Steric and Stereoelectronic Effects in Aza Crown Ether Complexes[1]

Vitally P. Solov'ev[a], Nadezhda N. Strakhova[a], Vladimir P. Kazachenko[a], Alexandr F. Solotnov[a], Vladimir E. Baulin[a], Oleg A. Raevsky[a], Volker Rüdiger[b], Frank Eblinger[b], and Hans-Jörg Schneider*[b]

Institute of Physiologically Active Compounds, Russian Academy of Science[a],
142432, Chernogolovka, Moscow Region, Russia

FR Organische Chemie, Universität des Saarlandes[b],
D-66041 Saarbrücken, Germany

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Stability constants and enthalpy changes determined by calorimetric titrations and supported by selected NMR titrations are reported for the complexation of sodium and potassium cations with 18 different crown ethers containing nitrogen atoms with different number, location and substitution pattern. The data, measured in methanol mostly with potassium salts, are compared to literature data; they show striking differences between all-oxygen analogs and the macrocycles with NH groups. In contrast, affinities with aza crown ethers bearing alkyl groups at the nitrogen as well as with the cryptand [2.2.2] come closer to the complexation free energies predicted from the number and electron donating capacity of the ligand heteroatoms. This is rationalised on the basis of molecular mechanics calculations, showing that a NH-containing crown predominates in conformations with axial N lone pairs, due to their repulsive electrostatic interactions with the ring oxygen atoms. Replacement of the hydrogen by alkyl groups forces the lone pairs to an equatorial position, thus enabling better complex formation, as borne out by experiment. In line with these arguments the lg$K$ differences are with some exceptions more due to ΔH than to $T\Delta S$ differences. The calorimetric data show linear isoequilibrium correlations between $T\Delta S$ and ΔH, with slopes between those observed with other crown ether and cryptand complexes. Preliminary investigations of some synthetic macrocyclic amide precursors yield appreciable complexation only, if the two carbonyl oxygens can come in close contact with the guest cation. Computer aided molecular modelling shows that this is possible in a small 15C5-derivative, in which the polyethylenglycol cycle only serves as ring template without binding contributions from the ether oxygen atoms.

In spite of countless investigations on synthetic ionophor complexes[2] the underlying binding mechanisms and the predictability of complex stabilities require further studies. One aim of our work is the prediction of crown ether and cryptand stabilities by as simple rules as possible, based on additive interaction increments between the ligand heteroatoms and the metal ion.[3] We have shown, that as long as strainfree matching between ligand sites and ion is possible dozens of complexation constants can be predicted with a standard deviation of $\Delta\lg K = 0.25$, if the electron donor capacity sum of the different coordination centres C_d of ligand is taken from measurements of hydrogen bond complexes of simple compounds with corresponding electron donor centres in lipophilic solvents.[3][4] Medium effects on crown ether and cryptand complex stabilities in various solvents can be described essentially by the change of free solvation energy of the ion in these solvents.[5] How mismatch between ligand sites and the cation lowers the affinities has been analysed on the basis of computer aided molecular modelling and NMR measurements with 18C5-potassium complexes.[6]

The present paper mainly addresses substantial, and at first sight unexpected variations in binding energies ΔG with some aza crown ether complexes. Thus, the stabilities of potassium complexes of the cryptand [2.2.2] (in methanol $\Delta G = 60$ kJ/mol, see Table 1) are quite in line with the $\Delta G = 57$ kJ/mol which we predict from the number and electron donor capacity of the ligand heteroatoms. However, the underlying 1,10-diaza-crownether, which has only 2 out of 8 heteroatoms less than the cryptand, shows with $\Delta G = 10$ kJ/mol an affinity which is very much smaller, also in comparison to that expected on the basis of simple additive interactions. In order to obtain insight into the origin of these apparent discrepancies, and to find a lead for predicting conditions for optimal complexation we studied a number of aza crown ether complexes in which substitution patterns and position of the nitrogen atoms was varied (Scheme 1). Furthermore we wanted to analyse enthalpic *vs.* entropic binding differences by calorimetric titrations with several aza crown ether complexes. Until now there are only scattered reports on the thermodynamics of azacrownether complexes[7][8] most frequently with transition metal cations. Table 1 also shows literature values[9] which are relevant in the context of the present work, often showing large deviations. These might be due partially to the pH dependence as consequence of partial nitrogen pro-

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tonation and H-bonding, and/or to neglected anion effects, and made it necessary to measure these complexes again under the same conditions as the new ones.

elling with the aid of the CHARMm field[10] helps to elucidate the origin of the unusual instability of the K^+-**2a** complex. Molecular dynamics simulations in a 15A di-

Table 1. Stability constants (lgβ units) and thermodynamic parameters (kJ/mol) for complexation of azacrown ethers with potassium cation in methanol at 298 K.[a]

No	Ligand	Salt	M:L[b]	lgβ[c]	$-\Delta G$	$-\Delta H$	$T\Delta S$
1	18C6	KSCN	1:1	>5.7	>32.5	54.7(1.0)	>−-22.2
		KI	1:1	6.22(0.04)[d]	35.5(0.2)[d]		
		K^+	1:1	6.07 [9a]	34.6[9a]	56.8[9a]	−22.2[9a]
2a	1,10-$N_2$18C6	KOH	1:1	2.25(0.25)	12.8(1.4)	3.2(0.3)	9.6(1.4)
		KI	1:1	1.76(0.03)[d]	10.0(0.2)[d]		
		K^+	1:1	1.83[9b]	10.4[9b]	4.7[9b]	5.7[9b]
		K^+	1:1	2.04[9h]	11.6[9h]		
		K^+	1:1		11.2(1)[9k]		
2b	1,10-(MeN)$_2$18C6	KCl	1:1	4.51(0.20)	25.7(1.1)	33.6(1.5)	−7.8(1.9)
		KOH	1:1	4.35(0.13)	24.8(0.7)		
		KI	1:1	5.18(0.06)[d]	29.6(0.3)[d]		
		K^+	1:1	4.10[9c]	23.4[9c]		
		K^+	1:1	5.3[9d]	30.2[9d]		
2c	1-BzN-10-N18C6	KCl	1:1	3.72(0.05)	21.2(0.3)	14.1(0.1)	7.1(0.3)
			1:2	6.16(0.08)	35.2(0.4)	26.0(0.6)	9.2(0.7)
3a	N18C6	KNO_3	1:1	3.78(0.19)	21.6(1.1)	22.0(1.2)	−0.4(1.6)
		KOH	1:1	3.67(0.08)	20.9(0.4)	20.7(1.0)	0.2(1.1)
		K^+	1:1	4.18[9i]	23.9[9i]		
		K^+	1:1	3.90[9h]	22.3[9h]		
3b	MeN18C6	KI	1:1	5.46(0.07)[d]	31.2(0.4)[d]		
3c	BzN18C6	KNO_3	1:1	4.83(0.66)	27.6(3.8)	44.5(2.2)	−16.9(4.4)
			1:2	7.78(1.08)	44.4(6.2)	64.2(5.6)	−19.8(8.4)
4a	1,7-$N_2$18C6	KCl	1:1	4.17(0.42)	23.8(2.4)	1.4(0.1)	22.4(2.4)
			1:2	5.97(0.44)	34.1(2.5)	6.1(0.6)	28.0(2.6)
4b	1,7-(MeN)$_2$18C6	KCl	1:1	4.92(0.58)	28.1(3.3)	28.5(1.8)	−0.4(3.8)
			1:2	8.60(0.73)	49.1(4.2)	44.6(1.3)	4.5(4.4)
4c	8,18-Dioxo-1,7-$N_2$18C6	KCl	1:1	2.1(0.2)	12(1)	−2.2(0.5)	14(1)
5a	1,4-$N_2$18C6	KCl	1:1	2.6(0.4)	14.8(2.3)	13(6)	2(6)
			1:2	5.5(0.2)	31.4(1.1)	11(1)	20(1)
5b	1,4-(MeN)$_2$18C6	KCl	1:1	4.71(0.54)	26.9(3.1)	19.8(0.8)	7.1(3.2)
			1:2	8.44(0.54)	48.2(3.1)	37.1(0.2)	11.1(3.1)
5c	5,18-Dioxo-1,4-$N_2$18C6	KCl	[e]				
6	15C5	KCl	1:1	3.25(0.03)	18.6(0.2)	30.1(0.2)	−11.5 (0.3)
			1:2	5.75(0.02)	32.8(0.1)	68.6(0.2)	−35.8(0.2)
		KI	1:1	3.46(0.05)	19.8(0.3)	29.6(0.3)	−9.8(0.4)
			1:2	5.95(0.05)	34.0(0.3)	66.5(0.5)	−32.5(0.6)
		KI	1:1	3.40(0.03)[d]	19.4(0.2)[d]		
			1:2	5.83(0.05)[d]	33.3(0.3)[d]		
		KI	1:1	3.35[9e]	19.1[9e]	32.6[9e]	−13.5[9e]
			1:2	6.00[9e]	34.2[9e]	69.4[9e]	−35.2[9e]
7a	1,7-(MeN)$_2$15C5	KCl	1:1	3.66(0.07)	20.9(0.4)	20.9(0.3)	0.0(0.5)
			1:2	5.98(0.20)	34.1(1.1)	24.7(0.7)	9.4(1.3)
7b	2,6-Dioxo-1,7-$N_2$15C5	KCl	[e]				
8a	1,4-$N_2$15C5	KCl	[e]				
8b	1,4-(MeN)$_2$15C5	KCl	1:1	1.93(0.02)	11.0(0.1)	15.1(0.4)	−4.1(0.4)
8c	5,15-Dioxo-1,4-$N_2$15C5	KCl	1:1	1.5	8.6	-10	19
			1:2	4.8(0.8)	27.4(4.5)	-6.5(1.2)	33.8(4.6)
222	[222]	K^+	1:1	10.49[9b]	59.9[9b]	75.0[9b]	−15.1[9b]
		K^+	1:1	10.41[9f]	59.4[9f]		
9	21C7	K^+	1:1	4.22[9g]	24.1[9g]	35.9[9g]	−11.8[9g]
10	1,10-$N_2$21C7	KNO_3	1:1	1.60(0.02)	9.1(0.1)	13.8(0.5)	−4.7(0.5)

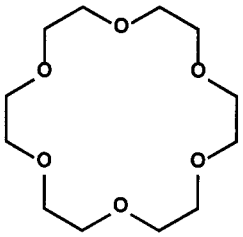
[a] For experimental conditions and details see text. − [b] Complexation data are given for equilibria: 1:1: $M^+ + L = [ML]^+$, 1:2: $M^+ + 2L = [ML_2]^+$, where applicable, see text. − [c] Uncertainties are given as standard deviations in brackets. − [d] Potentiometric titration with solid state potassium selective electrode. ionic strength: 0.05 M Et_4NI. − [e] Too low heat effect for calorimetry.

Results and Discussion

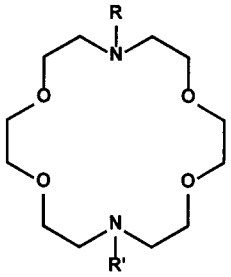
The free energy ΔG of complexation of the ligand 1,10DA18C6 (**2a**) with potassium (Table 1) as with sodium (Table 2) is only about 1/3 of that of 18C6 (**1**), which compared to the values known for the cryptand [2.2.2] is unexpected on the basis of number and electron donating capacity of the heteroatoms. Computer aided molecular mod-

ameter TIP3 water box with 428 water molecules yielded two distinct energy minima for the ligand **2a,** the one with two axially oriented lone pairs (conformer **2*aa***) at the nitrogen atoms being 9 kJ/mol more stable than the one with two equatorial lone pairs (**2*ee***) (Scheme 2). Dissection of energy terms from the CHARMm minimisation (Table 3) as well as AM1 calculations[11] show that the destabilisation of **2*ee*** compared to **2*aa*** is almost entirely due to electro-

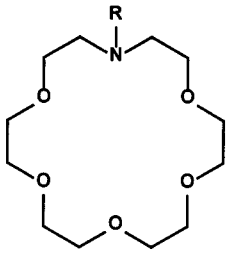
Scheme 1. Structures of ligands, with $-\Delta G$ values *−in italics−* [kJ/mol] of complexation with K^+ in methanol (other values see Table 1).



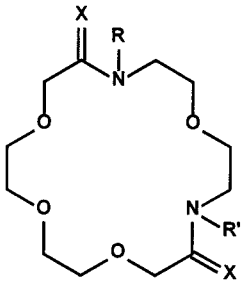
1 (18C6) ***35***



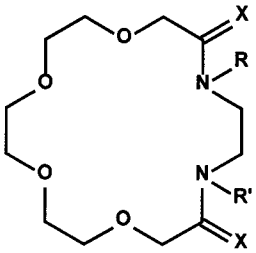
2a R=R'=H ***10***
2b R=R'=Me ***29***
2c R=H,R'=Bz ***21***



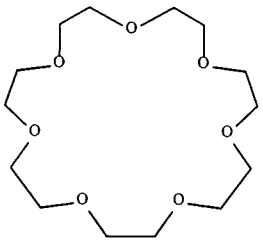
3a R=H ***22***
3b R=Me ***31***
3c R=Bz ***28***



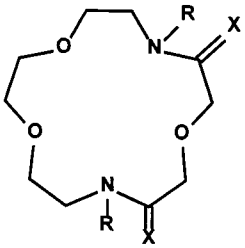
4a X=H_2; R=R'=H ***24***
4b X=H_2; R=R'=Me ***28***
4c X=0, R=R'=H ***12***



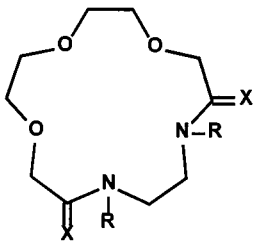
5a X=H_2; R=R'=H ***15***
5b X=H_2; R=R'=Me ***27***
5c X=0; R=R'=H



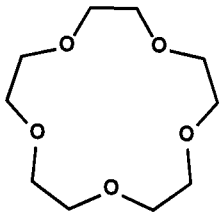
6 15C5 ***19***



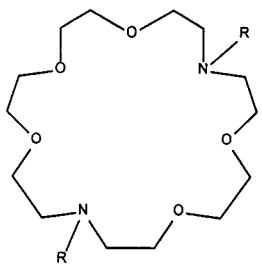
7a X=H_2; R=Me ***21***
7b X=0; R=H



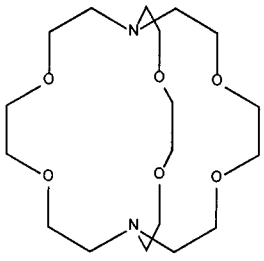
8a X=H_2; R=H
8b X=H_2; R=Me ***11***
8c X=0; R=H ***~8***



9 (21C7) ***24***



10 R=H ***9***



[222] ***59***

static repulsion between the ***ee*** lone pairs at the nitrogen and the electron pairs of the ring oxygen atoms. In contrast, the force field calculations show in agreement with literature computations[12] that the cryptand **222** predominates (vide infra) in the *in-in* lone pair conformation, thus enabling a maximum interaction with the metal cation.

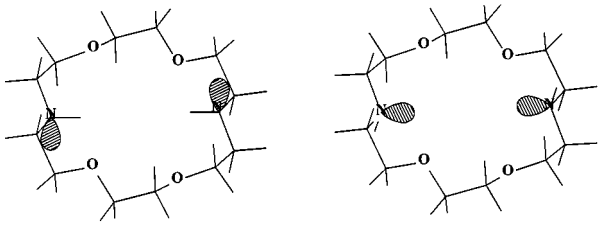
towards metal cations one should be able to revert this by exchanging the N−H hydrogen atoms in **2a** by methyl groups. The large methyl substituents force the lone pairs into the ***ee*** conformation necessary for optimal complex stability. It is gratifying, that the experiments (Table 1) support this mechanistic reasoning. In line with this, methylation

Table 2. Stability constants (lgβ units) and thermodynamic parameters (kJ/mol) for complexation of azacrown ethers with sodium cation in methanol at 298 K.[a]

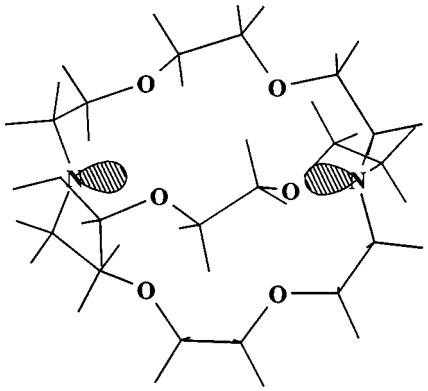
No	Ligand	Salt	M:L[b]	lgβ[c]	$-\Delta G$	$-\Delta H$	$T\Delta S$
1	18C6	NaI	1:1	4.36(0.02)[d]	24.9(0.1)[d]		
2a	1,10-$N_2$18C6	NaI	1:1	1.63(0.02)[d]	9.3(0.1)[d]		
2b	1,10-$(MeN)_2$18C6	NaI	1:1	3.53(0.08)[d]	20.1(0.5)[d]		
2c	1-BzN-10-N18C6	NaCl	1:1	1.54(0.05)	8.8(0.3)	15.8(1.2)	−7.0(1.2)
3a	N18C6	$NaNO_3$	1:1	2.78(0.06)	15.9(0.3)	10.5(0.3)	5.4(0.4)
		$NaNO_3$	1:1	1.96(0.12)[d]	11.2(0.7)[d]		
3b	MeN18C6	NaOH	1:1	4.01(0.08)	22.9(0.5)	19.5(0.4)	3.4(0.6)
		NaI	1:1	3.78(0.06)[d]	21.6(0.3)[d]		
		Na^+	1:1	3.93[9j]	22.4[9j]		
3c	BzN18C6	$NaNO_3$	1:1	3.02(0.06)	17.2(0.3)	27.9(0.8)	−10.7(0.9)
			1:2	6.23(0.04)	35.6(0.2)	47.4(0.5)	−11.8(0.5)
4a	1,7-$N_2$18C6	NaCl	1:1	2.4(0.4)	13.7(2.3)	−1.2(0.2)	15
4c	8,18-Dioxo-1,7-$N_2$18C6	NaCl	1:1	0.7	4	ENDO	
5c	5,18-Dioxo-1,4-$N_2$18C6	NaCl	1:1	1.1	6.3	−15	21
			1:2	2.8	16	−18	34
6	15C5	NaI	1:1	3.25(0.02)[d]	18.5(0.1)[d]		
			1:2	5.18(0.04)[d]	29.6(0.2)[d]		
7b	2,6-Dioxo-1,7-N_2−15C5	NaCl	[e]				

[a] For experimental conditions and details see text. − [b] Complexation data are given for equilibria: 1:1: $M^+ + L = [ML]^+$, 1:2: $M^+ + 2\,L = [ML_2]^+$, where applicable, see text. − [c] Uncertainties are given as standard deviations in brackets. − [d] Potentiometric titration with solid state potassium selective electrode; ionic strength: 0.05 M Et_4NI. − [e] Heat effect too low for calorimetry.

Scheme 2a. Force field calculated conformation of 1,10DA-18C6 **2a**: A with axial position of lone pairs; B with equatorial positions of lone pairs.



Scheme 2b. $LP_{in,in}$ Conformation of Cryptand **[222]**



If the unfavourable ***aa*** lone pair orientation in the diaza crown ether **2a** is essentially responsible for its low affinity

Table 3. Comparison of individual energy contributions from CHARMm-force field calculations of 1,10DA18C6 **2a**.[a]

	1,10DA18C6-$LP_{ax,ax}$	1,10DA18C6-$LP_{eq,eq}$
Total CHARMm energy	−9.834	−0.927
Bond energy	0.360	2.995
Angle energy	2.900	0.371
Dihedral energy	2.385	2.838
Inproper energy	0.000	0.000
Lennard-Jones energy	−31.115	−30.368
Electrostatic energy	15.663	23.236
Constraints, other	0.000	0.000

[a] All data in [kJ/mol].

leads to an substantial ΔG increase also for the mono aza crown ether complex **3a**. Similar increases, likely all due to stabilisation of *in*, or *equatorial*, orientation of the N lone pairs by alkyl groups at the nitrogen atoms are seen with other ligands such as **2c.** It should be noted that the increased stability of the *N*-alkyl crown ether complexes cannot be due the a higher electron donor capacity of these groups, which does not change within standard deviation limits of E_d and C_d upon alkylation.[4] The higher basicity of nitrogen compared to oxygen should lead to stronger hydrogen bonds with protic solvents; therefore one should expect stronger complexation increase in non-protic solvents than observed with normal all-oxygen crown ethers. In absence of reliable literature data on aza crown ether complexes in solvents like acetonitrile, chloroform etc this needs further investigation.

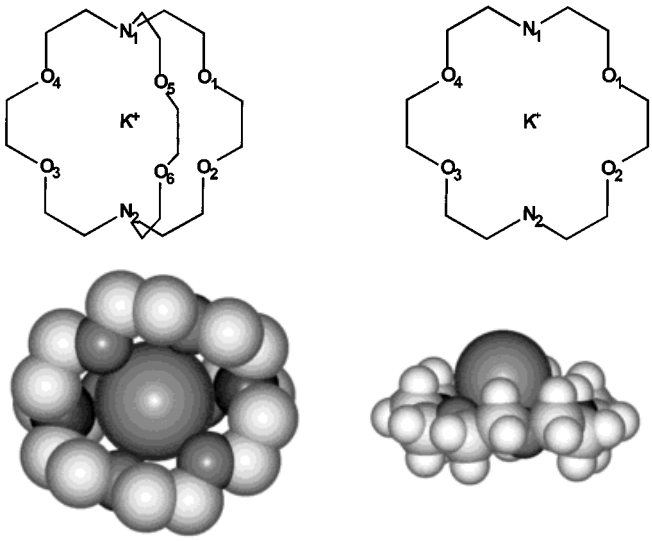
The experimentally observed binding energies ΔG for the Me−N crown ether complexes (**2b, 3b**) are, however, still below the ones predicted from additive increments, in sharp contrast to the cryptand **222** complexes (Table 4) The reason for this becomes evident from the CHARMm − calculated distances between the donor heteroatoms to the central potassium ion. These are after energy minimisation of the corresponding complexes on the average 0.2 A larger in the diaza crown ether complexes compared to those in the cryptate. At the same time the ion cannot fully immerse into the **2*ee*** cavity, again in contrast to the cryptate (Figure 1).

Table 4. Predicted and experimental (calorimetry) complexation free energies ΔG of K^+-azacrown and K^+-cryptand **[222]** complexes.[a]

Crown	ΔG_{exp}[b]	ΔG_{inc}[c]	$\Delta\Delta G$
N18C6 **3a**	−10.6	−40.4[d]	29.7
MeN18C6 **3b**	−31.1	−40.4	9.2
1,10-$N_2$18C6 **2a**	−10.0	−46.2[d]	36.2
1,10-$(MeN)_2$18C6 **2b**	−29.5	−46.2	16.7
[222] **222**	−60.0	−57.3	−2.7
18C6 **1**	−35.5	−34.5	−1.0

[a] In [kJ/mol]. − [b] Measured in MeOH. − [c] Calculated incrementally, see text. − [d] Data for the K^+-18C6 complex are given as reference.

Figure 1. Geometries of the 1,10DA 18C6-$LP_{ax,ax}$- (**2a**), 1,10DA 18C6-$LP_{eq,eq}$- (**2a**) and cryptand **[2.2.2]**-potassium complexes, from CHARMm calculations.



Calorimetric measurements were carried out with some other aza crown ethers (Scheme 1, Table 1). They show again relatively large ΔG values in comparison to the all-oxygen analogs as soon as the nitrogen atoms bear alkyl groups (cf. e.g., **4a/b**, **5a/b**; **7a/b**, **8a/b**). Vicinal nitrogen atoms as in the 1,4-diaza-18-crown-6 **5a** present a special case in view of the high pK_A for the first, and the low pK_A for the second step of the protonation.

NMR shift data as well as titrations (Figure 2) show, however, that all aza crown ether ligands are not protonated in methanol prior to complexation. NMR titrations of 1,10DA18C6**2a** with different potassium salts (KCl, KOH) were carried out in $[D_4]$MeOH with TMS as internal standard at 298 K. Practically there was no difference observed in the titration curves with the two different potassium salts. The NMR shifts in acidic medium (50 eq. of DCl in $[D_4]$MeOH) for the two observed CH_2 groups were: δ (α-CH_2) = 3.29 and δ (β-CH_2) = 3.77 ppm. The shifts in pure $[D_4]$MeOH were: δ (α -CH_2) = 2.74 and δ (β-CH_2) = 3.56. Therefore, the observed chemical shifts during the titration with potassium salts of the α- and β-methylene groups (adjacent to nitrogen) can only be due to complexation by the metal ion. This titration then is one of the few examples were one can follow a crown ether complexation by NMR, since normal all-oxygen crown ethers show no significant shift changes upon complexation. Association constants in agreement with the calorimetric data were obtained by non-linear least square fitting to a 1:1 complexation model (see Table 1 and Figure 2).

The observed thermodynamic parameters are for most cases in line with the essentially enthalpic arguments discussed above. Thus, the low stability of aza crown ether complexes with NH compared to he all-oxygen analogs is indeed largely due to ΔH disadvantages (cf. for instance **2a** or **3a** *vs.* **1**; or **10** *vs.* **9**). Also, the stabilising effect of substitution in the NR ligand complexes (**2b**, **2c**, **4b**) largely shows up in ΔH advantages. Striking differences are seen especially with the 1,7-diaza-18-crown-6 **4a,** where complexation is entirely driven by $T\Delta S$. Similar, although less pronounced favourable $T\Delta S$ contributions are also visible for the other aza crown ethers, even more for the observed $[ML_2]^+$ complexes. This is in sharp contrast to ligands such as 18C6 or 15C5 itself, where complexation is accompanied by $T\Delta S$ disadvantage which increases with the affinity, obviously as consequence of the then more limited mobility. In line with the arguments above, a similar situation with − although less pronounced − entropic disadvantage is observed with the *N*-substituted aza crown ethers such as **2b** or **3c,** which are again better disposed for stronger complexation.

Inoue et al.[13] have assembled many data on entropy−enthalpy compensations with ionophor complexes. Their correlations (for a selection see Table 5) suggest, that less preorganised ligands like glymes suffer from large entropy disadvantage which needs to be completely compensated by enthalpy contributions. This is less so for cryptand and crown ether complexes, which suffer only by 44% or 77% entropic disadvantage. Although the underlying isoequilibrium correlations seem to be of sufficient statistical quality one should keep in mind the danger of systematic errors in such correlations, particularly if they are based on temperature dependent equilibrium and not on calorimetric measurements. Inoue et al already noted some incongruencies with natural ionophores, which unexpectedly showed slopes of α = 0.93, closer to glymes or podands than to crown ethers.

Typically, most crown ethers also are expected to loose little conformational freedom upon complexation; the still

Figure 2. Experimental NMR shifts (dots) and fitted line for the NMR titration of 1,10-diaza 18C6 (**2a**) with KOH in [D_4]MeOH at 298 K. Association constant: 93+/−8; $\Delta G = -11.2$ kJ mol^{-1}; shifts at 100% complexation from fit: CIS (α) = 0.024 ppm, CIS (β) = 0.064 ppm.

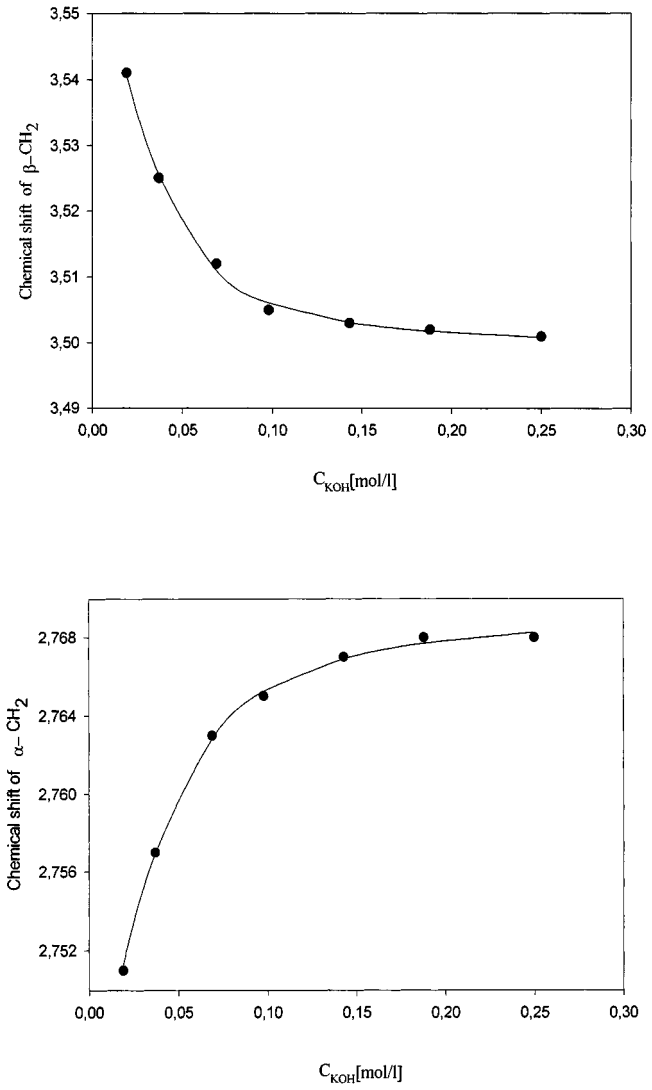


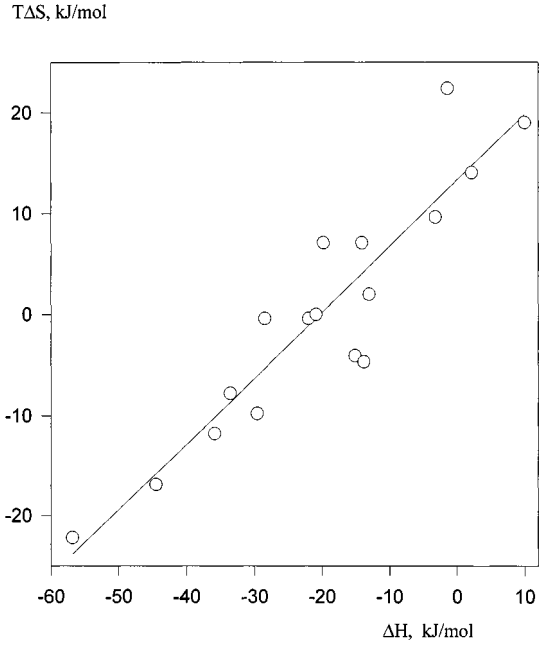
Table 5. Entropy-enthalpy compensations: $T\Delta S$ *vs* ΔH [kJ/mol units]; (from Table 1, Figure 4, and ref.[17]).

Complexes	N[a]	r[b]</entry'<εντρψ>α[c]	$T\Delta S$[d]	
all aza crown ethers complexes	27	0.828	0.59±0.16	17±6
only 1:1 cplxs	17	0.923	0.65±0.15	13±4
only 1:2 cplxs	9	0.958	0.81±0.22	32±8
crowns 1:1 cplxs[15]	598	0.88	0.77±0.02	11.7±0.4
crowns 1:2 cplxs[15]	85	0.98	0.94	13.4±0.8
glymes/podands[15]	151	0.98	1.02±0.02	15.5±0.8
cryptands[15]	160	0.65	0.44±0.04	14.6±1.7

[a] Number of points used. − [b] Linear correlation coefficient. − [c] Slope. − [d] Intercept.

high slopes observed by Inoue et al.[13] (α = 0.88) might well be due to solvation effects which are expected to play a larger role in crown ethers as compared to cryptands. Our own results with aza crown ether complexes (Table 5), which do not suffer from the error problems involved with the temperature dependent equilibrium measurements based on the van′t Hoff method, and are based on data in only one solvent, also show a satisfactory linear isoequilibrium correlation (Figure 3), although there are outliers which cannot be rationalised at this time. The observed slopes and intercepts (Table 5) are between those observed of crown and cryptand complexes, indicating entropic disadvantages which are compensated to about 65% by enthalpic contributions.

Figure 3. Correlation between ΔH and $T\Delta S$ for the complexation of K^+ with aza crown ethers, aza oxo crown ethers (amide crowns), 18-crown-6 and 15-crown-5 in MeOH for the $K^+ + L \rightleftharpoons (K_+)L$ equilibrium: $T\Delta S$ 13.2(3.9) + 0.65(0.15) ΔH, N = 17, R = 0.923, F = 86.5, SD = 4.8.

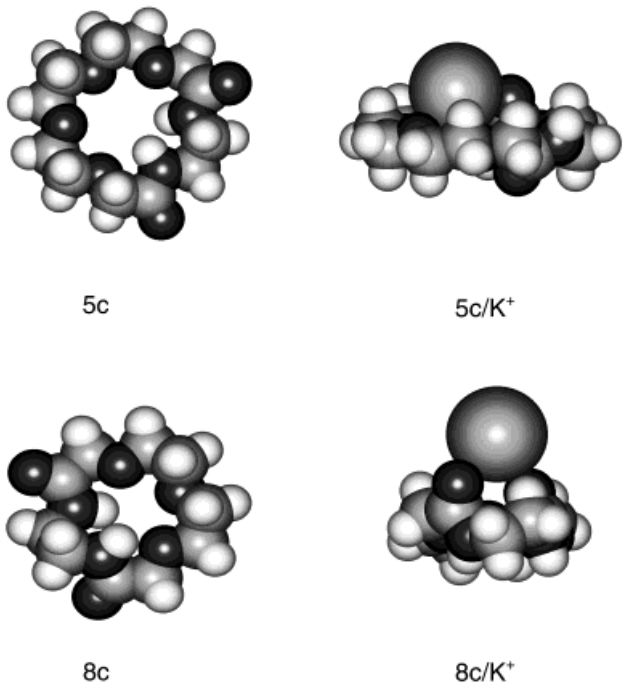


K^+-[222] K^+-1,10DA18C6LP$_{eq,eq}$

The cyclic amides **4c, 5c, 7b** and **8c** were available as synthetic precursors and were subjected to stability measurements. In natural ionophores such as valinomycin the negative partial charges of the oxygen atom in the carbonyl group of amide or ester functions can also contribute to binding, requiring, however, orientation of the C=O units towards the metal. In small cyclic amides this would induce large strain in the ligands in view of the strongly preferred transoid R-CO-NH-R′ conformation.[14] Moreover amide nitrogen have essentially lower electron donor capacity (E_d = 0.23 and C_d = 0.32), which is 8−10 times lower than those in aza crown ethers (E_d = 2.78 and C_d = 2.60) and in alkyl−aza crown ethers (E_d = 2.34 and C_d = 2.57).[4] Thus, the amide crown ethers have in fact only four coordination centers as 12-crown-4, which are available for the complexation with a metal cation.

The complexation energies are indeed smaller than the one of the analog without oxo group if we compare them

Figure 4. Quanta/CHARMm-minimized structures of amide-crown structures **5c** and **8c** and their K^+ complexes.



to the aza crown ether complexes without alkyl groups at nitrogen. The disadvantage of the NH containing ligands due to the predominant axial lone pair orientation does of course not exist in the amides. Ligand **8c** forms a remarkably strong 1:2 $[ML_2]^+$ complex as well as a moderately strong 1:1 complex. Preliminary molecular mechanics calculations show for the energy minimised K^+ **5c** complex with all-transoid amid conformations simultaneous interactions of the cation with 5 of 6 oxygen atoms, except with one of the amid oxygens (Figure 4), however with distances K···O much smaller than those in the ideal crown complex K^+18C6 (see Table 6). In addition, severe torsional changes at least around one angle are necessary to bring at least one of the two carbonyl oxygens close to the cation, leading to considerable built up of strain energy in the ligand. In consequence the cation can only be in poor contact, and only with 5 out of the 6 oxygen atoms, as visible in the corresponding CPK model (Figure 4), and the complexation is below the calorimetric detection limit. With the smaller macrocycle **8c** both carbonyl oxygens can be in contact with the cation − again after inducing considerable conformational change; this according to the molecular mechanics calculations costs, however, much less energy than in the case of **5c**. Even though in the optimal conformer of the **8c** K^+ complex (Figure 4) the ether oxygen atoms are far too distant (with d around 6 A) and lead to an outside location of the cation (see Figure 4), both electronegative carbonyl oxygen atoms can contact the cation and thus allow a moderately stable complex, based mostly on an enthalpic contribution with small entropic disadvantage (Table 1).

Table 6. Dihedral angles and K^+···O distances in the amide crowns **5c** and **8c** and their K^+ complexes.[a]

Dihedral Angles	**5c**	**5c**/K^+	Distances [Å]	**5c**/K^+
4−5−6−7	53.4	157.3	5-O	4.4
7−8−9−10	−63.8	−55.8	7	3.2
10−11−12−13	66.2	53.7	10	3.0
13−14−15−16	−64.0	−57.6	13	3.2
16−17−18−1	52.9	163.7	16	3.1
1−2−3−4	−63.9	−75.3	18-O	2.9
Dihedral Angles	**8c**	**8c**/K^+	**Distances [Å]**	**8c**/K^+
4−5−6−7	−20.3	41.6	5-O	3.0
7−8−9−10	−51.0	50.5	7	5.6
10−11−12−13	53.6	−52.0	10	6.6
13−14−15−1	−43.0	−35.7	13	5.6
1−2−3−4	−51.6	−48.9	15-O	3.0

[a] From CHARMm force field calculations.

Measurements of the complexes of aza crown ethers with sodium salts (Table 2) showed similar to the potassium complexes the strong ΔG increase with alkylation of the nitrogen atoms, indicating the same stereoelectronic effect as discussed above. The different range of stabilities observed with the amide-type ligands **4c** and **5c** are expected as consequence of the different ion diameters of Na compared to K, requiring a smaller degree of conformation and thus strain changes for complexation.

Conclusions

The data show how simple predictions of ionophore stabilities on the basis of additive increments for the interaction between ligand element and metal cation are limited by non-ideal conformations in the ligands. Computer aided molecular modelling provides a convenient tool to control the necessary conformational requirements and can be of great help not only in the understanding of measured binding energy differences, but also in the *de novo* design of synthetic ionophores. The results stress the significance of lone pair orientation in ionophores, which until now is not explicitly included in most of the available force fields.

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Experimental Section

Calorimetric Measurements: Determination of logβ and ΔH complexation values were carried out using the calorimetric titration technique at 298.15 K as described before.[5][6] The reaction heats were measured with a microcalorimetry system LKB (Model 2107/112). Total (overall) concentrations of reagents which were used in calorimetric and potentiometric measurements are given in Table 7.

The reliability of the calorimetric determinations was checked by measuring stability constants and enthalpy changes of the 18-crown-6 complexation with barium cation in water at 298K, yielding excellent agreement of our data with known log$K$ values, and satisfactory agreement for enthalpies (Table 8).

Table 7. Total (overall) concentrations of reagents used in calorimetric and potentiometric measurements; C^{o}_{S}, total concentration of a salt; C^{o}_{L} , total concentration of ligand.

	Ligand	Salt	C^{o}_{L} Mmol/l	C^{o}_{S} mmol/l
1	18C6	KI [a]	7.9−9.3	1.4−16.1
		KNCS	11.2−11.8	1.1−11.1
			0.8−14.9	11.7−12.9
		NaI[a]	7.3−8.3	1.3−15.7
2a	1,10-$N_2$18C6	KOH	1.5−17.9	12.0−12.8
		KI[a]	7.3−7.9	1.3−10.5
		NaI[a]	7.3−7.8	2.5−10.4
2b	1,10-$(MeN)_2$18C6	KCl	0.4−5.2	2.7−4.9
		KOH	0.7−5.2	4.2−4.5
		KI[a]	6.9−7.9	1.4−17.6
		NaI[a]	7.0−7.9	1.3−15.5
2c	1-(BzN)-10-N18C6	KCl	0.8−10.2	4.3−4.6
		NaCl	0.8−10.2	5.4−6.2
2d	1,10-$(BzN)_2$18C6	KCl	0.4−4.7	2.7−2.9
2e	1,10-$(AcN)_2$18C6	KOH	0.5−3.0	4.2−4.5
		KI[a]	6.4−6.9	1.0−8.7
3a	N18C6	KNO_3	0.5−6.1	4.2−4.5
		KOH	0.5−4.7	4.0−4.2
		$NaNO_3$	6.7−7.3	0.8−13.5
		$NaNO_3$[a]	8.9−9.8	1.2−13.6
3b	MeN18C6	KI[a]	7.0−8.0	1.3−15.2
		NaOH	0.8−8.6	4.6−5.1
		NaI[a]	6.9−7.8	1.3−15.5
3c	BzN18C6	KNO_3	0.5−11.5	4.0−4.5
		$NaNO_3$	7.0−7.7	0.8−13.5
4a	1,7-$N_2$18C6	KCl	0.8−6.0	4.3−4.6
		NaCl	1.6−12.6	5.4−6.1
4b	1,7-$(MeN)_2$18C6	KCl	0.5−6.2	4.3−4.6
4c	8,18-Dioxo-1,7-$N_2$18C6	KCl	1.1−8.5	4.0−4.5
		NaCl	1.1−8.5	5.4−6.1
5a	1,4-$N_2$18C6	KCl	0.8−10.2	4.0−4.6
5b	1,4-$(MeN)_2$18C6	KCl	0.8−10.2	4.3−4.6
5c	5,18-Dioxo-1,4-$N_2$18C6	KCl	1.5−10.0	4.0−4.1
		NaCl	1.5−12.2	5.4−6.1
6	15C5	KCl	1.6−21.1	6.6−7.1
		KI	1.6−21.1	5.8−6.2
		KI[a]	7.8−9.3	3.3−27.1
		NaI[a]	6.4−7.4	1.3−16.6
7a	1,7-$(MeN)_2$15C5	KCl	0.8−10.4	5.1−5.8
7b	2,6-Dioxo-1,7-$N_2$15C5	KCl	0.4−10.0	5.0−5.3
		NaCl	0.4−10.0	7.5−8.0
8a	1,4-$N_2$15C5	KCl	0.5−10.0	5.0−5.5
8b	1,4-$(MeN)_2$15C5	KCl	0.5−12.9	5.1−5.9
8c	5,15-Dioxo-1,4-$N_2$15C5	KCl	1.5−12.5	4.0−4.5
10	1,10-$N_2$21C7	KNO_3	1.0−11.5	6.0−6.8

[a] Potentiometric titration.

With the aza crown ethers average standard deviations were less than 0.25 in lg$K$, 0.6 kJ/mol in ΔH for the $M^+ + L = [ML]^+$ (M = K, Na) equilibria. Standard deviations (in brackets) of lg$K$ and ΔH values for the aza crown ethers were a little higher in comparison to normal crown ethers.[5][6] This can be due to often lower lg$K$ values, to ΔH values near zero, or also to slower complexation with aza crown ethers.

Non-linear least square fitting for the calculation of stability constants and enthalpy changes from experimental calorimetric and potentiometric titrations was performed with a new and extended 32-bit PC version of the general multifit program CHEM EQUI for WINDOWS 95/NT, which itself was described earlier[15a][15b] (available from Dr. V. Solov′ev).

The stoichiometries (compositions) of the complexes were calculated for series of $nM^+ + ml = [M_nL_m]^{n+}$ equilibrium models, taking into account variable number and combinations of complexes in a solution (M^+ = metal cation, L = ligand; n, m = 1, 2 and 3). The models given in Tables 1 and 2 are those for which a satisfactory fit of experimental data of several calorimetric titrations was obtained on the basis of statistical criteria. These were mainly the Hamilton R factor[16a][16b] and residuals ($Q_{exp.} - Q_{calcd.}$) analysis for fitness test,[16c][16d] were $Q_{exp.}$ and $Q_{calcd.}$ are calorimetric titration heats. Systematic deviations in the fitting to 1:1 models (complex $[ML]^+$) were frequently observed, in which cases satisfactory fit with Hamilton R-factors below 2% were obtained by evaluation of additional $[ML_2]^+$ complexes (see Tables 1 and 2). Available literature lgβ and ΔH values for the complexation of aza-18-crown-6, 1,10-diaza-18-crown-6, and N,N dimethyl-1,10-diaza-18-crown-6 with potassium cation in MeOH agreed with values obtained in this work (Tables 1 and 2).

Typical calorimetric titration curves with fitting are shown in Figures 5a−c. For controlling the possible influence of aza crown ether protonation we measured complexation of **2b** and **3a** not only with potassium salts KA (A = I^-, Cl^-, NO_3^-), but also with potassium hydroxide KOH. In line with NMR measurements (see below) the negligible difference between the KA and the KOH experiment shows, that at the low proton concentration in pure methanol the protonation of aza crown ethers is negligible.

Potentiometric measurements were carried out with using the titration technique at 298.15 K as described before,[5][6] using solid state potassium and sodium selective electrodes and a reference Ag/Ag^+ electrode. Ionic strength of the solutions was kept constant at 0.05 M Et_4NI in all experiments.

NMR titrations were carried out on a Bruker AM400 or DRX500 system at 298 K. The concentrations and ratios of observed and added compounds in a titration were chosen to pass a range of complexation between 20 and 80%. Evaluation of the obtained data was done by non-linear least square fitting with the program SigmaPlot (Jandel Scientific) using equations for 1:1 host/guest complexation.[17]

Reagents: The salts KX and NaX (X = Cl^-, I^-, SCN^-, OH^-, NO_3^-) were either commercially available and used without further purification, or were purified as described.[5][6] Methanol was rectified over magnesium methanolate under nitrogen.

Ligands: The structures of all new compounds were secured by elemental analysis and ^1H spectra. NMR spectra were recorded on Bruker CXP200 spectrometer in $CDCl_3$ with tetramethylsilane as internal reference. Melting points (uncorrected) were measured on a Boetius PHMK-05 instrument.

Table 8. Stability constant (lg$K$ units) and thermodynamic parameters (kJ/mol) for complexation of 18-crown-6 with barium cation in water at 298 K.

Ligand	Salt	Solvent	Reaction	lg$K$	ΔH, kJ/mol	Ref.
18-crown-6	$BaCl_2$	H_2O	$M^+ + L = [ML]^+$	3.80 (0.03)	−29.7(0.5)	this work
18-crown-6	$BaCl_2$	H_2O	$M^+ + L = [ML]^+$	3.87	−31.7	[19a,19b]

Figure 5a. Calorimetric titration curve for the complexation of 1,10-diaza-18C6 **2a** with KOH in MeOH at 298 K. Experimental interaction heats (cycles) and calculated titration curve vs. the reagents concentration ratio C^o_L/C^o_M. Experimental data: the ligand solution (C^o_L 80.7 mM and ΔV 0.0212 ml for each point) was added into the mixture (C^o_M 5.8 mM, C^o_L 0.84 mM, V_o 2.02 ml).

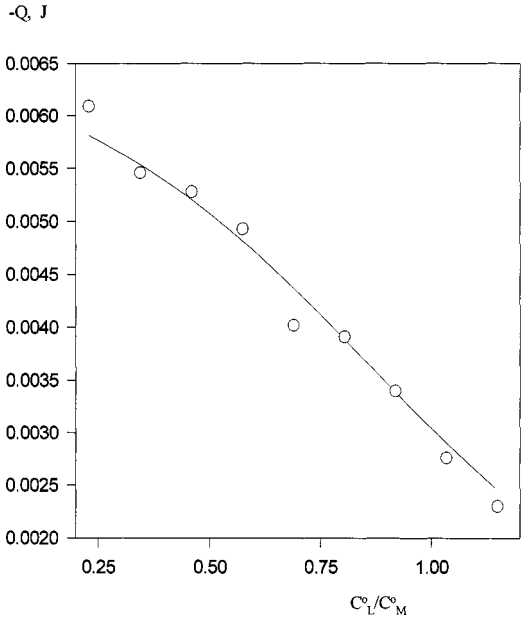
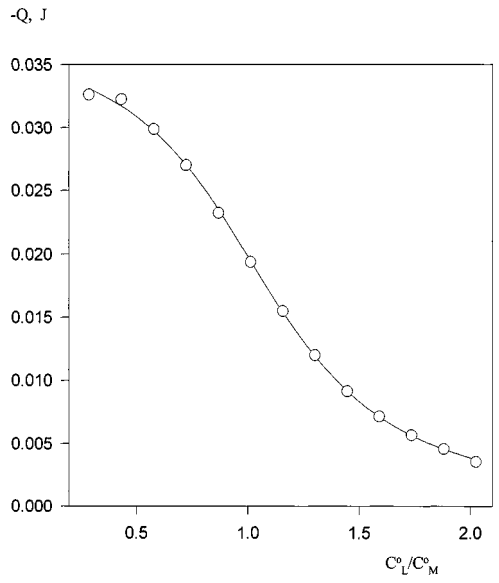


Figure 5b. Calorimetric titration curve for the complexation of 1,7-di(methylaza)-15-crown-5 **4b** with KCl in MeOH at 298 K. Experimental interaction heats (cycles) and calculated titration curve vs. the reagents concentration ratio C^o_L/C^o_M. Experimental data: the ligand solution (C^o_L 277 mM and ΔV 0.0106 ml for each point) added to the mixture (C^o_M 12.8 mM, C^o_L 1.5 mM, V_o 2.01 ml).

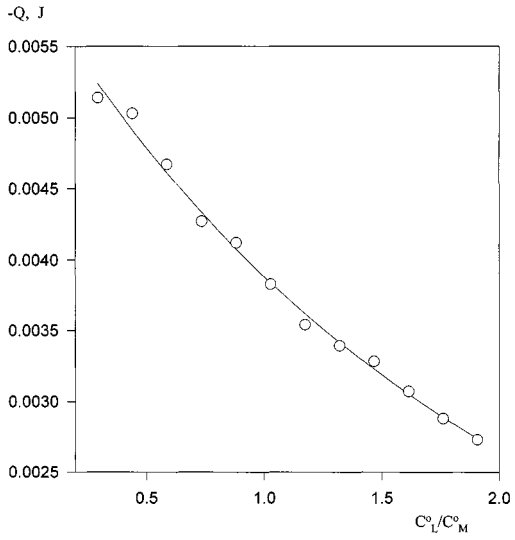


Synthesis of Ligands: 1,4,7,10,13,16-Hexaoxacyclooctadecane (**1**) was commercially available, and purified[5] before use.

1,4,13,18-Tetraoxa-7,16-diazacyclooctadecane (**2a**) was synthesized as described previously[18a].

N,N-Dimethyl-1,4,10,13,-tetraoxa-7,16-diazacyclooctadecane (**2b**): To a solution of 3.2 g (12.2 mmol) **2a** in 0.89 g (29.7 mmol) formaldehyde (as 30% aqueous solution) were added 5.6 g (122.0 mmol) of formic acid. The mixture was heated to 80−90°C or 24 h. After cooling to room temperature solid KOH was added until pH = 11 was reached; the mixture was extracted by $CHCl_3$ (3 × 5 ml) and the solvent was removed in vacuo. The residual oil was purified twice by distillation in vacuo. Yield 2.26 g (64%); b.p. 140−142°C/0.9 Torr. − $C_{14}H_{30}N_2O_4$; mol. mass 290.41; calcd. C 57.9, H 10.4, N 9.6; found C 57.8, 57.7; H 10.2, 10.2; N 9.5, 9.6. − ^{1}H NMR: δ = 2.31 (s, 6 H, 2 NCH_3), 2.70 (m, 8 H, 4 OCH_2N), 3.62 (m, 12 H, 2 OCH_2).

Figure 5c. Calorimetric titration curve for the complexation of 1,10-diaza-21-crown-7 **10** with KNO_3 in MeOH at 298 K. Experimental interaction heats (cycles) and calculated titration curve vs. the reagents concentration ratio C^o_L/C^o_M. Experimental data: ligand solution (C^o_L 95.1 mM and ΔV 0.0212 ml for each point) was added to the titrated mixture (C^o_M 6.8 mM, C^o_L 1.0 mM, V_o 2.02 ml).



N-Benzyl-1,4,10,13,-tetraoxa-7,16-diazacyclooctadecane (**2c**): 5.0 g (11.2 mmol) commercially available *N,N*-dibenzyl-1,4,10,13,-tetraoxa-7,16-diazacyclooctadecane were dissolved in 450 ml of dry ethanol. Palladium on charcoal (1.0 g) and 8 ml of glacial acetic acid were added and the mixture was hydrogenated for about 30 h at room temperature under atmospheric pressure. The composition of the reaction mixture was controlled by TLC and ^{1}H NMR. The reaction mixture was filtered and the solvent was evaporated in vacuo. 100 ml 15% NaOH were added and the mixture was extracted with $CHCl_3$ (7 × 40 ml). The extract was washed with water (2 × 30 ml) and evaporated in vacuo. The crude residue was purified by column chromatography [Al_2O_3/$CHCl_3$, $CHCl_3$/EtOH (20:1)]. − Yield 1.7 g (43%) as oil. − $C_{19}H_{32}N_2O_4$; mol. mass 352.47; calcd. C 64.8, H 9.2, N 8.0; found: C 64.6, 64.5; H 9.4, 9.3; N 7.9, 8.0. − ^{1}H NMR (CCl_4): δ = 2.20 (br. s, 1 H, NH), 2.70 (m, 8 H, 4 CH_2N), 3.48 (m, 16 H, 2 OCH_2), 3.64 (s, 2 H, NCH_2Ph), 7.26 (m, 5 H, Ar−H).

1,4,7,10,13-Pentaoxa-16-azacyclooctadecane (**3a**) was prepared as described previously[18b].

N-Methyl-1,4,7,10,13,-pentaoxa-16-azacyclodecane (**3b**) was obtained analogous to **2b** from 2.0 g (7.6 mmol) of **3a**, 0.54 g (18.2 mmol) formaldehyde (as 30% aqueous solution) and 3.5 g (76.0 mmol) of formic acid, 80−90°C, 24 h. − Yield 0.7 g (53%); b.p. 120−122°C/0.9 Torr, ref.[18b] 160°C/0.03 Torr. − $C_{13}H_{27}NO_5$; mol. mass 277.36; calcd. C 56.3, H 9.8, N 5.0; found C 56.5, 56.4; H 10.0, 10.1; N 5.0, 5.0. − ^{1}H NMR: δ = 2.30 (s, 3 H, NCH_3), 2.69 (m, 4 H, 2 CH_2N), 3.64 (m, 20 H, 10 OCH_2).

N-Benzyl-1,4,7,10,13,-pentaoxa-16-azacyclodecane (**3c**) was obtained as described before.[18f]

1,13-Diaza-4,7,10,16-tetraoxacyclooctadecane (**4a**) was obtained by reduction of 1.6 g (6.5 mmol) **4c** with 1.6 g (40 mmol) lithium aluminium hydride in tetrahydrofuran under reflux during 24 h. − Yield 2.3 g (49%). − Colourless crystals, m.p. 89−90°C (petroleum ether), ref.[18g] m.p. 89−90°C.

N,N-Dimethyl-4,7,10,16-tetraoxa-1,13,-diazacyclooctadecane (**4b**) was obtained analogous to **2b** from 2.0 g (7.6 mmol) of **4a**, 0.54 g (18.2 mmol) formaldehyde (as 30% aqueous solution) and 3.5 g (76.0 mmol) of formic acid, 80−90°C, 24 h. − Yield 0.7 g (53%); b.p. 120−122°C/0.9 Torr, ref.[18c] 160°C/0.03 Torr. − $C_{14}H_{30}N_2O_4$; mol. mass 290.41; calcd. C 57.9, H 10.4, N 9.6; found C 57.8, 57.7; H 10.3, 10.3; N 9.6, 9.7. − ^{1}H NMR: δ = 2.32 (s, 6 H, 2 NCH_3), 2.72 (m, 8 H, 4 CH_2N), 3.64 (m, 16 H, 2 OCH_2).

1,13-Diaza-4,7,10,16-tetraoxacyclooctadeca-2,12-dione (**4c**) was synthesized from 1.7 g (16.0 mmol) of 1,5-bis(diamino)-3-oxapentane and 4.0 g (16.0 mmol) of 3,6,9-trioxaundecanedioic acid dimethyl ester[18d] in 600 ml of dry methanol according to a method described earlier.[18e] Yield 2.3 g (49%) colourless crystals, m.p. 117−118°C (acetone). − $C_{12}H_{22}N_2O_6$; mol. mass 290.32; calcd. C 49.6, H 7.6, N 9.7; found C 49.8, 49.8; H 7.7, 7.8; N 9.6, 9.7. − ^{1}H NMR: δ = 3.49 (m, 8 H, 4 NCH_2 + 4 $HOCH_2$), 3.70 (m, 8 H, 4 OCH_2), 4.02 [s, 4 H, 2 OCH2C(O)], 7.18 (br. s, 2 H, 2 NH).

1,16-Diaza-4,7,10,13-tetraoxacyclooctaadecane (**5a**) was obtained analogous to **4a** by reduction of 1.3 g (4.5 mmol) **5c** with 2.0 g (52.6 mmol) of lithium aluminium hydride in refluxing tetrahydrofuran during 24 h. − Yield 0.7 g (59%); b.p. 125−125.7°C/0.8 Torr. − $C_{12}H_{26}N_2O_4$; mol. mass 262.35; calcd. C 54.9, H 10.0, N 10.7; found C 55.0, 54.9; H 10.0, 10.1; N 10.6, 10.7. − ^{1}H NMR: δ = 1.95 (s, 2 H, 2 NH), 2.64 (s, 4 H, NCH_2CH_2N), 2.68 (m, 4 H, 2 OCH_2CH_2N), 3.62 (m, 16 H, 8 OCH_2).

N,N-Dimethyl-4,7,10,13-tetraoxa-1,16,-diazacyclooctaadecane (**5b**) was obtained analogous to **2b** from 2.0 g (7.6 mmol) of **5a,** 0.54 g (18.3 mmol) formaldehyde (as 30% aqueous solution) and 3.5 g (76.0 mmol) of formic acid, 80−90°C. After 24 h additional 0.54 g (18.5 mmol) formaldehyde and 3.5 g (76.0 mmol) formic acid were added to the reaction mixture, which was heated to 80−90°C for another 24 h. − Yield 1.1 g (50%); b.p. 130−132°C/0.9 Torr. − $C_{14}H_{30}N_2O_4$; mol. mass 290.41; calcd. C 58.0, H 10.4, N 9.6; found C 57.8, 58.0; H 10.4, 10.0; N 9.9, 10.0. − ^{1}H NMR: δ = 2.32 (s, 6 H, 2 NCH_3), 2.68 (m, 8 H, 4 CH_2N), 3.64 (m, 16 H, 2 OCH_2).

1,16-Diaza-4,7,10,13-tetraoxacyclooctaadeca-2,15-dione (**5c**) was prepared similarly to **4c** from 1.1 g (18.0 mmol) ethylenediamine and 5.4 g (18.0 mmol) of 3,6,9,12-tetraoxatetradecanedioic acid dimethyl ester[18d] in 600 ml of dry methanol. The solvent was removed in vacuo, the residue was purified by column chromatography [Al_2O_3/$CHCl_3$, $CHCl_3$-EtOH (20:1)] to yield 1.6 g (31%) of compound **5c**, colourless crystals, m.p. 102−104°C (acetone). − $C_{12}H_{22}N_2O_6$; mol. mass 290.32; calcd. C 49.6, H 7.6, N 9.6; found C 49.8, 48.6; H 7.5, 7.4; N 9.6, 9.7. − ^{1}H NMR: δ = 3.46 (m, 4 H, 2 NCH_2), 3.70 (m, 12 H, 2 OCH_2CH_2), 4.02 [s, 4 H, 2 $OCH_2C(O)$], 7.68 (br. s, 2 H, 2 N−H).

1,4,7,10,13-Pentaoxacyclododecane (**6**) was a commercial sample.

N,N-Dimethyl-4,10,13-tetraoxa-1,7,-diazacyclopentane (**7a**) was obtained analogous to **2b** from 1.2 g (4.8 mmol) of **7b,** 0.35 g (11.7 mmol) formaldehyde (as 30% aqueous solution) and 2.2 g (48.0 mmol) of formic acid, 80−90°C. − Yield 0.70 g (53%); b.p. 110−112°C/0.9 Torr. − $C_{12}H_{26}N_2O_3$; mol. mass 246.35; calcd. C 58.5, H 10.6, N 11.4; found C 58.3, 58.4; H 10.7, 10.8; N 11.3, 11.4. − ^{1}H NMR: δ = 2.32 (s, 6 H, 2 NCH_3), 2.72 (m, 8 H, 4 OCH_2N), 3.64 (m, 12 H, 2 OCH_2).

1,7-Diaza-4,10,13-trioxacyclopentadeca-2,6-dione (**7b**) was obtained as described previously.[18e]

1,13-Diaza-4,7,10,-trioxacyclopentadecane (**8a**) was prepared analogous to **4a** by reduction of 1.1 g (4.5 mmol) of **8c** with 2.0 g (52.6 mmol) of lithium aluminium hydride in boiling tetrahydrofuran during 24 h. − Yield 0.58 g (60%); b.p. 123−125°C/0.9 Torr. − $C_{10}H_{22}N_2O_3$; calcd. C 55.0, H 10.2, N 12.8; found C 54.8, 54.9; H 10.0, 10.1; N 12.6, 12.7. − ^{1}H NMR: δ = 1.00 (t, ^3J = 7.0 2 H, 2 NH), 2.62 (m, 4 H, NCH_2CH_2N), 2.80 (m, 4 H, OCH_2CH_2N), 3.62 (m, 12 H, 2 OCH_2).

N,N-Dimethyl-4,7,10-triaoxa-1,13-diazacyclooctadecane (**8b**) was obtained analogous to **2b** from 1.7 g (7.7 mmol) of **8a,** 0.55 g (18.5 mmol) formaldehyde (as 30% aqueous solution) and 3.5 g (77.2 mmol) of formic acid. After 24 h at 80−90°C additional 1.7 g (7.7 mmol) formaldehyde and 3.5 g (76.0 mmol) formic acid were added, and the mixture was heated to 80−90°C for another 24 h. − Yield 1.3 g (68%); b.p. 118−120°C /0.8 Torr. − $C_{12}H_{26}N_2O_3$; mol. mass 246.35; calcd. C 58.5, H 10.6, N 11.4; found C 58.8, 58.7; H 10.4, 10.3; N 11.5, 11.4. − ^{1}H NMR: δ = 2.31 (s, 6 H, 2 NCH_3), 2.68 (m, 8 H, 4 CH_2N), 3.63 (m, 12 H, 2 OCH_2).

1,13-Diaza-4,7,10,-trioxacyclopentadecane-2,12-dione (**8c**) was obtained analogous to **4c** from 3.5 g (58.8 mmol) ethylenediamine and 14.7 g (58.8 mmol) of 3,6,9-trioxaundecanedioic acid dimethyl ester[18d] in 600 ml of dry methanol. The solvent was removed in vacuo, the residue was purified by column chromatography [Al_2O_3/$CHCl_3$, $CHCl_3$-EtOH (20:1)] to yield 5.8 g (40%) ester as colorless crystals, m.p. 157−159°C (acetone). − $C_{10}H_{18}N_2O_5$; mol. mass 246.27; calcd. C 48.8; H 7.4; N 11.4; found: C 48.8, 48.7; H 7.5, 7.4; N 11.1, 11.2. − ^{1}H NMR: δ = 3.48 (m, 4 H, 2 NCH_2), 3.70 (m, 8 H, 2 OCH_2CH_2), 4.02 (s, 4 H, 2 $OCH_2C(O)$), 7.48 (br. s, 2 H, 2 NH)

1,4,7,10,13,16,19-Heptaoxacycloheneicosane (**9**) was a commercial sample.

1,13-Diaza-4,7,10,16,19-pentaoxacycloheneicosane (**10**) was obtained analogous to **4a** by reduction of 1,5 g (4.5 mmol) of 1,13-diaza-4,7,10,16,19-pentaoxacycloheneicosa-2,12-dione[18e] with 2.0 g (52.6 mmol) of lithium aluminium hydride in boiling tetrahydrofuran during 24 h.

[1] Of the Saarbrücken series supramolecular chemistry this is paper 76. Paper 77: Y. Wang, H.-J. Schneider, *J. Chem. Soc., Perkin Trans. 2*, in print.

[2] For reviews see: Y. Inoue, G. W. Gokel, *Cation Binding by Macrocycles*; Marcel Dekker, New York **1990.** − *Comprehensive Supramolecular Chemistry,* Vol. 1; G. W. Gokel, Ed., Pergamon/Elsevier Oxford etc, **1996.** − S. R. Cooper, *Crown Compounds: Towards Future Applications*, VCH Publisher, New York, Weinheim, Cambridge, **1992**.

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[8] No complexation energies are available in the literature for the following ligands: (8,18-dioxo-1,7-N_2-18C6); 1,4-N_2-18C6, 1,4-(MeN)$_2$18C6, 5,18-dioxo-1,4-$N_2$18C6, 2,6-dioxo-1,7-$N_2$15C5, 1,4-(MeN)$_2$15C5 and 5,15-dioxo-1,4-$N_2$15C5. From the ligands in tables 1 and 2 the complexation of ligand **4a** was studied only with Ag^+ in MeCN[8a][8b], Pb^{2+} and Ag^+[8c], H^+[8d],with Tl^+ and Ag^+ in MeCN, Me_2CO and DMF[8e], with Co^{2+}, Ni^{2+}, Cu^{2+} and Zn^{2+} ions in H_2O[8f]; with **4b** in CH_2Cl_2 with chiral and achiral (phenylalkyl)ammonium thiocyanates[8g]; **7a** also forms complexes with alkylammonium cations in organic solvents[8h][8i] and with metal cations in H_2O and $CHCl_3$.[8j] Thermodynamics of lanthanide complexation in various solvents[8k] and stability constants with Co^{2+}, Ni^{2+}, Cu^{2+} and Zn^{2+} ions[8f] were studied with the ligand **8a**. – [8a] V. P. Barannikov, S. S. Guseinov, A. V. Matveev, A. I. V′yugin, *Russ. J. Coord. Chem. (Transl. of Koord. Khim.)*, **1996**, *22*, 263. – [8b] S. S. Guseinov, V. P. Barannikov, A. I. V′yagin, G. A. Krestov, *Zh. Khim. Termodin. Termokhim*. (*Russ.*), **1992**, *1*, 122. – [8c] K. E. Krakowiak, G. E. Maas, J. S. Bradshaw, J. K Hathaway, R. M. Izatt, *J. Heterocycl. Chem*., **1995**, *32*, 179. – [8d] V. P. Vasil′ev, T. D. Orlova, N. Yu. Goncharova, *Zh. Fiz. Khim.(Russ.)*, **1994**, *68*, 12. – [8e] A. Jabbari, M. Hasani, M. Shamsipur, *J. Inclusion Phenom. Mol. Recognit. Chem*., **1993**, *15*, 329. – [8f] E. Luboch, A. Cygan, J. F. Biernat, *Inorg. Chim. Acta*, **1983**, *68*, 201. – [8g] L. C. Hodgkinson, M. R. Johnson, S. J. Leigh, N. Spencer, I. O. Sutherland, R. F. Newton, *J. Chem. Soc., Perkin Trans.*, *1*, **1979**, 2193. – [8h] A. B. Kyte, K. A. Owens, I. O. Sutherland, R. F. Newton, *J. Chem. Soc., Perkin Trans. 1*, **1987**, 1921. – [8i] M. R. Johnson, N. F. Jones, I. O. Sutherland, R. F. Newton, *J. Chem. Soc., Perkin Trans. 1*, **1985**, 1637. – [8j] P. Gramain, Y. Frere, *Nouv. J. Chim*., **1979**, *3*, 53. – [8k] F. Arnaud, *Eur. J. Solid State Inorg. Chem*., **1991**, *28*, 229.

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