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Coordination Chemistry of Lipoic Acid and Related Compounds V [1]. New Heteroditopic Ligands Derived from Monoazacrown Ethers and Lipoic Acid[a]

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Summary. Lipoyl imidazolide reacts with aza-15-crown-5 (1,4,7,10-tetraoxa-13-azacyclopentadecane) or aza-18-crown-6 (1,4,7,10,13-pentaoxa-16-azacyclooctadecane) to afford new *N*-lipoylated azacrown compounds in good yields. These compounds can be transformed into 1,3-dithiols and amines by reduction with complex hydrides of the disulfide and/or amide group of the lipoyl chain. The new pendant-arm macrocycles react as heteroditopic ligands by forming dithiolate and disulfide complexes with the 'soft' metal ions Ni^{2+} and Pd^{2+}, respectively, and an amine complex with the 'hard' Li^{+} ion. Semiempirical and DFT calculations on the complexation of a lithium ion give a most favourable structure in which the azacrown and two solvent molecules are in contact with the metal but not the pendant arm.

Keywords. Complexation; Crown compounds; Lipoic acid; Lithium; Quantum chemical calculations.

Introduction

Heterotopic ligands can accommodate different metal ions in different parts of their molecules. The resulting complexes may possess unusual properties, for example in redox reactions, electronic exitations, the formation of supramolecular structures, controlled molecular motions ('molecular machines'), or as catalysts. The small biomolecule lipoic acid (**1**; 5-(1,2-dithiolan-3-yl)pentanoic acid) appears to be a promising building block for such ligands. **1** contains the redox-active 1,2-dithiolane ring and can reversibly be reduced to the 1,3-dithiol dihydrolipoic acid

[a] Dedicated to Prof. Dr. *Ernst Anders* on the occasion of his 60th birthday

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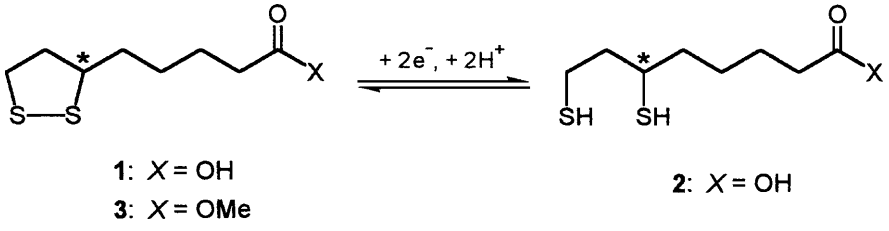

Scheme 1

(**2**; 6,8-dimercaptooctanoic acid) as shown in Scheme 1. In recent years, **1** (as well as its methyl ester **3**) and **2** have been used in the synthesis of disulfide and dithiolate complexes, respectively, which were characterized, *inter alia*, by X-ray crystal structure analyses. A common feature of these complexes is the presence of 'soft' coordination centers such as $PdCl_2$, $PdBr_2$, CuI [2], CuCl [3], $PhAs^{2+}$ [4], $PhHg^{+}$, and Hg^{2+} [5]. The electronically soft character of the sulfur-containing groups is also reflected by the ease with which self-assembled monolayers (SAMs) of derivatives of **1** form on gold surfaces [6].

The present study is based on the idea that new heteroditopic ligands should be accessible *via* covalent attachment of the lipoyl group to suitable sets of 'hard' donor atoms. Recently we have shown that the imidazolide method [7] allows the facile synthesis of lipoamides from amines and **1** [1, 5, 8]. Therefore, monoaza-crown ethers, representing a special class of monoamines, have been chosen as the second building block of the target ligands. Our approach, the attachment of a side arm to an azacrown ether, thus belongs to the field of lariat ether chemistry pioneered by *Gokel* and coworkers [9]. In the same way as the parent crown ethers, the monoaza derivatives form rather stable complexes with 'hard' metal ions. For example, in acetonitrile solution the stability constants of the 1:1 complexes between Li^{+} or Na^{+} and aza-15-crown-5 (1,4,7,10-tetraoxa-13-azacyclopentadecane) or aza-18-crown-6 (1,4,7,10,13-pentaoxa-16-azacyclooctadecane) fall in the range of $\log K = 3.1–5.2$ [10]. In this paper, we report the syntheses of lipoylated aza-15-crown-5 and aza-18-crown-6, various reduction products thereof, and the complexation behaviour of these new ligands towards selected metal ions in solution. Quantum chemical calculations were performed in order to explore the possibility of a simultaneous coordination of the 'hard' and 'soft' parts of a given ligand molecule to the same metal ion.

Results and Discussion

Syntheses and characterization of the ligands

Covalent attachment of the lipoyl group to the nitrogen atoms of monoazacrown ethers was accomplished by reacting lipoyl imidazolide with the respective aza-crown compound (Fig. 1). Before the final purification step, unreacted imidazolide was transformed into ethyl lipoate by addition of an excess of ethanol to the reaction mixture, thus facilitating the subsequent column separation. By this method the new compounds **4** and **5** were obtained in high yields from aza-15-crown-5 and aza-18-crown-6, respectively, as analytically pure yellow oils.

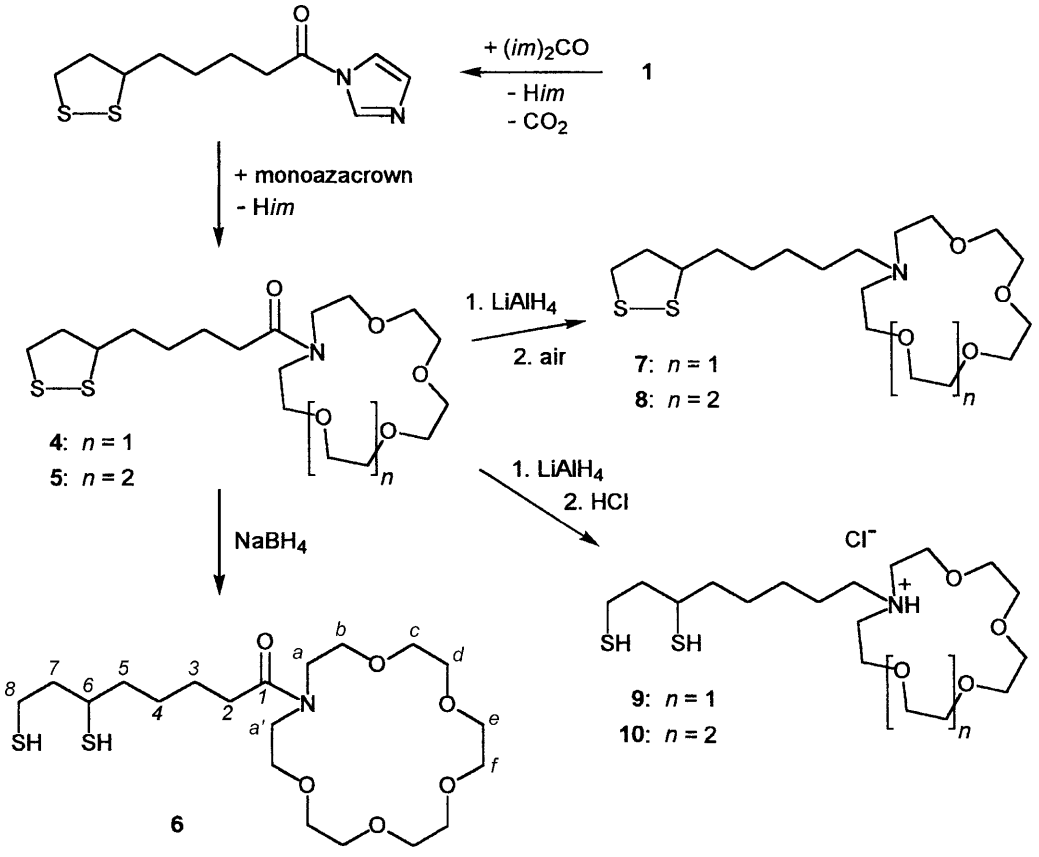

Fig. 1. Syntheses of the new compounds **4**–**10**; the atom labelling scheme used with the NMR results is exemplified; $(im)_2CO = N,N'$-carbonyldiimidazole; H*im* = imidazole

Reactions of **4** and **5** with complex hydrides opened up synthetic routes to several other potentially heteroditopic ligands. Thus, reduction of **5** with sodium borohydride in an ethanol/water mixture afforded the dithiol **6**. In **6**, the amide group is still intact. In order to reduce this group, too, lithium aluminum hydride in tetrahydrofuran was employed. This method allowed the preparation of the amines **7**–**10**, which were isolable in yields above 80%. The reductions with $LiAlH_4$ were performed under a protective atmosphere. When the reaction mixtures were acidified before they came into contact with air, the dithiols **9** and **10** could be isolated (Method B, see Experimental). However, when the alkaline reaction mixtures were immediately exposed to air for 24 h, the sulfur atoms were reoxidized, and the disulfides **7** and **8** were obtained (Method A). Recently, a similar method has independently been used by *Morita et al.* to prepare the disulfide 5-(1,2-dithiolan-3-yl)pentylamine from lipoamide ($X = NH_2$ in the left formula of Scheme 1) [6e].

The disulfides **4**, **5**, **7**, and **8** are visually distinguishable from the dithiols **6**, **9**, and **10** by their light yellow color, which is caused by the UV/Vis absorption characteristics of the 1,2-dithiolanyl ring [11]. The infrared spectra are unexceptional. They show, for example, the expected strong absorptions of the asymmetric C–O–C stretching vibrations near 1120 cm^{-1} (**4**–**10**) and the C=O stretching vibrations near 1640 cm^{-1} (**4**–**6**). The ^1H and, especially, the ^{13}C NMR spectra

are most suitable for identifying and checking the purity of the compounds. The unequivocal assignment of the majority of the NMR signals formed the basis for the metal ion complexation studies described below. The pendant-arm azacrowns **4**–**10** possess favourable solubility properties. They are readily soluble in polar organic solvents, *e.g.* in chloroform, dichloromethane, acetonitrile, methanol, ethanol, diethyl ether, tetrahydrofuran, and 1,4-dioxane.

Metal ion complexation in solution

The ligand properties of the newly synthesized compounds **4**–**10** have still to be systematically explored. In order to get preliminary information about the coordination behaviour, reactions of some of these compounds with Ni^{2+}, Pd^{2+}, and Li^{+} have been studied.

The Ni^{2+} ion is known to form a variety of different thiolate complexes [12]. We therefore added a methanolic solution of $Ni(NO_3)_2 \cdot 6H_2O$ to a solution of the dithiol amine hydrochloride **10** (one equivalent) and ethyl diisopropylamine as an auxiliary base (three equivalents) in the same solvent. The experiment was performed under a protective atmosphere of pure nitrogen. The final concentrations of the metal and the ligand were 0.04 *M* each. Upon addition of the green Ni^{2+} solution, no precipitation occurred, and the colorless solution of the ligand immediately turned intensely reddish-brown. This color is characteristic of nickel(II) thiolates. In a control experiment, equimolar amounts of aza-18-crown-6 and $Ni(NO_3)_2 \cdot 6H_2O$ in methanol produced only a green solution. *Sletten* and *Kovacs* have shown that the prototypical 1,3-dithiolate ligand propane-1,3-dithiolate (pdt^{2-}) forms the hexanuclear complex *cyclo*-[$Ni_6(pdt)_6$] which contains the nickel(II) ions in planar S_4 environments [13]. From these observations we conclude that the 1,3-dithiolate that derives from **10** probably forms an oligomeric neutral nickel(II) thiolate complex, too. The core of this complex should be similarly structured, but need not necessarily have the same nuclearity as the pdt^{2-} complex. So far, attempts to obtain single crystals in order to verify this conjecture by X-ray structure analysis were unsuccessful.

It has been shown that $PdCl_2$ reacts with two equivalents of methyl lipoate (**3**) in dichloromethane or tetrahydrofuran to afford the dark red coordination compound [$PdCl_2$(**3**)$_2$] [2]. In crystals of this compound, two organic ligands of opposite chirality coordinate to a *trans*-$PdCl_2$ unit *via* their S_8 atoms. The stable coordination of a disulfide to palladium(II) was not unexpected since Pd^{2+} is a typical 'soft' cation whose absolute hardness amounts to only 6.75 eV [14]. The Ni^{2+} ion has a comparable value (8.50 eV), whereas the absolute hardness of the 'hard' Li^{+} ion is much larger (35.12 eV). When 0.5 equivalents of $PdCl_2$ were dissolved in a 0.1 *M* solution of aza-15-crown-5 in dichloromethane, a deep yellow color appeared. In contrast to this, the same experiment with the disulfide **7** instead of aza-15-crown-5 yielded a dark red solution, indicating S-coordination of the ligand and the possible formation of [$PdCl_2$(**7**)$_2$]. Preliminary NMR studies support this conclusion. However, the ^{1}H and ^{13}C NMR spectra are rather intricate – a situation which has also been encountered with [$PdCl_2$(**3**)$_2$]. In this latter case we could demonstrate that the complex is highly dynamic in solution. Candidates for the processes involved are the alternation of S_6 and S_8 as donor atoms, inversion at

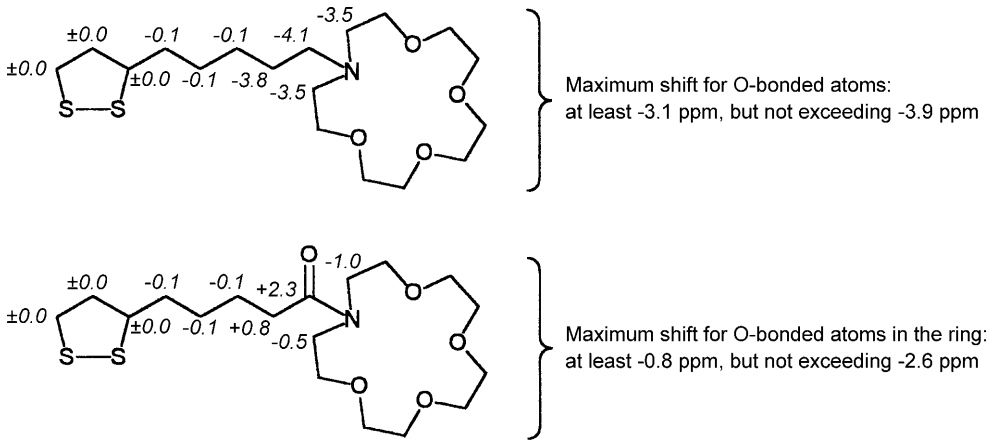

Fig. 2. Lithium(I) induced shifts of the ^{13}C NMR resonances of **7** (above) and **4** (below); values in ppm; conditions: CD_3CN, 0.3 *M* ligand, 0.3 *M* $LiClO_4$, 300 K

the coordinated S atom, and ligand exchange; the last two can lead to the presence of diastereomeric complexes. At least two of these processes are simultaneously operative in solutions of $[PdCl_2(\mathbf{3})_2]$ at room temperature. Attempts to crystallize the supposed complex $[PdCl_2(\mathbf{7})_2]$ yielded dark red oils.

In order to study the complexation of lithium(I), ^{13}C NMR spectra of a 0.3 *M* solution of **7** in CD_3CN were recorded before and after addition of one equivalent of $LiClO_4$. The changes of the chemical shifts that were induced by coordination to the Li^+ ion are given in Fig. 2. Strong upfield shifts were observed for the C atoms in the vicinity of the nitrogen atom, *i.e.* for C_1 (-4.1 ppm), C_2 (-3.8 ppm), and C_a (-3.5 ppm). A somewhat smaller relative shift for C_a (-1.9 ppm) was determined by *Tsukube et al.* in the aza-15-crown-5/$LiClO_4$/acetonitrile system at a concentration of 0.05 *M* [15]. The shifts caused by protonation of the nitrogen atom are also informative. For example, upon proceeding from **7** to **9**, shifts of -2.3 (C_1), *ca.* -3.0 (C_2), and -1.4 ppm (C_a) occur (see Experimental). Comparison between the H^+ and the Li^+ system unequivocally reveals that the Li^+ ion is bonded to the nitrogen atom of **7**. In this respect, the lithium complex of **7** differs from that of an *N*-aryl substituted aza-15-crown-5 ligand described by *Reiss et al.* [16]. In the latter, the Li^+ ion is not coordinated to the nitrogen atom but to the oxygen atoms of the ring, at least in the solid state. The situation is less clear for the amide **4** where the Li^+ induced shifts are smaller than in the case of **7** (Fig. 2). Especially the shift for the atoms C_a and $C_{a'}$ is only -0.8 ppm (mean value). C_1 and C_2 show downfield shifts. It appears that lithium is more weakly complexed by **4** than by **7** and possibly bonded to the carbonyl oxygen atom. From the absence of metal ion induced shifts in the dithiolanyl rings it can be concluded that, in accordance with the prediction of the HSAB principle, the 'soft' sulfur atoms of both **4** and **7** do not coordinate to the 'hard' Li^+ ion. It is, however, unclear to which extent the ether oxygen atoms are involved in lithium ion binding. The chemical shifts of the O-bonded carbon atoms C_b–C_e are too similar to allow individual assignments. Therefore, it was only possible to determine a lower and an upper limit for the maximum Li^+-induced shift. For **7**, this means that one of the atom types C_b–C_e is shifted by a value in the range

of -3.1 to -3.9 ppm, whereas the shifts of the others are smaller. This ambiguity about the exact coordination of the lithium(I) ion to the azacrown ring of **7** was a main reason to perform quantum chemical calculations.

Quantum mechanical results

In principle, the free ligand **7** can exist in several conformations. We therefore started our theoretical study with a semiempirical PM3 [17, 18] examination of its potential energy surface and found two important minima: a stretched structure where the pendant arm is directed away from the azacrown, and a bent one with an orientation of the dithiolanyl ring above the azacrown, offering an additional complexation site to a metal ion (Fig. 3). Both conformations possess essentially the same energy, hence from these calculations we have gained no information about a preferred ligand orientation in a metal complex.

The above-mentioned experimental NMR data on the complexation of a lithium ion by **7** indicate that the metal is in contact with the nitrogen atom but not with the sulfur atoms. This is a strong hint for the occurrence of a complex where the ligand coordinates to the metal only through its azacrown heteroatoms. We therefore calculated several possible complexes of the ligand (both in its stretched and bent forms) with a lithium cation. Since the NMR experiments were performed in deuterated acetonitrile, one or more molecules of CH_3CN were included. Four distinct types of structures (**A**–**D**, Fig. 4) were found. The first one, **A**, retains the stretched geometry of the free ligand, and the lithium cation is in contact to the ring nitrogen atom (Li–N 2.36 Å) and all four ring oxygen atoms (Li–O 2.11–2.44 Å) with a sixth coordination site occupied by an acetonitrile molecule (Li–N 2.02 Å). Similarly, in **B** the azacrown ring offers one nitrogen atom (Li–N 2.42 Å) and three oxygen atoms (Li–O 2.12–2.30 Å) as donors; here, however, an additional donor comes from the

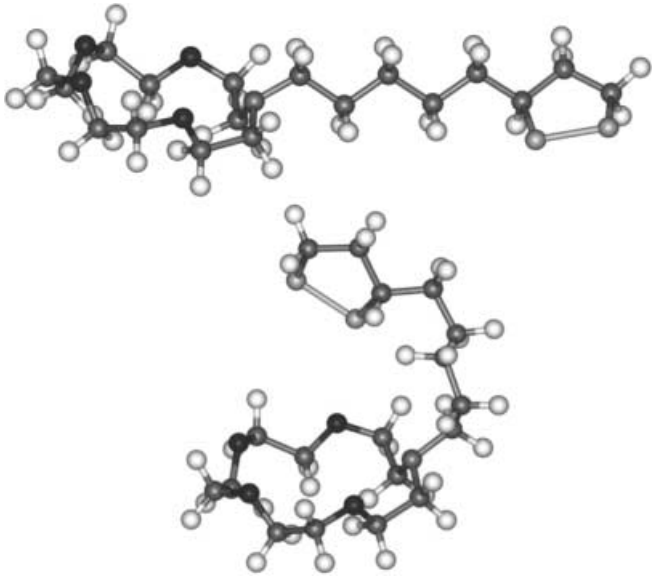

Fig. 3. PM3-calculated linear and bent geometries of the uncoordinated ligand **7**

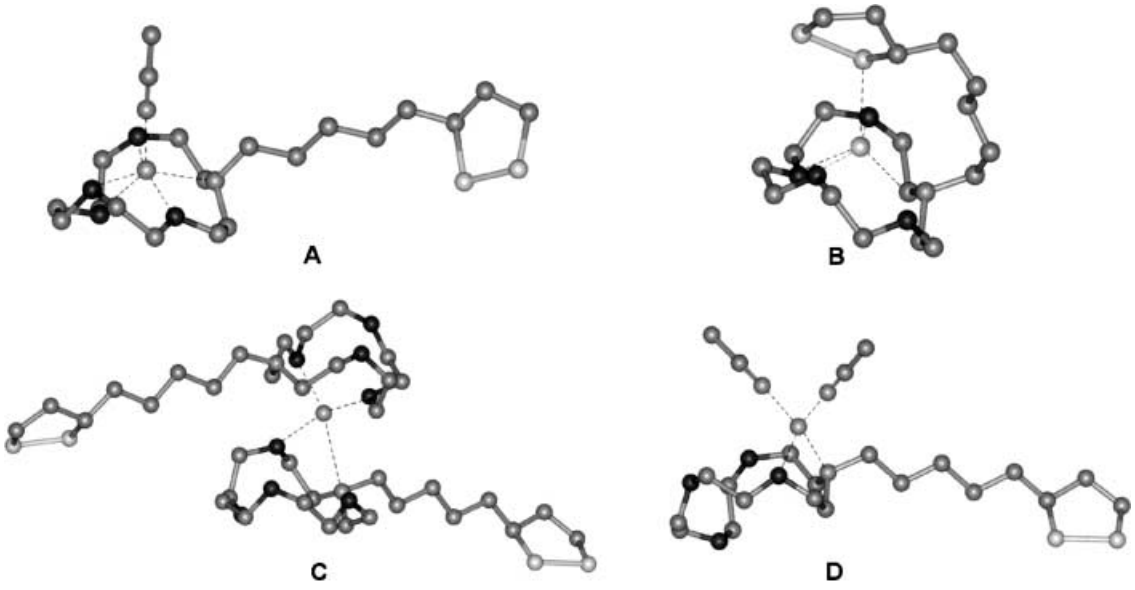

Fig. 4. PM3-calculated geometries of the complexes **A**–**D** of ligand **7**

dithiolanyl ring (Li–S 2.79 Å). Type **C** is a 'sandwich-type' complex where two ligands accommodate the metal cation between their azacrown rings. In this complex, the lithium is four-coordinate with three oxygen atoms at *ca*. 2.1 Å and one nitrogen atom at 2.52 Å. Finally, we have also examined a type **A** complex where a second acetonitrile molecule was available. In this case, geometry **D** resulted where the lithium cation is only in contact with two ring atoms (Li–N 2.25 and Li–O 2.08 Å) and two acetonitrile ligands (Li–N 2.01 Å).

In order to compare the different structures, we have calculated complexation energies for the reaction $[Li(CH_3CN)_4]^+ + m\mathbf{7} \rightarrow [Li(\mathbf{7})_m(CH_3CN)_n] + (4-n)$ CH_3CN ($m = 1, 2$; $n = 0$–2) at the PM3 level of theory under inclusion of thermodynamical properties and solvation effects (Table 1). Gas-phase entropies were evaluated, and the free energies at 298 K are reported. Note that the solvation free energies use gas-phase entropies due to the inability of the Chem3D MOPAC 2000 implementation to calculate them in a solvent field. A dielectric constant of 35 for acetonitrile was used in the COSMO calculation. From the data in Table 1, it is obvious that the complex **C** which forms from two molecules of **7** and a lithium

Table 1. PM3-calculated complexation enthalpies and free energies (kcal $\cdot$ mol^{-1}) of the structures **A**–**D** in vaccum and acetonitrile ($\varepsilon = 35$)

	Gas phase		Solvation	
	ΔH_R	ΔG_R	ΔH_R	ΔG_R[a]
A	63.0	19.0	57.0	12.9
B	83.2	33.8	71.2	21.8
C	89.7	87.6	78.2	76.1
D	40.5	4.8	38.4	2.7

[a] Entropic contribution calculated in the gas phase (see text for details)

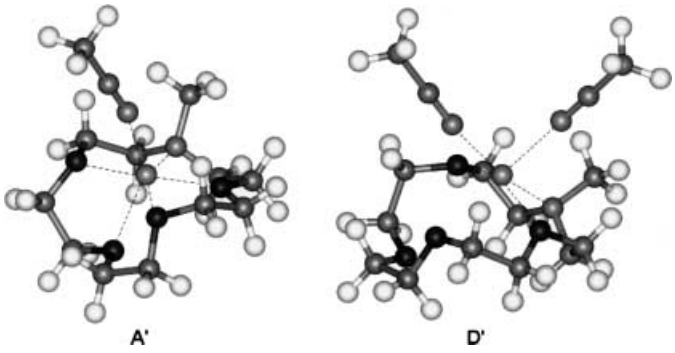

Fig. 5. B3LYP/6-31G(d)-optimized structures of the model complexes **A′** and **D′**

cation is least stable, independent of the employed approach. The complexation of Li^+ by only one molecule of **7** is more likely from an energetic point of view. Structure **A**, which contains one molecule of acetonitrile, is calculated with a complexation energy similar to that of **B** but is slightly more stable. However, it turned out that a type **D** geometry is even more favourable with respect to complexation of a lithium cation. The calculated overall complexation reactions are all endothermic; even that leading to the formation of **D** requires about $3\,kcal \cdot mol^{-1}$. This appears to be due to a slight underestimation of the Li–O interaction present in the lithium parametrization [18–20], since the reaction obviously takes place.

The density functional approach B3LYP [21], together with the 6-31G(d) basis set, was then used to optimize the complexes **A′** and **D′**. These complexes are models of the two most favourable structures **A** and **D**, in which the pendant arms were replaced by methyl groups (Fig. 5). As shown above, the pendant arm is not involved in the coordination of the lithium cation in **A** and **D**; hence, the substitution is justified for computational efficiency. The bond lengths are similar to those derived with the PM3 method (**A′**: Li–N 2.27 Å, Li–O 2.07–2.32 Å (4×), Li–N(acetonitrile) 2.17 Å; **D′**: Li–N 2.37 Å, Li–O 2.11–2.14 Å (2×), Li–N(acetonitrile) 2.27 Å (2×)). The calculated energies confirm that **D′** is slightly preferred. Its complexation energy ($-6.7\,kcal\,mol^{-1}$) is by $2\,kcal \cdot mol^{-1}$ more exothermic than the corresponding energy of **A′**.

Since ^{13}C NMR spectroscopy has extensively been used in the study of the lithium ion complexation, it appeared straightforward to also calculate NMR chemical shifts, here at the B3LYP/6-31G(d) level of theory. Calculations on *N*-methyl-aza-15-crown-5, the ligand of the above-mentioned model complexes **A′** and **D′**, give very good agreements with literature values [22], usually within 2 ppm, indicating the suitablity of the used approach. Our intention was to see whether there is a change in the chemical shifts upon lithium ion coordination similar to that observed in the experiment. Unfortunately, the calculated changes of the ^{13}C NMR shifts behave more or less randomly, *i.e.* no correlation between experimental and theoretical metal-induced changes of the chemical shifts can be observed. We assume that the observed NMR spectra of the flexible crown ether/lithium systems are the result of dynamic behaviour of the complexes in solution. However, the chemical shift calculations, which are very sensitive to changes in geometries, refer to vacuum and derive the magnetic properties from only one geometry. Thus, it is not surprising to obtain only poor agreement between theory and experiment.

Experimental

Aza-15-crown-5 and aza-18-crown-6 were prepared according to a published procedure [23]. The oligoethylene glycol di(*p*-toluenesulfonates) [24] used in these syntheses were prepared from the respective oligoethylene glycol, *p*-toluenesulfonyl chloride, and triethylamine in dichloromethane. *THF* was refluxed over Na for 4 h and then destilled to remove the stabilizer 2,6-di(*tert*-butyl)-4-methylphenol. Other solvents were dried over 3 Å molecular sieve. The remaining starting materials, including racemic lipoic acid ($\geq$98%), were purchased from commercial sources and used as received.

IR spectra (thin films between KBr plates) were obtained on a Bio-Rad FTS 7PC spectrometer. NMR spectra were recorded at 300 K on Bruker AM 300 and ARX 500 instruments. Chemical shifts are given relative to $SiMe_4$ ($\delta = 0.00$ ppm). In the ^{13}C NMR spectra, the solvent signal ($CDCl_3$; 77.00 ppm) was used as internal reference. Signal assignments were obtained from 2D NMR spectra and by comparison with published spectra [25] of **1**, **2**, lipoamide, and dihydrolipoamide ($X = NH_2$ in Scheme 1). Mass spectra were measured with a Finnigan MAT 212 instrument. Elemental analyses (C/H/N/S) of the parent compounds **4** and **5** were performed by the Analytical Laboratories Malissa and Reuter, Lindlar (Germany); experimental and calculated values were in excellent agreement ($\Delta < 0.3\%$). The purity of compounds **6**–**10**, which were all directly prepared from **4** or **5**, was checked by NMR spectroscopy.

1,2-Dithiolanyl compounds are susceptible to ring-opening polymerization, especially as oils. Compounds **4**, **5**, **7**, and **8** were therefore stored as dilute solutions in CH_2Cl_2 or *THF* in a refrigerator. The dithiols **6**, **9**, and **10** are not markedly air-sensitive; nevertheless, they were stored under an atmosphere of pure N_2 to avoid slow oxidation by air.

General procedure for the preparation of compounds **4** *and* **5**

3.24 g of *N*,*N*′-carbonyldiimidazole (20.0 mmol) were added to a solution of 4.13 g of *rac*-lipoic acid (20.0 mmol) in 50 cm^3 of anhydrous *THF*. The reaction mixture was stirred at room temperature for 8 h. After addition of the azacrown ether (20.0 mmol), the solution was refluxed for 48 h. If unreacted imidazolide of lipoic acid was still present (checked by TLC), 20 cm^3 of EtOH were added, and the solution was again refluxed until the imidazolide was no longer detectable (2–4 h). Then, most of the solvent was removed under reduced pressure. The remaining yellow oil was subjected to column chromatography (length: 50 cm, diameter: 6 cm; silica gel 60, particle size: 0.063–0.200 mm (70–230 mesh ASTM); *n*-hexane : *THF* = 1:2). The lipoylated azacrown formed the second band and was obtained as a yellow oil after evaporation of the solvent *in vacuo*.

5-(1,2-Dithiolan-3-yl)-1-(1,4,7,10-tetraoxa-13-azacyclopentadec-13-yl)pentan-1-one (**4**; $C_{18}H_{33}NO_5S_2$)

Yield: 7.1 g (87%); IR (neat): $\tilde{\nu} =$ 2924s, 2859s, 1643s, 1462m, 1447m, 1420m, 1354m, 1296m, 1252m, 1125s, 934m, 835w cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): $\delta = 1.41$ (m, 2H, H_4), 1.62 (m, 4H, H_3/H_5), 1.85 (m, 1H, H_7), 2.29 (t, 2H, H_2), 2.39 (m, 1H, $H_{7'}$), 3.08 (m, 2H, H_8), 3.45 (t, 2H), 3.48–3.65 (m, 17H), 3.73 (t, 2H) (H_6/H_a–H_e) ppm; ^{13}C NMR ($CDCl_3$, 125.8 MHz): $\delta = 24.90$ (C_3), 28.93 (C_4), 32.78 (C_2), 34.66 (C_5), 38.34 (C_8), 40.09 (C_7), 49.12 (C_a), 50.24 ($C_{a'}$), 56.34 (C_6), 69.59, 69.68, 70.01, 70.24, 70.55, 71.52 (C_b–C_e), 172.99 (C_1); CI-MS (isobutane): $m/z = 408$ (100%, $[M+H]^+$); $R_f \approx 0.60$ (silica gel 60 (layer thickness: 0.2 mm), *n*-hexane : *THF* = 1:2).

5-(1,2-Dithiolan-3-yl)-1-(1,4,7,10,13-pentaoxa-16-azacyclooctadec-16-yl)pentan-1-one (**5**; $C_{20}H_{37}NO_6S_2$)

Yield: 7.9 g (87%); IR (neat): $\tilde{\nu} =$ 2922s, 2864s, 1642s, 1462m, 1449m, 1420m, 1352m, 1296m, 1254m, 1119s, 943m, 843w cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): $\delta = 1.41$ (m, 2H, H_4), 1.62 (m,

4H, H_3/H_5), 1.85 (m, 1H, H_7), 2.30 (t, 2H, H_2), 2.39 (m, 1H, $H_{7'}$), 3.08 (m, 2H, H_8), 3.49–3.64 (m, 25H, H_6/H_a–H_f) ppm; ^{13}C NMR ($CDCl_3$, 125.8 MHz): $\delta = 24.85$ (C_3), 28.93 (C_4), 32.68 (C_2), 34.65 (C_5), 38.32 (C_8), 40.07 (C_7), 46.71 (C_a), 48.83 ($C_{a'}$), 56.32 (C_6), 69.41, 69.85, 70.23, 70.43, 70.52, 70.57, 70.65, 70.75 (C_b–C_f), 172.84 (C_1) ppm; CI-MS (isobutane): $m/z = 452$ (100%, $[M + H]^+$); $R_f \approx 0.55$ (silica gel 60 (layer thickness: 0.2 mm), *n*-hexane : *THF* = 1:2).

6,8-Dimercapto-1-(1,4,7,10,13-pentaoxa-16-azacyclooctadec-16-yl)octan-1-one
(**6**; $C_{20}H_{39}NO_6S_2$)

1.35 g of **5** (3.0 mmol) were dissolved in 20 cm^3 of EtOH. After addition of 20 cm^3 of H_2O, 1.25 g of $NaBH_4$ (33 mmol) were added in small portions to the stirred solution. After stirring for 12 h, further 50 cm^3 of H_2O were added, and the *pH* value of the slurry was adjusted to 3 with concentrated HCl. The resulting clear solution was extracted three times with 40 cm^3 of $CHCl_3$. The combined extracts were washed with H_2O and dried over $MgSO_4$. After complete removal of the solvent *in vacuo*, the product remained as a colorless oil.

Yield: 1.11 g (82%); IR (neat): $\tilde{\nu} =$ 2930s, 2864s, 2542w, 1640s, 1464m, 1449m, 1420m, 1352m, 1296m, 1250m, 1121s, 943m, 845w cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 1.25$ (d, 1H, HS_6), 1.29 (t, 1H, HS_8), 1.34–1.74 (m, 7H, $H_3/H_4/H_5/H_7$), 1.85 (m, 1H, $H_{7'}$), 2.31 (t, 2H, H_2), 2.63 (m, 2H, H_8), 2.87 (m, 1H, H_6), 3.50–3.67 (m, 24H, H_a–H_f) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz): $\delta = 22.22$ (C_8), 24.84 (C_3), 26.80 (C_4), 32.84 (C_2), 38.87 (C_5), 39.33 (C_6), 42.73 (C_7), 46.82 (C_a), 48.92 ($C_{a'}$), 69.48, 69.97, 70.32, 70.53, 70.62, 70.73, 70.82 (C_b–C_f), 172.98 (C_1) ppm; CI-MS (isobutane): $m/z = 454$ (100%, $[M + H]^+$).

General procedure for the preparation of compounds **7**–**10**

Under a protective atmosphere of dry N_2, a solution of **4** or **5** in 20 cm^3 of *THF* was slowly dropped into a stirred suspension of the sixfold molar amount of $LiAlH_4$ in 30 cm^3 of *THF*. Then, the reaction mixture was refluxed under nitrogen for 6 h and subsequently hydrolized by gentle application of 20 cm^3 of H_2O at 0°C. The working-up procedure depended on whether the disulfides (Method A) or the dithiols (Method B) were to be obtained.

Method A: The strongly alkaline reaction mixture was stirred in an open flask at room temperature for 24 h. During this time, the white suspension turned pale yellow. Then, the solvent was completely removed *in vacuo*, and the anhydrous residue was extracted twice with 40 cm^3 of $CHCl_3$. From the combined extracts, the product was obtained as a yellow oil after complete removal of the solvent *in vacuo*.

Method B: The *pH* value of the reaction mixture was adjusted to 3 by addition of concentrated HCl. After complete removal of the solvent *in vacuo*, the anhydrous residue was extracted twice with 40 cm^3 of $CHCl_3$. Complete evaporation of the combined extracts *in vacuo* left the product as a colorless oil.

13-(5-(1,2-Dithiolan-3-yl)pentyl)-1,4,7,10-tetraoxa-13-azacyclopentadecane
(**7**; $C_{18}H_{35}NO_4S_2$)

Prepared from 1.02 g of **4** (2.5 mmol) and 0.57 g of $LiAlH_4$ (15 mmol) according to Method A; yield: 0.84 g (85%); IR (neat): $\tilde{\nu} =$ 2928s, 2859s, 1464m, 1449m, 1354m, 1296m, 1258m, 1125s, 936m, 847w, 802w cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 1.30$ (m, 2H, H_3), 1.45 (m, 4H, H_2/H_4), 1.67 (m, 2H, H_5), 1.91 (m, 1H, H_7), 2.46 (m, 1H, $H_{7'}$), 2.52 (t, br, 2H, H_1), 2.76 (t, 4H, H_a), 3.14 (m, 2H, H_8), 3.59 (m, 1H, H_6), 3.66 (m, 16H, H_b–H_e) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz): $\delta = 26.67$, 26.88 (C_2/C_3), 28.95 (C_4), 34.59 (C_5), 38.17 (C_8), 39.99 (C_7), 54.09 (C_a), 56.34 (C_1/C_6), 69.53, 69.86, 70.03, 70.59 (C_b–C_e) ppm; CI-MS (isobutane): $m/z = 394$ (100%, $[M + H]^+$).

16-(5-(1,2-Dithiolan-3-yl)pentyl)-1,4,7,10,13-pentaoxa-16-azacyclooctadecane
(**8**; $C_{20}H_{39}NO_5S_2$)

Prepared from 1.26 g of **5** (2.8 mmol) and 0.64 g of $LiAlH_4$ (16.8 mmol) according to Method A; yield: 1.00 g (82%); IR (neat): $\tilde{\nu}$ = 2918s, *ca.* 2870sh, 1454m, 1352m, 1296m, 1277m, 1248m, 1107s, 953m, 835m cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ = 1.27 (m, 2H, H_3), 1.41 (m, 4H, H_2/H_4), 1.63 (m, 2H, H_5), 1.87 (m, 1H, H_7), 2.43 (m, 1H, $H_{7'}$), 2.46 (t, br, 2H, H_1), 2.72 (t, 4H, H_a), 3.12 (m, 2H, H_8), 3.55 (m, 1H, H_6), 3.60 (m, 20H, H_b–H_f) ppm; ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ = 26.75, 26.81 (C_2/C_3), 28.84 (C_4), 34.51 (C_5), 38.06 (C_8), 39.89 (C_7), 53.69 (C_a), 55.50 (C_1), 56.25 (C_6), 69.56, 70.05, 70.41, 70.50 (C_b–C_f) ppm; CI-MS (isobutane): m/z = 438 (100%, $[M+H]^+$).

8-(1,4,7,10-Tetraoxa-13-azacyclopentadec-13-yl)octane-1,3-dithiol hydrochloride
(**9**; $C_{18}H_{38}ClNO_4S_2$)

Prepared from 1.35 g of **4** (3.3 mmol) and 0.75 g of $LiAlH_4$ (19.8 mmol) according to Method B; yield: 1.24 g (87%); IR (neat): $\tilde{\nu}$ = 2926s, 2863s, 2450m/br, 1452m, 1358m, 1296m, 1252m, 1123s, 936m, 835w cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.30 (m, 4H, H_3/SH), 1.36–1.75 (m, 5H, $H_4/H_5/H_7$), 1.83 (m, 3H, $H_2/H_{7'}$), 2.63 (m, 2H, H_8), 2.85 (m, 1H, H_6), 3.17 (m, 2H, H_1), 3.40 (m, 4H, H_a), 3.51–3.70 (m, 12H, H_c–H_e), 3.90–4.08 (m, 4H, H_b), 11.6 (s, br, 1H, NH^+) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 21.99 (C_8), 23.76 (C_2), 26.05, 26.17 (C_3/C_4), 38.35 (C_5), 39.02 (C_6), 42.48 (C_7), 52.65 (C_a), 54.04 (C_1), 65.37 (C_b), 69.54, 69.96, 70.28 (C_c–C_e) ppm; CI-MS (isobutane): m/z = 396 (100%, $[M-Cl]^+$).

8-(1,4,7,10,13-Pentaoxa-16-azacyclooctadec-16-yl)octane-1,3-dithiol hydrochloride
(**10**; $C_{20}H_{42}ClNO_5S_2$)

Prepared from 1.94 g of **5** (4.3 mmol) and 0.98 g of $LiAlH_4$ (25.8 mmol) according to Method B; yield: 1.70 g (83%); IR (neat): $\tilde{\nu}$ = 2926s, 2870s, 2460m/br, 1470m, 1452m, 1354m, 1296m, 1250m, 1117s, 951m, 835w cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.30 (m, 4H, H_3/SH), 1.36–1.75 (m, 5H, $H_4/H_5/H_7$), 1.82 (m, 3H, $H_2/H_{7'}$), 2.64 (m, 2H, H_8), 2.84 (m, 1H, H_6), 3.15 (m, 2H, H_1), 3.38 (m, 4H, H_a), 3.56 (m, 16H, H_c–H_f), 3.86–4.08 (m, 4H, H_b), 11.8 (s, br, 1H, NH^+) ppm; ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ = 22.14 (C_8), 23.62 (C_2), 26.24, 26.31 (C_3/C_4), 38.55 (C_5), 39.17 (C_6), 42.64 (C_7), 52.59 (C_a), 52.64 ($C_{a'}$), 54.24 (C_1), 65.31 (C_b), 69.76, 70.29, 70.38, 70.42 (C_c–C_f) ppm; CI-MS (isobutane): m/z = 440 (100%, $[M-Cl]^+$).

Computational details

All semiempirical calculations were performed using MOPAC 2000 [26] as implemented in Chem3D 7.0 [27], employing MOPAC's COSMO module [28] for the solvent calculations (ε = 35). Thermodynamical properties were evaluated at 298 K and only in the gas phase due to the inability of the COSMO/MOPAC2000/CHEM3D package to run the necessary calculations. For the DFT part, the B3LYP/6-31G(d) level of theory was used for both optimization and NMR evaluation; zero-point vibrational energies are included in the relative energies. The results were obtained with the Gaussian 98 program package [29].

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