Design of a Neutral Macrocyclic Ionophore: Synthesis and Binding Properties for Nitrate and Bromide Anions

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In memory of Prof. W. Grahn[‡]

Keywords: Anions / Receptors / Density functional calculations / Environmental chemistry / Macrocycles

A macrocyclic neutral ionophore **8** (X = O) capable of binding weakly coordinating anions such as nitrate and bromide in DMSO solution has been designed by a stepwise, deductive approach. The optimum geometrical arrangement of the hydrogen bond donor sites in the target ionophore was determined by DFT calculations. From these data, a suitable macrocyclic molecular framework was constructed. The 24-membered macrocyclic ionophore was synthesized by standard macrocyclization methods. NMR titrations revealed molecular complexes with defined 1:1 stoichiometries in DMSO for **8** (X = O) with nitrate, hydrogensulfate, acetate, cyanide, iodide, and bromide ions, while dihydrogenphosphate, sulfate, and chloride ions yielded aggregates of higher stoichiometry. The nitrate binding constants of **8** (X = O) are substantial for a neutral ionophore with defined binding sites in pure DMSO solution. Bromide ions, which have a similar ion radius, are bound with an even higher affinity. Chloride is obviously too small, and iodine too large, to form 1:1 complexes. The binding motif of **8** (X = O) was compared with related molecules of similar structure, such as **8** (X = S) and **19**. As predicted from calculations, the small structural variations give rise to a complete loss of nitrate and bromide ion binding ability in DMSO. This sensitivity to geometrical changes and the affinity of **8** (X = O) to nitrate and bromide ions, which are poor hydrogen bond acceptors, confirm the predicted complementarity of ionophore binding site and anion geometry. According to DFT and MD calculations the higher affinity of **8** (X = O) to bromide than to nitrate is mainly due to the greater flexibility of the bromide complex and thus to its higher entropy.

Introduction

The selective detection of anions is of importance in environmental monitoring, medicinal diagnostics, and the analysis of biological samples.[1] While spherical cations can be distinguished by their diameter, the shape-selective recognition of anions is more demanding:[2] anions are larger, with smaller charge-to-radius ratios. Attractive electrostatic forces in recognition events are therefore much weaker than with cations. Other implications are protonation, and thus neutralization, at low pH and the need for large and structurally well-defined receptor molecules complementary to the shape, charge distribution, and hydrogen bonding pattern of nonspherical anions. High selectivities can only be achieved in neutral receptor molecules, because the merely distance-dependent Coulomb forces are much stronger than the spatially more specific hydrogen bonding.

Commercial anion-selective electrodes separate anions mostly by their hydration energy, and the observed selectivities strictly follow the Hofmeister series.[3] This results in strong interference by anions of similar hydration energy, such as nitrate and chloride. While several neutral artificial receptors[4–7] and sensors have been reported for selective binding of halides,[8–12] phosphates[13,14] or carboxylates[15,16] in competitive solvents, recognition of the weakly basic anions, such as the nitrate ion, remains a challenge,[17] in particular with neutral, uncharged receptor molecules. Anslyn et al. have reported a cage-like receptor **1**, which binds acetate and nitrate ions in CH_3CN/CH_2Cl_2 and $MeOH/CH_2Cl_2$ solution (Figure 1).[18,19] Lippert et al. showed that a macrocyclic platinum palladium complex binds nitrate and PF_6 ions simultaneously,[20] while a plat-

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inum complex bearing nicotinamide ligands was presented by Loeb et al.[21] In a recent paper Hamilton et al. reported the macrocyclic receptor **2**,[22] which binds iodine, chloride, nitrate, and tosylate ions in a chloroform/DMSO solvent mixture in a stepwise 2:1 and 1:1 equilibrium. X-ray structures of cage compounds with inside-bound nitrate have been published by Bowman-James et al.[23] and Barbour et al.[24] Jurczak et al. reported a macrocyclic polylactam-type receptor for anions, which binds acetate in DMSO solution.[25] Strong binding of weakly basic anions, with selectivity for spherical anions such as chloride and bromide, was found for the urea-substituted porphyrins **3**.[26] However, the binding cavity of this ionophore contains solvent molecules as well as the anionic guests, so that no direct assessment of the geometry of the binding motif is possible. Acyclic ionophores[13,27,28] for anion binding show affinity to basic anions, such as phosphate or acetate, in DMSO. Interaction with weakly basic anions, such as nitrate or halides, is generally not observed.

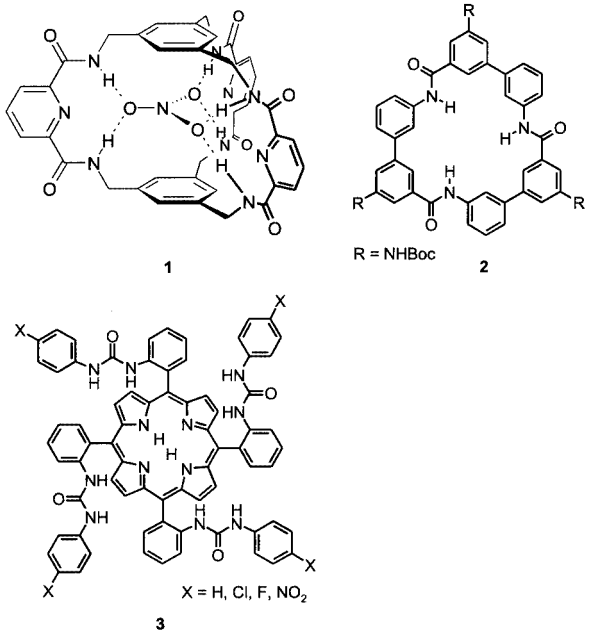


Figure 1. Structures of recently reported neutral macrocyclic anion receptors

We report here our results from a rational design approach to a neutral macrocyclic ionophore with binding affinity towards the weakly coordinating anions nitrate and bromide in polar solvents.

Results and Discussion

Design of the Receptor Structure

The starting point of our design approach was to construct a neutral ligand to bind nitrate. In the NO_3^- ion, there are six hydrogen bond acceptor sites arranged in D_{3h} symmetry. It was thus straightforward to place the ion in the C_3 axis of a hexagonal grid and in a first approach to cut the molecular frame from the chicken wire pattern.[28b]

We introduced thiourea units as hydrogen bond donors, since this motif is often found in crystal structures of nitrate salts (usually with one urea or thiourea unit per nitrate) and because thiourea provides the correct hydrogen bond angles (a pair of parallel N−H bonds each, see b in Figure 2). This approach is crude, since the graphite pattern provides a very coarse grid and we could hardly expect to obtain the optimum geometry for binding at this first attempt. However, there are three positions X (see b in Figure 2) that can be used for "fine tuning" of the geometry. Depending on the group (X = S, O, NH, CH_2), the size of the cavity should change slightly. To find the optimum arrangement of the three urea units relative to the anion, we performed density functional theory calculations on the 3:1 complex of thiourea with nitrate (Figure 3). The optimized structure is

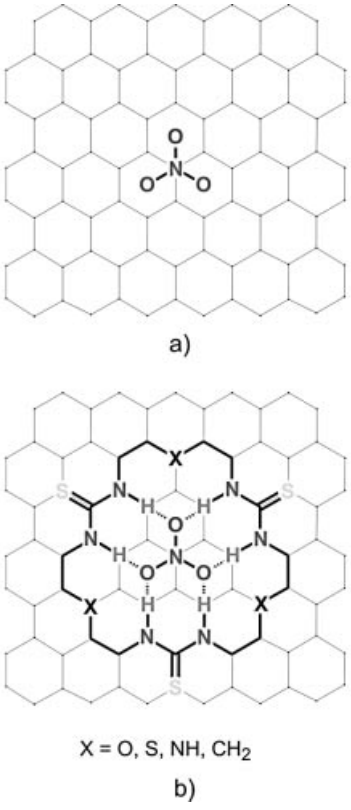


Figure 2. "Chicken wire" approach to the design of a nitrate receptor

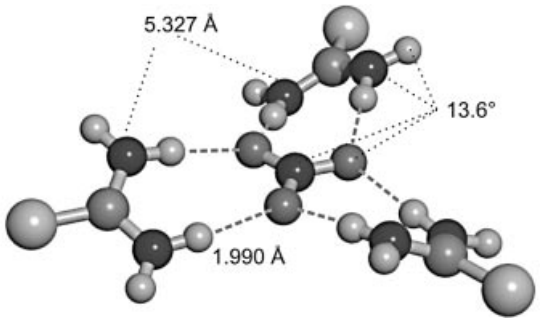


Figure 3. B3LYP/6-31G*-optimized structure of NO_3^- complexed with three thiourea units (D_3 symmetry)

slightly twisted out of plane (HONO dihedral angle 13.6°) and has D_3 symmetry. The "cavity size" (average distance of hydrogen atoms involved in hydrogen bonding from the center of mass of the molecule) is 2.799 Å.

For optimum preorientation of the ligand, we therefore had to find a spacer that would connect the thiourea units in or close to this geometry.

Density functional theory (DFT) calculations (at the B3LYP/6-31G* level of theory) on the macrocycles with X = S and O and with C_3 symmetry (the highest point group in which all macrocycles are minima) predict a cavity size of 2.727 Å for X = O and 2.922 Å for X = S. Interestingly, the macrocycles with X = NH and X = CH_2 or CH, such as Göbels macrocycle **19**[29] (the size of which is between that of the O- and that of S-macrocycle) can be ruled out as potential receptors, because the hydrogen atoms in the spacer group X would sterically interfere with a bound nitrate and with the thiourea N−H groups. This leaves the macrocycles with X = O and S as possible candidates for synthesis. According to the DFT calculations, the cavity diameter of the oxygen derivative is closer to the optimum value and thus provides better preorientation.

The six hydrogen bond donor sites in **8** (X = O) and **8** (X = S) are located in a suitable position to bind NO_3^-, although ions with spherical symmetry and of similar size to nitrate should also fit in the cavity. In the series of halogen ions, the ion radius of bromide is very close to that of nitrate. Thus Br^- is a good candidate to bind, whereas chloride is too small and iodide too large to form a 1:1 complex (Table 1).

Table 1. Ion radii of halogens and nitrate[30]

Ion	Ion radii [Å]
F^-	1.24
Cl^-	1.80
Br^-	1.98
NO_3^- eq	2.06
(NO_3^- ax)	(1.26)
I^-	2.25

According to DFT calculations[31] (B3LYP/6-31G*) including solvent effects by use of the polarized continuum model (PCM),[32,33] the enthalpy of complexation [**8** (X = O) + X^- → **8** (X = O)·X^-] within the C_3 point group strongly depends on the dielectric constant of the solvent (DMSO: ε = 46.7; water: ε = 78.39). In the absence of solvent interactions, the formation of the bromide complex is more exothermic by 5.0 kcal mol^{-1}, while in water nitrate is bound with a more negative enthalpy of complexation ($\Delta\Delta H_{compl.}$ = 6.8 kcal mol^{-1}) (Table 2).

To estimate entropy effects we performed MD simulations, based on the MM2 force field, on **8** (X = O)·Br^- and **8** (X = O)·NO_3^-.[34,35] The molecular dynamics calculations were performed for 1000 ps at 600 K (bath relaxation).[36] The conformational spaces of both complexes and the free ligands defined by the trajectories were projected onto 2D hypersurfaces by the use of an artificial neural network of the Kohonen type[37] with 25 × 25 neurons. The structure represented by each neuron was energy-minimized. The potential energy of each of these 625 conformations is coded by color (low energies blue, high energies red; Figure 4). The energies are relative with respect to the lowest-energy structure and the potential energy range covered from blue to red is 10 kcal mol^{-1}.

Table 2. DFT/PCM-calculated enthalpies of complexation

X^-	$\Delta H_{compl.}$ **8** (X = O) + X^- → **8** (X = O)·X^- Vacuum	DMSO	Water
NO_3^-	−75.4	−28.8	−22.9
Br^-	−80.4	−25.2	−16.0
$\Delta\Delta H_{compl.}$	−5.0	3.6	6.8

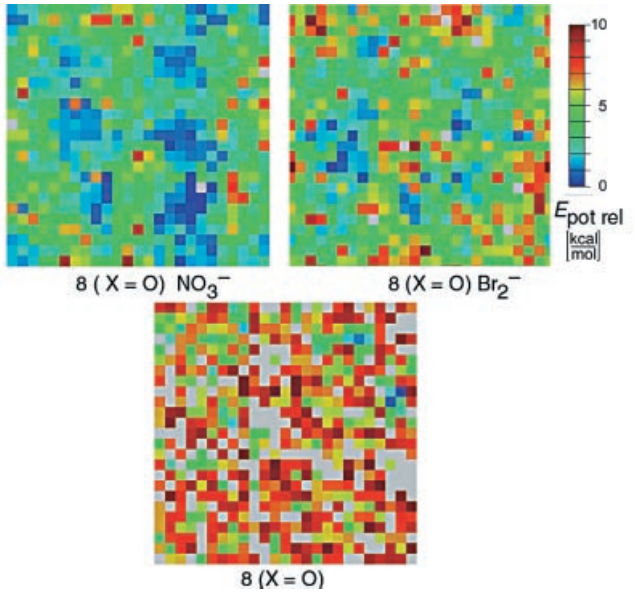


Figure 4. Potential energy hypersurfaces of the conformations of **8** (X = O)·NO_3^-, **8** (X = O)·Br^-, and **8** (X = O); both complexes and the ligand were simulated by molecular dynamics (1000 ps, 600 K) and the resulting conformational space was projected in two dimensions through use of Kohonen artificial neural networks (25 × 25 neurons); the colors indicate the relative potential energies ($E_{pot,rel}$ in kcal mol^{-1}) of the conformations represented by the corresponding neuron; relative energies above 10 kcal mol^{-1} are in white

The Kohonen map of the nitrate complex **8** (X = O)·NO_3^-, in comparison with that of the bromide complex **8** (X = O)·Br^-, exhibits discrete and much larger areas for conformations with low potential energy (blue). The nitrate complex thus occupies conformations of low potential energy more frequently than the bromide complex. Inspection of the conformations in both Kohonen maps reveals that the nitrate complex structures are relatively planar, whereas the bromide complexes do not exhibit this kind of restriction. The fact that the bromide complex at the same temperature passes a larger number of conformations of higher potential energy can be interpreted in terms of a larger conformation space and a higher entropy than for the nitrate complex. The free ligand is even more flexible.

Reoptimization of the most stable conformations within the low potential energy areas from the Kohonen map of **8** (X = O)·Br^- at the B3LYP/6-31G* level of DFT theory confirmed three conformations of C_3, C_s, and C_1 symmetry as the lowest minima on the energy hypersurface, the C_1 and C_s structures being about 0.5 kcal mol^{-1} more stable than the C_3 structure.

To prove our theoretical concept, we decided to synthesize **8** (X = O) and **8** (X = S) and to investigate their anion-binding properties.

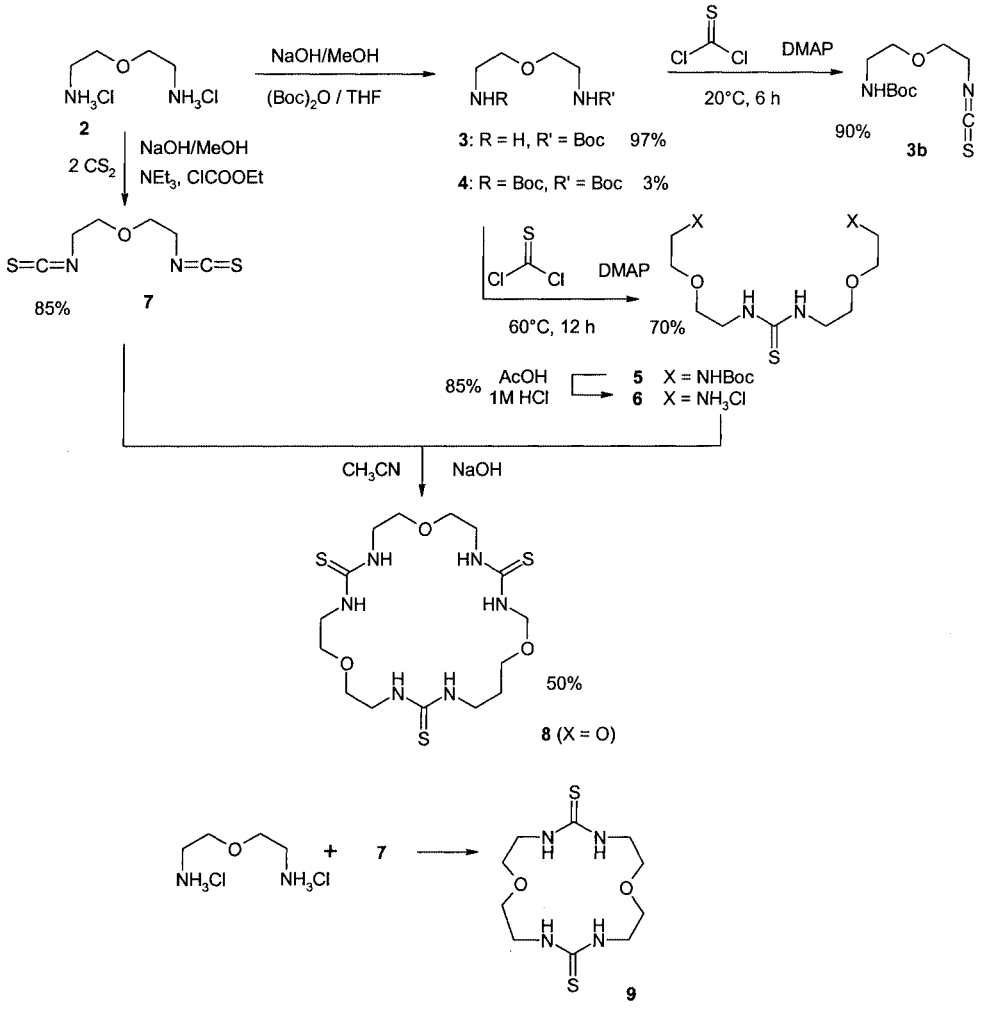
Synthesis

Our strategy for the formation of **8** (X = O) and **8** (X = S) is similar to that reported by Lehn et al.,[38] which focused on the addition of amines and isothiocyanates, and that reported by Göbel et al.,[29] in which a thiourea unit bearing two terminal amines reacts with a diisothiocyanate in the final macrocyclization step. Treatment of a twofold excess of diamine **2** with Boc anhydride, with use of a continuous extraction method for product isolation, gave a mixture of 97% monoprotected **3** and 3% diprotected diamine **4**. Treatment of **3** with thiophosgene at room temperature yielded the corresponding isothiocyanate, which could be isolated in 90% yield. However, heating of the solution at reflux in chloroform overnight, without intermediate workup, resulted in the formation of the desired protected diamine **5** in 70% yield. Deprotection to give the diamine **6** (dihydrochloride) was achieved with 1.0 M HCl in acetic acid/dichloromethane, in 85% yield.

Bis(thioisocyanate) **7**, as the second reaction component for macrocyclization, was obtained from **2** by treatment with CS_2 according to a modified procedure reported by Luk'yanenko et al.[39] Macrocyclization was performed by dissolving the dihydrochloride salt of **6** with triethylamine or NaOH and addition of the diisothiocyanate **7** in acetonitrile at room temperature. The target compound **8** (X = O) was obtained in 50−55% yield (Scheme 1).

The structure was confirmed by all spectroscopic data. Proton NMR spectra suggest unrestricted intramolecular motion of the macrocycle in solution. Crystals suitable for X-ray analysis were obtained from acetone. The structure in the solid state shows three intramolecular hydrogen bonds of N−H to the ether oxygen atoms (Figure 5).

As a minor reaction product compound **9** was isolated. The diprotected amine **4**, formed as a by-product in 3% yield in the first Boc protection step, survives treatment



Scheme 1. Synthesis of macrocycles **8** (X = O) and **9**

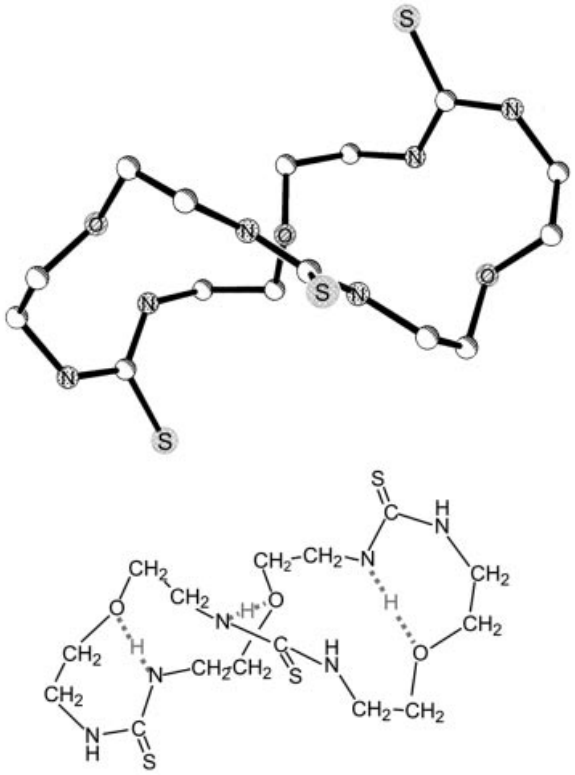


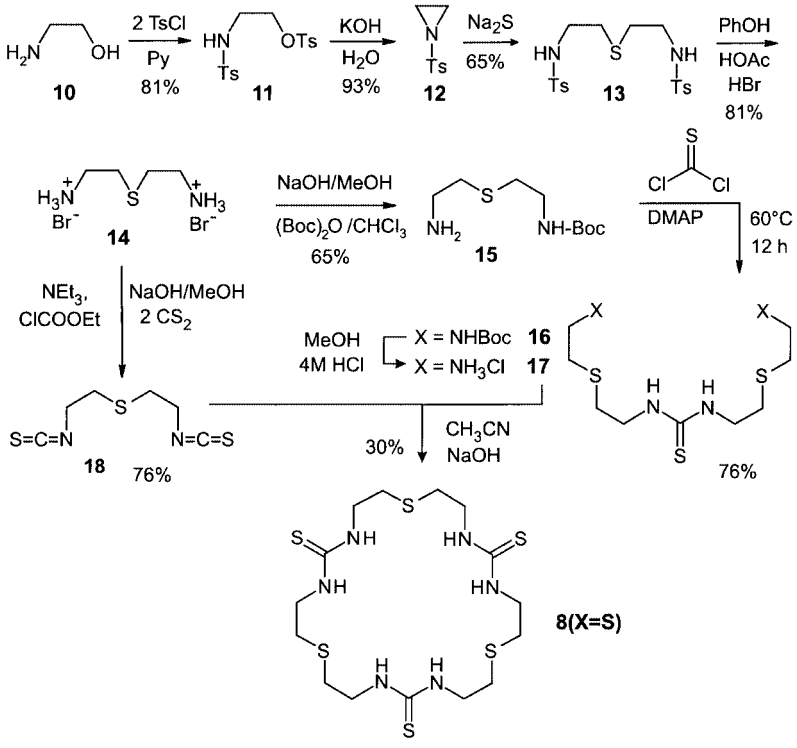
Figure 5. Structure of **8** (X = O) in the solid state

with thiophosgene and workup. In the subsequent acid treatment it is deprotected together with **5** and reacts in the final macrocyclization step to give **9**. The structure of **9** was also confirmed by X-ray analysis. Other spectroscopic properties are in agreement with known data.[40]

Bis(2-aminoethyl) thioether dihydrobromide (**14**) was synthesized by slight modification of the published procedures[41−45] (Scheme 2). The components **17** and **18** for macrocyclization were prepared similarly to the oxa analogues **6** and **7**. Treatment of **15** (unlike the oxo derivative **3**) with thiophosgene at room temperature directly afforded the diprotected diamine **16**. Macrocyclization of the thia compound required higher temperatures (70 °C) than needed for the oxa derivative (20 °C).

Evaluation of Binding Properties

The anion-binding properties of macrocycle **8** (X = O) were investigated by NMR titration in deuterated DMSO. Association constants were derived from the observed complex-induced shifts (see Exp. Sect. for details) and are summarized in Tables 3−6 (Figure 6).[46] The binding of **8** (X = O) with nitrate, acetate, cyanide, bromide, iodide, and hydrogensulfate ions yield data (see Table 3) consistent with 1:1 stoichiometries, as confirmed by Job's plot analysis and Scatchard plots. In the case of HSO_4^- it is most likely that protonation of **8** (X = O) by the acidic anion gives rise to a charged receptor **8** (X = O) H^+. From the titration of **8** (X = O) with $NaNO_3$ an association constant $K_{11} = 23.2 \pm 0.6$ L mol^{-1} was derived. The increase of binding strength relative to that of Bu_4NNO_3 may be attributable to the coordination of the sodium counter-ion to the ether oxygen atoms, which should result in higher anion affinity of the ionophore. The binding constants of **8** (X = O) for nitrate ions in pure DMSO are among the highest values reported



Scheme 2. Synthesis of **8** (X = S)

Table 3. Association constants K_{11} of **8** (X = O) with tetrabutylammonium salts in deuterated DMSO

Anion[a]	K_{11} [L·mol^{-1}]	pK_S [47]	R[b]	$\Delta\delta_{max}$ (obsd.)	$\Delta\delta_{max}$ (calcd.)	$\Delta G°$ [kJ·mol^{-1}]
NO_3^-	17.1 ± 0.4	−1.32	0.9999	0.23 (16 equiv.)	0.32	−7.0
OAc^-	1260 ± 260	+4.75	0.9987	0.76 (5.0 equiv.)	0.76	−17.7
CN^-	1300 ± 570	+9.31	0.9956	0.31 (3.0 equiv.)	0.31	−17.8
Br^- [c]	400 ± 40	ca. −9	0.9991	0.26 (10 equiv.)	0.26	−14.9
I^-	< 2	ca. −10	0.9984	0.03 (15 equiv.)	–	–
HSO_4^-	58 ± 4	+1.92	0.9978	0.24 (30 equiv.)	0.24	−10.1

[a] All anions were used as their Bu_4N^+ salts. [b] Correlation coefficient of regression. [c] Binding constant and stoichiometry of binding were independently confirmed by calorimetric titration.

Table 4. Association constants of more complex aggregates of **8** (X = O) and tetrabutylammonium salts in DMSO as determined by NMR titration

Anion[a]	Model[b]	K	pK_a [47]	$\Delta\delta_{max}$ (obsd.)	$\Delta\delta_{max}$ (calcd.)
SO_4^{2-}	2:3	–[c]	ca. −3	1.8 (15 equiv.)	–
$H_2PO_4^-$	2:1	$5.3\cdot10^4$ L^2·mol^{-2}	+2.12	1.3 (7.5 equiv.)	1.4
Cl^-	1:2	200 L^2·mol^{-2}	ca. −6	0.41 (40 equiv.)	0.44

[a] All anions were used as their Bu_4N^+ salts. [b] Stoichiometry of binding used to emulate the experimental data by mathematical model. [c] The very strong association does not allow meaningful data to be derived.

Table 5. Association constants K_{11} of tetrabutylammonium nitrate binding of **8** (X = O), **8** (X = S), and **19** in DMSO

Compound	K_{11} [L·mol^{-1}]	R[a]	$\Delta\delta_{max}$ (obsd.)	$\Delta\delta_{max}$ (calcd.)	$\Delta G°$ [kJ·mol^{-1}]
8 (X = O)	17.1 ± 0.4	0.9999	0.23 (16 equiv.)	0.32	−7.0
8 (X = S)	< 1	0.9982	0.10 (40 equiv.)	–	–
19	< 1	0.9972	0.08 (40 equiv.)	–	–

[a] Correlation coefficient of regression.

Table 6. Association constants K_{11} of tetrabutylammonium bromide binding of **8** (X = O), **8** (X = S), and **19** in DMSO as determined by NMR titration

Compound	K_{11} [L·mol^{-1}]	R[a]	$\Delta\delta_{max}$ (obsd.)	$\Delta\delta_{max}$ (calcd.)	$\Delta G°$ [kJ·mol^{-1}]
8 (X = O)	400 ± 40	0.9991	0.26 (10 equiv.)	0.26	−14.9
8 (X = S)	2.6 ± 0.1	0.9994	0.25 (40 equiv.)	0.37	−2.4
19	2.8 ± 0.2	0.9993	0.18 (40 equiv.)	0.33	−2.6

[a] Correlation coefficient of regression.

for neutral ionophores with defined binding motifs.[18,19,22]

The formation of molecular aggregates of **8** (X = O) with stoichiometries other than 1:1 was observed for $H_2PO_4^-$, Cl^-, and SO_4^{2-} anions in deuterated DMSO. While the experimental data (see Table 4) are in good agreement with a 2:1 binding model for $H_2PO_4^-$ and a 1:2 model for chloride,[46] a tight association of **8** (X = O) with sulfate did not allow meaningful values to be derived.[48]

The ability of anions to act as hydrogen bond acceptors is correlated with the pK_a value of their corresponding acid. Although there is no direct relationship,[49] the plot of K_{11} association constants of **8** (X = O) vs. pK_a should show an approximately linear interdependence. Figure 7 shows that this is indeed the case, with one exception: the binding of bromide ions is much stronger than expected. This suggests that macrocycle **8** (X = O), although well suited to form hydrogen bonds to the weakly basic nitrate anion even in competition with the polar solvent DMSO, does not exhibit exceptional nitrate binding selectivity. On the contrary, it shows a remarkable binding selectivity for bromide ions, which are even poorer hydrogen bond acceptors.

How important, though, is the exact geometry of the binding site of **8** (X = O) for defined association with nitrate and bromide ions in DMSO? To answer this question, the nitrate-binding abilities of macrocycles **8** (X = S) and **19**[29] (Scheme 3)– with related, but slightly different structures – were determined in DMSO by NMR titration. For comparison, compound **9**, which has only two thiourea binding sites, was also tested. Compounds **8** (X = S) and **19** showed weak nitrate ion binding in DMSO with association

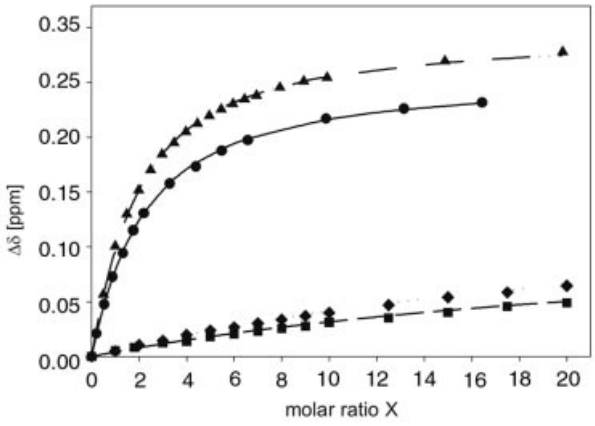


Figure 6. Observed induced chemical shifts of **8** (X = O) upon titration with $NaNO_3$ (▲) and Bu_4NNO_3 (•); observed induced chemical shifts of **8** (X = S) (◆) and **19** (■) upon titration with Bu_4NNO_3; see Exp. Sect. for details of measurements

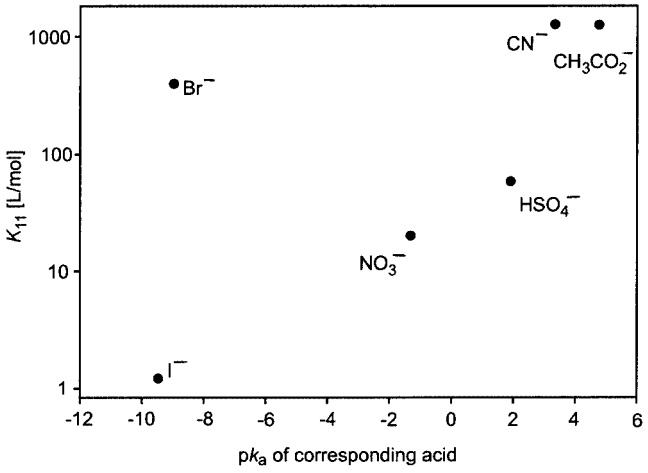


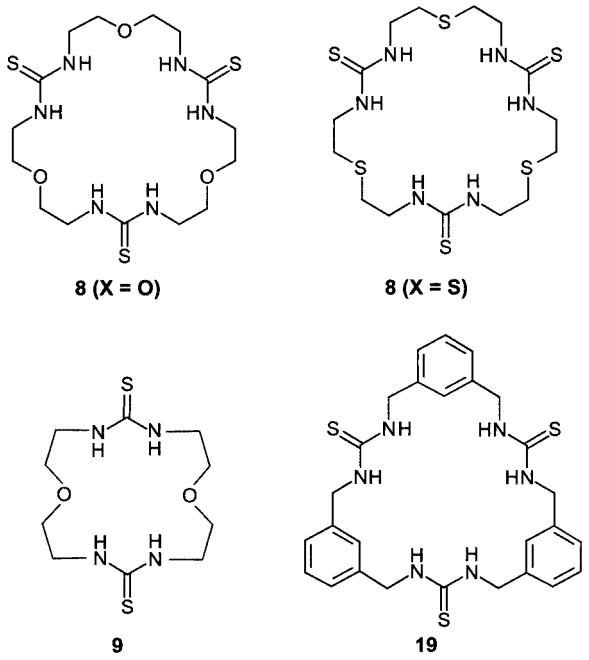
Figure 7. Association constants K_{11} of tetrabutylammonium salts with **8** (X = O) vs. pK_a of the corresponding acids of the anions

constants $K_{11} < 1$ L mol^{-1}, but a defined 1:1 stoichiometry (see Figure 6 for titration curves, Table 3 for data). Compound **9** bound nitrate ions very weakly without defined stoichiometry.

The same strong sensitivity of binding ability to structural changes is observed in bromide binding. The association constants drop by a factor of more than 100 on comparison of **8** (X = O) with **8** (X = S) and **19**. The stoichiometry of binding clearly remains 1:1 in all three cases.

Conclusion

By means of a novel systematic approach we have designed a neutral receptor molecule for binding of weakly basic anions such as nitrate and bromide ions. The most promising structure **8** (X = O) and two other macrocycles were synthesized. Binding studies of **8** (X = O) indeed confirmed its affinity for nitrate ions even in DMSO, a solvent that strongly competes for intermolecular interactions. The derived association constants for nitrate binding in DMSO are among the highest values so far reported for neutral defined ionophores. Small structural variations, such as in **8** (X = S), which is slightly larger than our first target, or **19**, which exhibits steric interactions with bound NO_3^-, result in almost complete loss of binding activity.



Scheme 3. Structures of macrocycles evaluated for nitrate binding

The Br^- ion, which has an ion radius similar to that of nitrate, exhibits an even larger affinity for **8** (X = O), whereas iodide is obviously too large and chloride (which is bound in a 2:1 complex) is too small to fit in the cavity. The high affinity for bromide relative to nitrate cannot be explained on enthalpic grounds. According to molecular dynamics simulations, the bromide complex undergoes rapid conformational changes and thus has a higher entropy than the nitrate complex.

Experimental Section

General Methods: Melting points were taken with a hot-plate microscope apparatus and are uncorrected. NMR spectra were recorded with a Bruker AC 400 spectrometer at 400 MHz (^{1}H) and 100 MHz (^{13}C) in $CDCl_3$ solutions unless otherwise stated. The multiplicity of the ^{13}C signals was determined with the DEPT technique and quoted as: (+) for CH_3 or CH, (−) for CH_2 and (C_{quat}) for quaternary carbon atoms. Chemical shifts are reported on the δ scale relative to tetramethylsilane. Mass spectra were determined with a MAT 8430 mass spectrometer at an ionizing voltage of 70 eV.

Crystal Structure Determination of 8 (X = O): Crystal data: Monoclinic, space group *C*2/*c*, *a* = 20.975(4), *b* = 9.5033(16), *c* = 10.934(2) Å, β = 94.207(4)°, *V* = 2173.6 Å^3, *Z* = 4, *T* = −130 °C.

Data collection: A ca. 0.4 × 0.3 × 0.1 mm crystal was used to record 7081 intensities with a Bruker SMART 1000 CCD diffractometer (Mo-K_α radiation, $2\theta_{max} = 56.6°$). Structure refinement: The structure was refined anisotropically on F^2 (G. M. Sheldrick, SHELXL-97, Univ. of Göttingen). The molecule possesses crystallographic twofold symmetry. The atoms C7, C8, O9, C10, C11, and S2 are disordered over two positions, but a suitable disorder model could be refined by use of similarity restraints. Hydrogen atoms were included by use of a riding model. Refinement proceeded to $wR2 = 0.120$, $R1 = 0.047$ for 192 parameters, 247 restraints, and 2691 unique reflections; $S = 1.03$, max. $\Delta\rho = 0.54$ e Å^{-3}.

^{1}H NMR Titrations in [D$_6$]DMSO: All titrations were performed at room temperature with ionophore concentrations of 30 mmol L^{-1} and were repeated three times to confirm results.[50] Anions were added, unless otherwise stated, as their tetrabutylammonium salts from stock solutions (0.9 mol L^{-1}). NMR spectra were recorded with a 400 MHz spectrometer. Association constants were derived from the induced chemical shifts of several protons with the program HYP NMR 2000.[46] A minimum of 10 data points with p values (probability of binding) between 0.2 and 0.8 were used for data analysis in each case. To exclude self association of the investigated ionophores, NMR spectra of [D$_6$]DMSO solutions were recorded over a wide rage of concentrations. The observed shifts of proton resonance are very small and can be neglected. For Job's plot analysis solutions of ionophore and salt (each 30 mmol L^{-1}) were mixed in different ratios.

***tert*-Butyl [2-(2-Aminoethoxy)ethyl]carbamate (3):** The solid dihydrochloride salt of diamine **2** (2.0 g, 11.3 mmol, 1 equiv.) was added to a suspension of NaOH (0.81 g, 20.3 mmol, 1.8 equiv.) in methanol (120 mL). The mixture was heated to 60−65 °C with a heat gun for 2−3 min and then stirred for 0.5 h to allow the solid to dissolve. A solution of di-*tert*-butyl dicarbonate (1.24 g, 5.7 mmol, 0.5 equiv.), dissolved in THF (40 mL), was then added dropwise over 15 min to the methanol mixture. After the mixture had been stirred at room temperature for 24 h, all solvents were removed in vacuo, which yielded a white, oily solid. This was dissolved in distilled water and placed in a continuous extractor apparatus already containing dichloromethane. After heating under reflux for 24 h, the dichloromethane was removed in vacuo to yield 1.13 g (97%) of pure *tert*-butyl [2-(2-aminoethoxy)ethyl]carbamate (**3**), as a yellowish oil. ^{1}H NMR: δ = 1.43 (s, 9 H), 2.77 (t, J = 5.4 Hz, 2 H), 3.26 (t, J = 5.4 Hz, 2 H), 3.54 (t, J = 5.4 Hz, 2 H), 3.57 (t, J = 5.4 Hz, 2 H) ppm. ^{13}C NMR: δ = 28.5 (+), 40.5 (−), 40.7 (−), 70.1 (−), 72.7 (−), 81.5 (C$_{quat}$), 159.1 (C$_{quat}$) ppm.

[2-(*tert*-Butoxycarbonylamino)ethoxy]-2-isothiocyanatoethane (3b): An orange solution of thiophosgene (2.04 mmol, 1.0 equiv.) in 10 mL of chloroform was added dropwise over 0.5 h to a clear solution of *tert*-butyl [2-(2-aminoethoxy)ethyl]carbamate (**3**, 1.25 g, 6.12 mmol, 3 equiv.) and 4-(dimethylamino)pyridine in 100 mL of chloroform. After 6 h of stirring at room temp., the chloroform was removed in vacuo to give a crude yellow oil. Flash chromatography (90% dichloromethane/10% methanol) afforded the desired product **4**, as a clear, colorless oil in 90% yield. IR (neat): $\tilde{\nu}$ = 3360 (N−H), 2980, 2930, 2880, 2195 (N=C=S), 2110 (N=C=S), 1705 (C=O), 1520, 1185, 1130 cm^{-1}. ^{1}H NMR (200 MHz, CDCl$_3$): δ = 1.45 (s, 9 H), 3.32−3.35 (m, 2 H), 3.57−3.60 (m, 2 H), 3.66 (br. s, 4 H), 5.05 (vbs, 1 H) ppm. ^{13}C NMR (50.3 MHz, CDCl$_3$): δ = 28.3, 40.2, 45.3, 68.9, 70.2, 79.2, 134.0 (S=C=N), 155.9 ppm.

1,3-Bis{2-[2-(*tert*-butoxycarbonylamino)ethoxy]ethyl}thiourea (5): An orange solution of thiophosgene (0.15 mL, 2.04 mmol, 1.0 equiv.) in 10 mL of chloroform was added dropwise over 0.5 h to a clear solution of *tert*-butyl [2-(2-aminoethoxy)ethyl]carbamate (**3**, 1.25 g, 6.12 mmol, 3 equiv.) and 4-(dimethylamino)pyridine (0.75 g, 6.12 mmol) in 100 mL of chloroform. After the mixture had been stirred for 1 h at room temperature, the yellow mixture was heated under reflux overnight and the chloroform was removed in vacuo, to yield a white solid as crude product. Flash chromatography (50% dichloromethane/50% ethyl acetate) then afforded 0.64 g of the desired product, 1,3-bis{2-[2-(*tert*-butoxycarbonylamino)ethoxy]-ethyl}thiourea (**5**), as a white solid (m.p. 99−101 °C), in 70% yield. ^{1}H NMR: δ = 1.39 (s, 18 H), 3.20−3.30 (m, 4 H), 3.49 (t, J = 5.1 Hz, 4 H), 3.57 (t, J = 4.6 Hz, 4 H), 3.65 (br. s, 4 H) ppm. ^{13}C NMR: δ = 28.2 (+), 40.0 (−), 44.3 (−), 69.6 (−), 70.2 (−), 79.2 (−), 155.9 (C=O), 182.8 (C=S) ppm. MS(EI): m/z (%) = 450 (100), 307, 289, 164, 146, 57, 44.

1,3-Bis[2-(2-aminoethoxy)ethyl]thiourea Dihydrochloride (6): A solution of 1,3-bis{2-[2-(*tert*-butoxycarbonylamino)ethoxy]ethyl}-thiourea (**5**, 0.29 g, 0.64 mmol) in 10 mL of dichloromethane was stirred for 15 min, and acetic acid (2.0 M, 20 mL) and HCl (1.0 M, 20.0 mL) were added. The solution was stirred vigorously for 3 h. All solvents were removed under high vacuum. The crude product was purified by recrystallization from methanol/ethyl acetate (1:1) to yield a white solid (0.175 g, 85%), m.p. 186−188 °C. IR (KBr): $\tilde{\nu}$ = 3429, 3277, 3010, 2966, 2963, 1560, 1119, 1101 cm^{-1}. ^{1}H NMR ([D$_4$]methanol): δ = 3.18 (t, J = 5.1 Hz, 4 H), 3.67 (t, J = 5.3 Hz, 4 H), 3.74 (t, J = 5.1 Hz, 4 H), 3.77 (br. s, 4 H) ppm. ^{13}C NMR ([D$_4$]methanol): δ = 40.7 (−), 44.9 (−), 67.6 (−), 70.7 (−), 191.5 (C=S).

1-Isothiocyanato-2-[2-(isothiocyanato)ethoxy]ethane (7): 1-Isothiocyanato-2-[2-(isothiocyanato)ethoxy]ethane (**7**) was prepared according to the procedure described in the literature, with a few minor changes.[39] Triethylamine (0.74 g, 1 mL, 2 equiv.) was added by syringe at room temperature to a stirred solution of bis(2-aminoethyl) ether dihydrochloride (**1**, 0.65 g, 3.67 mmol) and NaOH (0.279 g, 6.97 mmol, 1.9 equiv.) in methanol (30 mL). After 0.5 h of stirring, carbon disulfide (1.12 g, 14.7 mmol, 4 equiv.) was slowly added dropwise to the solution, which was stirred for another 2 h. At this point, the reaction mixture was cooled to 0 °C, and ethyl chloroformate (1.6 g, 1.4 mL, 14.7 mmol, 4 equiv.) was added dropwise. This was followed by slow warming of the solution to room temperature and further stirring for 2 h. The resulting mixture was then extracted with dichloromethane (3 × 100 mL), the organic phase was dried with $MgSO_4$, and the solvent was removed in vacuo. The residue was heated at 100−130 °C under vacuum (40 mbar) until the evolution of ethanol and carbon oxide sulfide ceased. The temperature was then raised to 160 °C at 1 mbar pressure, and the desired product distilled off as a clear, colorless liquid (0.62 g) with a yield in the range of 80−90% (ref.[39] 75%), b.p. 150 °C at 9 mbar (ref.[39] 150 °C/1 Torr). ^{1}H NMR (200 MHz, CDCl$_3$): δ = 3.69 (bs) ppm. ^{13}C NMR (50.3 MHz, CDCl$_3$): δ = 45.3 (−), 69.3 (−) ppm.

1,9,17-Trioxa-4,6,12,14,20,22-hexaazacyclotetracosane-5,13,21-trithione [8 (X = O)]. Method A: 1,3-Bis[2-(2-aminoethoxy)ethyl]thiourea dihydrochloride (**6**, 0.2 g, 0.62 mmol, 1 equiv.) was added to a stirred solution of triethylamine (1.9 g, 2.6 mL, 18.6 mmol, 30 equiv.) in acetonitrile (250 mL). The resulting suspension was sonicated for 30 min until it completely dissolved, and 1 equiv. of 1-isothiocyanato-2-[2-(isothiocyanato)ethoxy]ethane (**7**) was then added by syringe. The mixture was stirred for 16 h and the solvent and triethylamine were then removed in vacuo to afford a white

solid. The solid was dried under high vacuum for several hours. ^{1}H and ^{13}C NMR spectra of this white solid revealed that 2 equiv. of Et_3N were probably bound by the desired product macrocycle. ^{1}H NMR (200 MHz, [D$_6$]DMSO): δ = 1.25 (t, *J* = 6.7 Hz, 6 H), 3.14 (q, *J* = 6.7 Hz, 4 H), 3.50 (t, *J* = 5.2 Hz, 12 H), 3.65 (t, *J* = 5.2 Hz, 12 H), 7.93 (s, 6 H) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 9.5, 44.2, 46.0, 69.5, 182.5 ppm. Flash chromatography (20% methanol/80% ethyl acetate) afforded 0.22 g (55%) of the desired product as a white solid. **Method B:** 1,3-Bis[2-(2-aminoethoxy)ethyl]thiourea dihydrochloride (**6**, 0.3 g, 0.93 mmol, 1 equiv.) was added to a stirred solution of NaOH (74 mg, 1.86 mmol, 2 equiv.) in acetonitrile (250 mL). The resulting suspension was sonicated for 30 min, and 5.0 mL of water was added to dissolve all reagents. 1-Isothiocyanato-2-[2-(isothiocyanato)ethoxy]ethane (**7**, 160 mg, 0.93 mmol) was added to this solution by syringe. The mixture was stirred vigorously for 16 h and the solvent was removed in vacuo to yield a white solid. Flash chromatography (methanol/ethyl acetate, 1:4) gave 210 mg (50%) of the desired product as a white solid; m.p. 231−232 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 3.54 (br. s, 12 H), 3.58 (vbs, 12 H), 7.56 (br. s, NH, 6 H) ppm. ^{13}C NMR (100.6 MHz, [D$_6$]DMSO): δ = 44.0 (−), 68.9 (−), 182.5 (C=S) ppm. MS(FAB): *m*/*z* (%) = 439.2 (100) $[M + H]^+$.

2-(*p*-Tolylsulfonamido)ethyl *p*-Toluenesulfonate (11):[41] A mechanically stirred suspension of *p*-toluenesulfonyl chloride (80.6 g, 0.42 mol) in 50 mL of pyridine was cooled to −15 °C with an ice/salt bath. A pre-cooled (0 °C) solution of 2-aminoethanol (12.2 g, 0.2 mol) in 20 mL of pyridine was then added dropwise over a period of 0.5 h, and the mixture was stirred at this temperature for 2 h and at 0 °C for 5 h, and kept at 0 °C overnight. Ice/water was added to the reaction mixture and the residue was filtered off. The solid was dissolved in $CHCl_3$ (500 mL), washed with water (3 × 100 mL), and dried with anhydrous Na_2SO_4. The solvent was removed under vacuum and the product was crystallized from CCl_4 to afford **11** as a white solid (60 g, 81%); m.p. 82 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.42 (s, 3 H), 2.45 (s, 3 H), 3.17−3.26 (m, 2 H), 4.04 (t, *J* = 5.0 Hz, 2 H), 4.84 (t, 1 H), 7.27−7.37 (m, 4 H), 7.67−7.76 (m, 4 H) ppm.

***N*-(*p*-Tolylsulfonyl)aziridine (12):**[42−44] A solution of 20% aqueous KOH was rapidly added to **11** (25 g, 67 mmol) in 700 mL of freshly distilled benzene. The two-phase mixture was vigorously stirred. After a pink color and a white solid had appeared, stirring was continued for 0.5 h. The benzene layer was washed with water and dried with anhydrous Na_2SO_4. The solvent was removed under vacuum in the presence of catalytic amounts of 4-*tert*-butylcatechol to avoid polymerization. The brownish solid was crystallized from a mixture of dichloromethane and hexane to provide a white solid, yield 11 g (93%); m.p. 51 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.36 (s, 4 H), 2.44 (s, 3 H), 7.32−7.36 (m, 2 H), 7.82−7.84 (m, 2 H).

1,5-Bis(*p*-tolylsulfonamido)-3-thiapentane (13):[41,45] *N*-(*p*-Tosyl)aziridine (**12**, 11 g, 0.067 mol) was added to a solution of $Na_2S{\cdot}9H_2O$ (9 g, 33 mmol) in 30% aqueous ethanol. The mixture was heated under reflux for 5 h, the ethanol was removed under reduced pressure, and the mixture was acidified with aqueous 5% HCl. The product was extracted with ethyl acetate (300 mL) and the organic layer was washed successively with water, $NaHCO_3$ solution, and brine and dried with anhydrous Na_2SO_4. The solvent was evaporated under vacuum to afford a light yellow semi-solid, which was sufficiently pure for use in the next step without further purification. Yield 9.5 g (65%). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.40 (s, 6 H), 2.51 (t, *J* = 6.0 Hz, 4 H), 3.03 (q, *J* = 6.0 Hz, 4 H), 5.32 (t, *J* = 6.0 Hz, 2 H), 7.25−7.32 (m, 4 H), 7.68−7.76 (m, 4 H).

Detosylation of 13:[45] A mixture of **13** (9 g, 21 mmol), phenol (18 g), and HBr in acetic acid solution (30%, 500 mL) was gently heated under reflux for 50 h. The solvent was completely removed under vacuum. The residue was washed successively with ethyl acetate and decanted, giving **14** as a brown solid. Yield 4.8 g (81%); m.p. 122−125 °C. ^{1}H NMR (200 MHz, D_2O): δ = 2.92 (t, *J* = 6.5 Hz, 4 H), 3.27 (t, *J* = 6.5 Hz, 4 H) 4.81 (s, 6 H).

[5-(*tert*-Butoxycarbonylamino)-3-thiapentyl]amine (15): A mixture of **14** (5 g, 17.9 mmol) and NaOH (1.42 g, 35.7 mmol) in methanol (100 mL) was stirred for 0.5 h to obtain the neutral diamine. A solution of di-*tert*-butyl dicarbonate (1.55 g, 7.14 mmol) in $CHCl_3$ (4 mL) was then added dropwise. The reaction mixture was stirred for 24 h, methanol was removed under vacuum, and water (50 mL) was added. The residue was extracted with CH_2Cl_2 (2 × 100 mL), and the organic layer was dried with anhydrous Na_2SO_4 and concentrated under vacuum. The solid residue was subjected to column chromatography on silica gel (ethyl acetate/methanol, 8:2) to afford the monoprotected amine as a colorless oil. Yield 1.02 g (65%). IR (neat): $\tilde{\nu}$ = 3355, 1696 cm^{-1}. ^{1}H NMR (400 MHz, D_2O): δ = 1.40 (s, 9 H), 2.63(t, *J* = 6.6 Hz, 4 H), 2.78 (t, *J* = 6.6 Hz), 3.23(t, *J* = 6.6 Hz), 4.73 (b, 3 H) ppm. ^{13}C NMR (100 MHz, D_2O): δ = 30.3 (+), 33.5 (−), 36.2 (−), 45.3 (−), 83.6 (C_{quat}), 160.75 (C_{quat}) ppm. MS(FAB): *m*/*z* (%) = 221 (100) $[M + H]^+$.

1,3-Bis[5-(*tert*-butoxycarbonylamino)-3-thiapentyl]thiourea (16): A CH_2Cl_2 solution of thiophosgene (2.5 m, 0.7 mL 1.6 mmol), dissolved in 4 mL chloroform, was added dropwise at room temperature to a stirred solution of mono-Boc-protected amine **15** (750 mg, 3.2 mmol) in dry $CHCl_3$ (40 mL) and triethylamine (1.4 g, 12.7 mmol). The mixture was stirred overnight and then washed with 4 M acetic acid (3 × 15 mL), saturated $NaHCO_3$ solution, and brine. After drying with anhydrous Na_2SO_4, the filtrate was concentrated to dryness in vacuo. The residue was purified by column chromatography (ethyl acetate/hexane, 3:7; R_f = 0.35 in ethyl acetate/hexane, 1:1) to yield **16** (580 mg, 76%) as a soft, light yellow solid. IR (neat): $\tilde{\nu}$ = 3330, 1686 cm^{-1}. ^{1}H NMR: δ = 1.38 (s, 18 H), 2.59 (t, *J* = 6.5 Hz, 4 H), 2.71 (t, *J* = 6.4 Hz, 4 H), 3.25 (q, *J* = 6.4 Hz, 4 H), 3.65−3.75 (m, 4 H), 4.97−5.23 (brs, 2 H), 7.12 (brs, 2 H) ppm. ^{13}C NMR: δ = 28.4 (+), 31.5 (−), 32.5 (−), 40.0 (−), 43.8 (−), 79.7 (C_{quat}), 156.3 (C_{quat}), 181.66 (C=S) ppm. MS (FAB): *m*/*z* (%) = 483 (100) $[M + H]^+$.

1,3-Bis(5-amino-3-thiapentyl)thiourea Dihydrochloride (17): HCl solution (4 M, 10 mL) was added to a stirred solution of **16** (482 mg, 1 mmol) in 15 mL of methanol. The reaction was monitored by TLC and was complete within 8 h. The solvent was removed under vacuum to afford **17** as a colorless semi-solid. Yield 340 mg (95%). IR (neat): $\tilde{\nu}$ = 3251, 2966, 2924 cm^{-1}. ^{1}H NMR (400 MHz, [D$_4$]MeOH): δ = 2.82 (t, *J* = 6.8 Hz, 4 H), 2.91 (t, *J* = 6.8 Hz, 4 H), 3.22 (t, *J* = 6.8 Hz, 4 H), 3.73 (b, 4 H), 4.89 (brs, 8 H) ppm. ^{13}C NMR (100 MHz, [D$_4$]MeOH): δ = 29.3 (−), 30.9 (−), 39.6 (−), 44.3 (−).

3-Thiapentane-1,5-diyl Diisothiocyanate (18): The synthesis of **18** was performed according to general literature procedures[39] for the synthesis of diisothiocyanates from diamines. A mixture of **14** (1 g, 3.54 mmol) and NaOH (300 mg, 7.18 mmol) in methanol (25 mL) was stirred for 1 h. Triethylamine (725 mg, 7.19 mmol) and carbon disulfide (0.85 mL, 14.2 mmol) were added dropwise to this solution at room temperature. After 2 h of stirring, the reaction mixture was cooled to 0 °C, and ethyl chloroformate (1.53 g, 14.2 mmol) was added dropwise from a dropping funnel. Stirring was continued for another 2 h at 20 °C. The methanol was removed under vacuum and the residue was dissolved in water and $CHCl_3$. The

organic layer was washed successively with water and brine, dried with anhydrous Na_2SO_4, and concentrated under vacuum. The residue was distilled at 120−130 °C/2−3 mbar until the evolution of ethanol and carbon oxide sulfide ceased. The deep brown residue was then immediately subjected to column chromatography on silica gel with hexane and ethyl acetate (7:3) as the eluent to afford **18** (550 mg, 76%) as an orange oil; R_f = 0.75 (ethyl acetate/hexane, 3:7). IR (neat): $\tilde{\nu}$ = 2102−2188 (−N=C=S) cm^{-1}. ^1H NMR: δ = 2.92 (t, *J* = 6.8 Hz, 4 H), 3.77 (t, *J* = 6.8 Hz, 4 H) ppm. ^{13}C NMR: δ = 32.6 (−), 45.4 (−), 133.2 (C_{quat}) ppm. MS (EI): *m/z* (%) = 204 (100). HRMS: $C_6H_8N_2S_3$ (203.9848) [M^+] = 203.9849 ± 0.3 ppm.

1,9,17-Trithia-4,6,12,14,20,22-hexaazacyclotetracosane-5,13,21-trithiane [8 (X = S)]: A mixture of **17** (355 mg, 1 mmol) and NaOH (90 mg, 2.2 mmol) in dioxane was stirred with 4 mL of water for 1 h. Compound **18** (204 mg, 1 mmol), dissolved in 4 mL of dioxane, was then added to this solution. After stirring for 12 h, the mixture was heated to 70 °C for 4 h, and the solvent was then removed under vacuum. The residue was dissolved in acetone and subjected to column chromatography (ethyl acetate/hexane, 7:3; R_f = 0.54, ethyl acetate) to yield **8** (X = S) (150 mg, 30%) as a white solid, m.p. 175−176 °C. IR (neat): $\tilde{\nu}$ = 3200, 1558 cm^{-1}. ^1H NMR (400 MHz, [D_6]DMSO): δ = 2.71 (t, *J* = 6.8 Hz, 12 H), 3.52−3.62 (m, 12 H) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 30.1 (−), 43.4 (−), 181.0 (C_{quat}) ppm. MS(FAB): *m/z* (%) = 487 (100) [M + H]$^+$. $C_{15}H_{30}N_6S_6$ (486.80): calcd. C 37.03, H 6.22, N 17.28, S 39.46; found C 37.04, H 6.14, N 16.75, S 38.72.

Acknowledgments

This work was supported by the Deutsche Bundesstiftung Umwelt, which is gratefully acknowledged. T. F. thanks the Grand Duchy of Luxembourg and the Free State of Bavaria for graduate fellowships. We thank Prof. Michael Göbel for providing us a sample of compound **19**.

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Received April 5, 2002
[O02192]