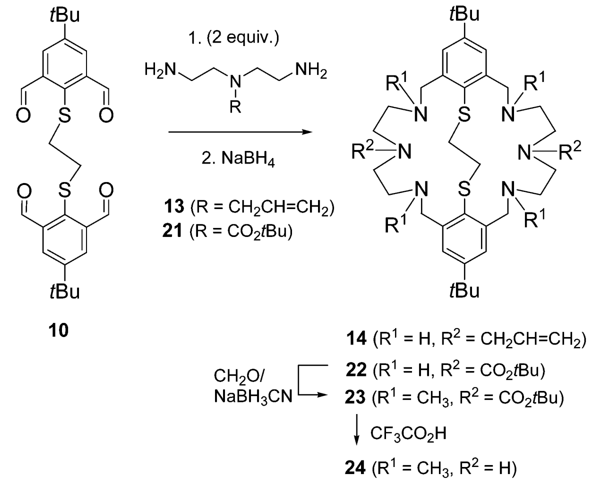
Table 1 Selected crystallographic data for compounds **8**, **15**, **17**·3DMSO, **19**·2DMSO·2H$_2$O, **20**, and **23**

Compound	**8**	**15**	**17**·3DMSO[a]	**19**·2DMSO·2H$_2$O[b]	**20**	**23**
Formula	$C_{52}H_{80}N_6S_2$	$C_{52}H_{74}N_{12}S_2$	$C_{56}H_{92}N_6O_{14}S_4$	$C_{48}H_{76}N_6O_8S_2$	$C_{48}H_{84}N_6O_4S_2$	$C_{48}H_{80}N_6O_4S_2$
Diffractometer	IPDS-2	IPDS-1	IPDS-2	IPDS-2	IPDS-2	IPDS-1
T/K	180(2)	213(2)	180(2)	180(2)	180(2)	213(2)
Formula weight [g mol^{-1}]	853.34	931.35	1201.60	929.27	873.33	869.30
Space group	$C2/c$	$I2/a$	$P\bar{1}$	$I2/a$	$C2/c$	$P2_1/c$
a, Å	27.300(2)	19.481(4)	12.894(2)	18.934(3)	27.580(4)	13.007(3)
b, Å	10.0280(6)	9.905(2)	13.432(2)	10.294(3)	9.948(2)	10.269(2)
c, Å	20.646(1)	26.740(5)	20.463(3)	31.857(5)	19.845(3)	19.285(4)
α, deg	90.00	90.00	91.86(2)	90	90	90
β, deg	111.911(4)	99.08(3)	100.24(2)	105.36(2)	109.50(2)	97.50(3)
γ, deg	90.00	90.00	106.80(2)	90	90	90
V, Å^3	5243.9(5)	5095(2)	6476(2)	5987(2)	5132(2)	2553.7(9)
Z	4	4	2	4	4	2
D_{calcd}, g cm^{-3}	1.081	1.214	1.200	1.031	1.130	1.131
Cryst. size, mm^3	0.25 × 0.20 × 0.10	0.15 × 0.15 × 0.15	0.23 × 0.23 × 0.10	0.39 × 0.23 × 0.18	0.15 × 0.27 × 0.18	0.20 × 0.15 × 0.05
μ(Mo Kα), mm^{-1}	0.140	0.153	0.205	0.136	0.149	0.150
R_1[c] (R_1 all data)	0.0547 (0.0754)	0.0427 (0.0618)	0.0506 (0.0951)	0.0458 (0.0566)	0.0677 (0.0875)	0.0360 (0.1038)
wR_2[d] (wR_2 all data)	0.1458 (0.1552)	0.1029 (0.1078)	0.1019 (0.1127)	0.1321 (0.1387)	0.2012 (0.2136)	0.0446 (0.0519)
Max, min peaks, e Å^{-3}	0.654/−0.394	0.505/−0.264	0.260/−0.426	0.431/−0.228	1.598/−0.519	0.147/−0.132
CCDC	1436363	1436364	1436365	1436366	1436367	1436368

[a] Three DMSO solvate molecules were located from the Fourier map but one was heavily disordered such that it was removed from the structure. [b] The DMSO and H$_2$O solvate molecules were located from the Fourier map but were heavily disordered such that they were all removed from the structure, see Experimental section. [c] $R_1 = \Sigma\|F_o| - |F_c\|/\Sigma|F_o|$. [d] $wR_2 = \{\Sigma[w(F_o^2 - F_c^2)^2]/\Sigma[w(F_o^2)^2]\}^{1/2}$.



Scheme 1 Synthesis of compounds **8**, **9**, and **15–20**.



Scheme 2 Synthesis of compounds **14** and **22–24**.

corresponding tetraallylated system **9** (75%) as colorless needles after recrystallization from CHCl$_3$/EtOH. The reductive amination of tetraaldehyde **10** with *N*^{1}-(3-aminopropyl)-*N*^{1}-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 LiAlH$_4$, diborane or H$_2$-RANEY®-Nickel.[37–39] In our hands, the nitrile **15** failed to react in this fashion. Therefore, an alternative protocol involving reduction with LiBH$_4$/Me$_3$SiCl 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 N$_6$S$_2$-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 LiBH$_4$/Me$_3$SiCl. As an illustration of the utility of this sequence, the *N*,*N*′-dimethyl derivative **2** was also quantitatively derivatized giving the bicyclic macrocycles **19** and **20**, respectively.

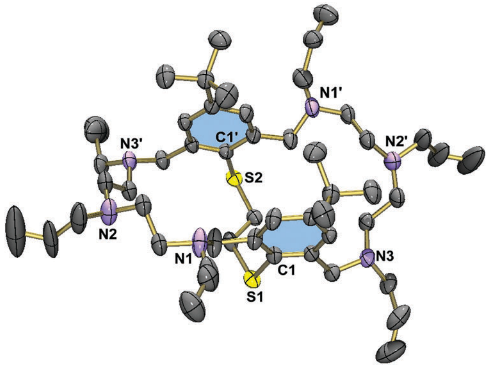


Fig. 2 Molecular structure of **8** in the crystal with atomic numbering for key atoms. Thermal ellipsoids are drawn at the 50% probability level. Hydrogen atoms have been omitted for clarity. Symmetry code used to generate equivalent atoms: 1 − *x*, *y*, 0.5 − *z*.

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 $NaBH_3CN$ to give the tetramethylated derivative **23** in 75% yields, which was fully characterized including X-ray crystallography. Finally, deprotection of **23** with trifluoroacetic acid gave the desired amine **24**.

All new compounds were characterized by elemental analysis, IR, ^{1}H and ^{13}C 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 C_2 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 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).[41] In contrast to the hexaallylated macrocycle, molecules of **15** are connected *via* intermolecular CH_2···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 tetramethoxyethylated 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·$2H_2O$ (Fig. 4, right). This compound crystallizes also

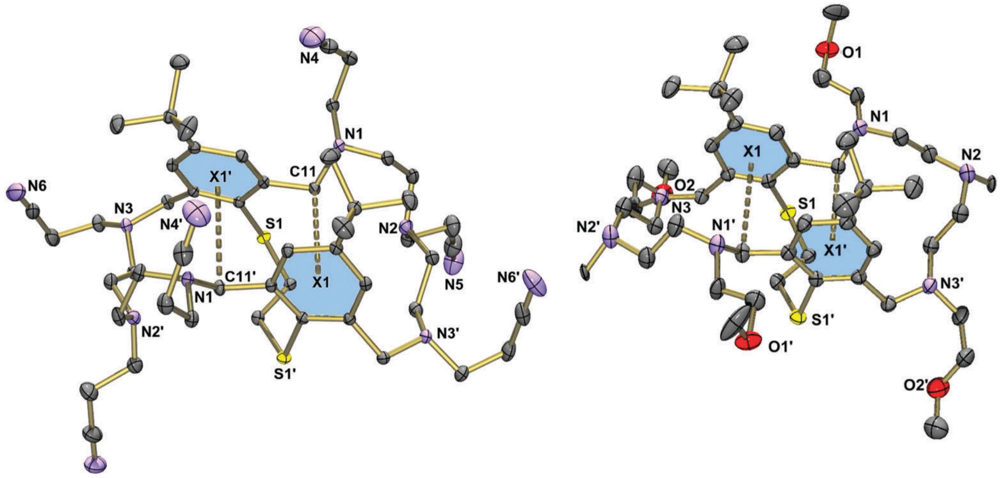


Fig. 3 Left: Molecular structure of **15** in the crystal with atomic numbering for key atoms and centroids of aromatic rings. Thermal ellipsoids are set at 30% probability. Symmetry code used to generate equivalent atoms: 1/2 − *x*, *y*, 1 − *z*. Right: Molecular structure of **20** in the crystal. Hydrogen atoms have been omitted for clarity. Symmetry code: −*x*, *y*, 1/2 − *z*. CH···π interactions indicated by dashed lines.

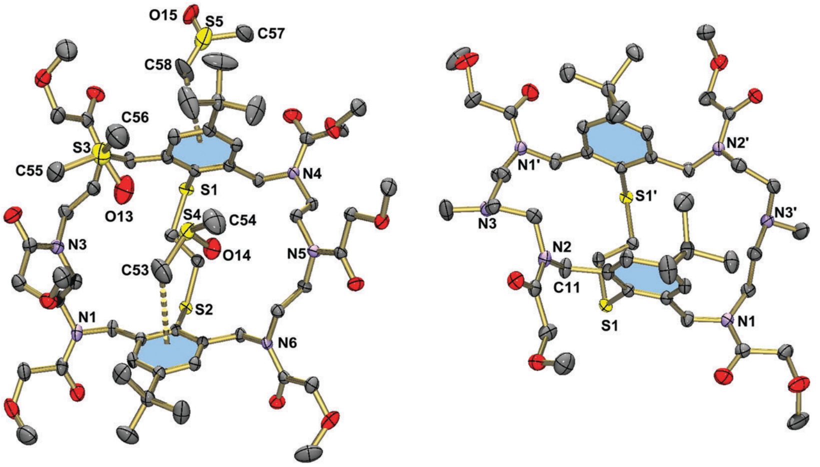


Fig. 4 Left: Molecular structure of **17**·3DMSO in the crystal. The atom N3 is obscured by a DMSO molecule (O(13)S(3)C(56)C(57)). The DMSO molecule O(15)S(5)C(58)C(59) is disordered over two positions. Only one orientation is displayed. Right: Molecular structure of **19**·2DMSO·2H$_2$O in the crystal. Thermal ellipsoids are set at 50% probability. Hydrogen atoms have been omitted for clarity.

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$\cdots\pi$ interactions with the adjacent benzyl group (C11$\cdots$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$\cdots\pi$ interactions. The corresponding CH$\cdots\pi$ distances at 3.428 Å (C11$\cdots$centroid(aromatic ring)) are significantly shorter than in **15** or **20**. This compound crystallizes without guest molecules.

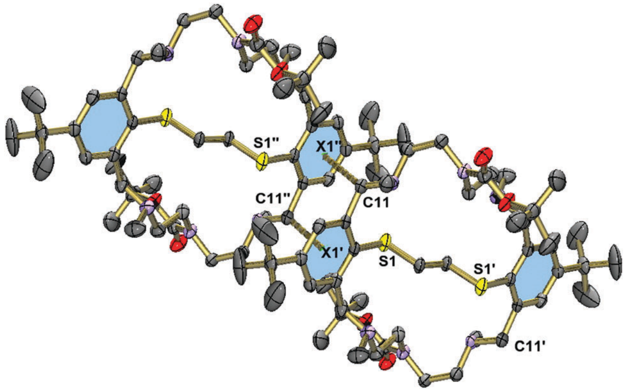


Fig. 5 Molecular structure of compound **23** in the crystal showing the intermolecular CH$\cdots\pi$ interactions. Hydrogen atoms are omitted for clarity. Selected bond lengths [Å]: C1–S1 1.789(3) Å. Symmetry codes: $-x, 1-y, -z$ ('); $-x, 2-y, -z$ ('').

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$_2\cdots\pi$ 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$_3\cdots\pi$ interaction would be consistent with this in view.

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