Open-Chain Polyethers. Influence of Aromatic Donor End Groups on Thermodynamics and Kinetics of Alkali Metal Ion Complex Formation

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Abstract: A series of noncyclic neutral ionophores has been synthesized by the linkage of various aromatic and heteroaromatic residues with tetraethylene glycol, triethanolamine, and ethylene glycol—analogue compounds with aromatic and heteroaromatic chain segments, respectively. The stoichiometry and the stability of the alkali metal ion complexes of these noncyclic polyethers in methanol at 25 °C were determined by spectrophotometric titrations; the enthalpy, molar heat capacities, and rate constants of complex formation were evaluated from temperature-jump relaxation experiments. The ligands form 1:1 complexes with alkali metal ions with stability constants between 10^0 and 10^4 M^{-1}, depending upon cation size and ligand structure as given by the number of coordinating sites and the number, donor strength, and rigidity of the aromatic residues. The complexones exhibit peak selectivity, but according to the high flexibility of the ligands the discrimination between metal ions of different ionic radius is low (e.g., $2 < K(K^+)/K(Na^+) < 10$). The strongest complexing agents (I, VII, and X) possess a second nonequivalent binding site. Complex formation is characterized by large negative enthalpies (-70 kJ $mol^{-1} < \Delta H^\circ < -20$ kJ mol^{-1}) and negative entropies (-180 J K^{-1} $mol^{-1} < \Delta S^\circ < 0$ J K^{-1} mol^{-1}). In the case of tris(8-quinolyloxyethyl)-amine the enthalpies and entropies of complexation decrease with increasing ionic radius; in the case of the aromatic and heteroaromatic glyme analogues I and IV the opposite behavior is observed. The analysis of the thermodynamic data reveals that the desolvation of the metal ion and the conformational change of the ligand due to complexation contribute to different extent to the changes of ΔH° and ΔS°. Complexone I recombines with alkali metal ions with rate constants between 10^7 and 10^9 M^{-1} s^{-1}. The complexes dissociate with frequencies of at least 5×10^3 s^{-1}. The selectivity of the ligand is reflected in the dissociation rates; the formation rates, however, which comprise the diffusion-controlled encounter of the reactants and the stepwise desolvation of the metal ion by the multidentated complexone, monotonically increase with increasing ionic radius.

Introduction

The molecular recognition of sodium and potassium ions by membrane-integrated ligands is one of the fundamental processes of living cells. The present concepts of the essential structural features of such carrier molecules have been derived from studies on model compounds, which form stable lipophilic complexes with alkali metal ions.[2] The complexation properties of ionophores, e.g., of the synthetic "crown ethers"[3] and "cryptands",[4] have been investigated extensively in recent years.[2]

Open-chain polyethers with aromatic end groups[5] represent a class of molecules that has an intermediate position with respect to nonspecific solute-solvent interactions and to the highly specific uptake of metal ions into the intramolecular cavity of mono- or bicyclic host molecules. The noncyclic compounds[6] fill the gap between linear oligoethylene glycol dimethyl ethers (glymes) and the common crown ethers. Whereas from glymes no crystalline complexes with alkali metal ions could be obtained,[3a,7] the substitution of the methyl groups by aromatic donors leads to powerful complexones, which easily form crystalline complexes with a variety of metal ions.[5]

We synthesized a series of these open-chain compounds in order to elucidate to which extent the individual structural units control the thermodynamics and kinetics of complex formation of alkali metal ions. Their basic molecular frame was altered by changes of topology,[4b] by variation of donor groups in the ortho position of the aromatic residues, symmetrically or asymmetrically, or by insertion of aromatic chain segments into the middle of the ether chain. The stability constants and the stoichiometries of complexes were determined spectrophotometrically; enthalpies of reaction and rate constants were evaluated from the analysis of temperature-jump relaxation experiments.

The stability and selectivity ratios, the enthalpic and entropic contributions to the free enthalpy, and the reaction rates of the complex formation were investigated as functions of ligand structure and cation size, in order to obtain more detailed information about the molecular nature of the interactions between noncyclic neutral ionophores and alkali metal ions.

Experimental Section

A. Synthetic Section.[8] Analytical and Spectral Data. Elemental analyses were performed by the microanalytical section of the Institut für Organische Chemie und Biochemie, Bonn, West Germany. Mass spectra (MS) were recorded on an AEI MS 50 mass spectrometer. Nuclear magnetic resonance spectra (NMR) were obtained on an Varian EM 360 (60 MHz) spectrometer. Chemical shifts are denoted in parts per million (ppm) downfield from Me_4Si (δ 0) in δ units and coupling constants in hertz (Hz). The purity of the products was checked by thin layer chromatography on alumina sheets, silica gel 60F 254 (Merck, Darmstadt, West Germany).

1-Phenoxy-11-chloro-3,6,9-trioxaundecane (XI). To a solution of phenol (9.40 g, 100 mmol) and KOH (5.60 g, 100 mmol) in 250 mL of boiling 1-butanol, 1,11-dichloro-3,6,9-trioxaundecane[3a] (92.4 g, 400 mmol, excess) was added and the mixture was refluxed for 20 h. After the fine precipitate (KCl) formed was filtered off, the solution was evaporated to dryness under vacuum. The residue was taken up in chloroform and washed several times with dilute NaOH and water. The organic phase was separated, dried over Na_2SO_4, and concentrated. Excess dichloride was subsequently removed by fractional distillation under vacuum: bp of the yellowish oil 145–150 °C (0.01 mmHg); yield 52%; NMR ($CDCl_3$) δ 6.70–7.30 (m, 5, aromatic CH), 3.40–4.25 (m, 16, CH_2OCH_2); high-resolution mass spectrum, 288.1154 (calcd for $C_{14}H_{21}ClO_4$, 288.1128); R_f value (80% toluene/20% ethanol, v/v) 0.71.

Preparation of "Open-Chain Crown" Compounds I, II, V, and VII–X. The procedure is analogous to that previously described for I and VII;[5a] 1,11-dibromoundecane,[9] 2,6-bis(bromomethyl)pyridine,[10] 1,3-bis(bromomethyl)benzene,[11] 1,4-bis(bromomethyl)benzene,[11a] tris(2-chloroethyl)amine hydrochloride,[12] phenol, and 8-

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Table I. Analytical Data and Properties of the Synthesized Complexes of II-VI, VIII, and X

starting ligand	complex with	stoichiometry ligand:salt	yield, %	mp, °C	anal. data (C, H, N, S)[a]
II	KSCN	1:1	75	95	C 47.27, 4.53, 7.87 F 47.27, 4.54, 7.87
III	$Ca(SCN)_2 \cdot 4H_2O$	1:1	72	166	C 51.99, 5.29, 4.33 F 51.50, 5.37, 4.35
IV	$Ca(SCN)_2 \cdot 4H_2O$	1:1	54	120 dec	C 48.80, 4.44, 4.74 F 48.80, 4.64, 4.54
V	$Ba(SCN)_2 \cdot 2H_2O$	1:1 ($1H_2O$)	65	85 dec	C 42.76, 4.56, 4.53 F 42.81, 4.43, 4.54
VI	KSCN	1:1 $\left(\frac{1}{2}H_2O\right)$	70	91-92	C 57.23, 5.60, 5.56 F 57.21, 5.41, 5.59
VIII	KSCN	2:3	36	184-186	C 61.37, 3.76, 9.10, 8.93 F 61.73, 3.92, 8.86, 8.79
X	NaSCN	1:1 ($1H_2O$)	69	126-128	C 64.85, 5.12, 11.12 F 64.98, 5.05, 11.29
	KSCN	1:1	71	184-186	C 65.04, 4.82, 11.16 F 64.92, 4.95, 11.21
	RbI	1:1	77	115-118 (104-106)[b]	C 53.34, 4.07, 7.54 F 52.95, 4.07, 7.20
	NH_4SCN	1:1	67	128-130 (118)[b]	C 67.30, 5.65, 13.85 F 67.30, 5.81, 13.71
	$Ni(ClO_4)_2 \cdot 6H_2O$	1:1 ($1H_2O$)	71	234-237	C 49.16, 4.00, 6.95 F 48.86, 4.17, 6.60
	$H_2PtCl_6 \cdot 6H_2O$	1:1 ($1H_2O$)	82	195-200	C 38.46, 3.91, 5.44 F 38.42, 3.66, 5.36

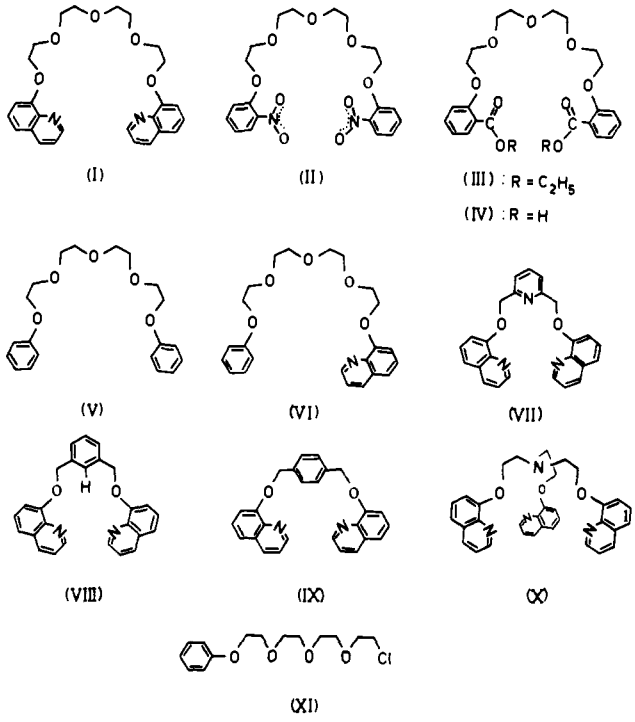
[a] C = calcd; F = found. [b] Sintering of crystals.

hydroxyquinoline were used as starting materials.

II: yellowish, viscous oil; yield 47%; NMR ($CDCl_3$) δ 3.71-4.40 (m, 16, CH_2OCH_2); R_f value (94% $CHCl_3$/6% ethanol, v/v) 0.40. For the analysis of the crystalline KSCN complex see Table I.

V: colorless oil; yield 65%; NMR ($CDCl_3$) δ 3.68-4.2 (m, 16, CH_2OCH_2); high-resolution mass spectrum, 346.1789 (calcd for $C_{20}H_{26}O_5$; 346.1780); R_f value (94% $CHCl_3$/6% ethanol, v/v) 0.56.

VIII: colorless needles (from CCl_4/hexane); yield 36%; mp 52-55 °C; NMR ($CDCl_3$) δ 5.40 (s, 4, benzylic $-CH_2$). Picrate of compound VIII: yellow needles, mp 228-230 °C. Anal. Calcd for $C_{38}H_{26}N_8O_{16}$ (dipicrate): C, 53.65; H, 3.08; N, 13.17. Found: C, 53.68; H, 3.34; N, 12.99.



IX: colorless crystals (from ethanol); yield 53%; mp 179-181 °C; NMR ($CDCl_3$) δ 5.36 (s, 4, benzylic $-CH_2$). Anal. Calcd for $C_{26}H_{20}N_2O_2$: C, 79.57; H, 5.14; N, 7.14. Found: C, 79.61; H, 5.18; N, 7.11.

X: yellowish, viscous oil; yield 53%; NMR ($CDCl_3$) δ 3.45 (t, 6, J = 7 Hz, CH_2N), 4.44 (t, 6, J = 7 Hz, CH_2O). Anal. Calcd for $C_{33}H_{30}N_4O_3$: C, 74.70; H, 5.70; N, 10.56. Found: C, 75.00; H, 6.01; N, 10.63.

Preparation of III and IV. Sodium ethoxide (4.08 g, 60 mmol), dissolved in 50 mL of anhydrous ethanol, was added slowly with stirring under nitrogen to a solution of ethyl salicylate (9.97 g, 60 mmol) in 100 mL of anhydrous ethanol. To this refluxing solution 1,11-bis(4-toluenesulfonyl)-3,6,9-trioxaundecane[13] (15.07 g, 30 mmol), dissolved in anhydrous ethanol/DMF (1:2, 40 mL), was added dropwise with stirring within 1 h. The mixture (colorless precipitate) was refluxed for 2 h. The reaction mixture was cooled and after filtration of the precipitate the solvent was removed by distillation under vacuum to afford a viscous oil which was taken up in chloroform and washed with water. The organic layer was dried ($MgSO_4$) and concentrated by distillation under vacuum to a volume of 10 mL. Chromatography on silica gel 60 (Macherey, Nagel + Co, 0.063-0.1 mm) with chloroform (2% ethanol) gave III as a colorless, viscous oil: yield 75%; NMR ($CDCl_3$) δ 1.40 (t, 6, J = 7 Hz, ethyl $-CH_3$), 4.00 (m, 16, CH_2OCH_2), 4.40 (q, 4, J = 7 Hz, ethyl $-CH_2$); high-resolution mass spectrum; 490.2212 (calcd for $C_{26}H_{34}O_9$, 490.2203); R_f value (94% $CHCl_3$/6% ethanol, v/v) 0.34.

IV was obtained by hydrolysis of III with KOH in refluxing H_2O/ethanol. Acidification with concentrated HCl gave IV as a colorless, viscous oil: yield 91%; NMR ($CDCl_3$) δ 3.50-4.50 (m, 16, CH_2OCH_2), 10.40 (s, 2, COOH); R_f value (94% $CHCl_3$/6% ethanol, v/v) 0.12. For the analysis of the crystalline $Ca(SCN)_2$ complex see Table I.

Preparation of VI. 8-Hydroxyquinoline (2.90 g, 20 mmol) and KOH (1.12 g, 20 mmol) were dissolved in 100 mL of boiling 1-butanol. After XI (5.77 g, 20 mmol) was added, the mixture was refluxed for 20 h. The procedure for the workup was the same as for XI (see above). The product was purified by chromatography on silica gel (eluent toluene/ethanol, 9:1): colorless, viscous oil; yield 58%; NMR ($CDCl_3$) δ 6.75-9.00 (m, 11, aromatic -CH), 3.45-4.55 (m, 16, CH_2OCH_2); high-resolution mass spectrum, 397.1905 (calcd for $C_{23}H_{27}NO_5$, 397.1889); R_f value (80% toluene/20% ethanol, v/v) 0.50.

Preparation of Crystalline Complexes of II–VI, VIII, and X. The procedure is analogous to that previously described for I and VII.[5a] Yields, melting points, stoichiometry, and analytical data are summarized in Table I.

B. Equilibrium and Kinetic Measurements. Sample Preparation. The purity of all samples of complexones was checked by thin layer chromatography. All salts were of the highest grade commercially available (p.a. or Suprapur, Merck). The ligands and salts were dissolved in methanol (p.a. Merck, 0.01% water). Contamination of the samples by Na^+, K^+, Ca^{2+}, Mg^{2+}, and Cu^{2+} was checked by atomic absorption spectrometry using a Varian 1200.

All absorption measurements were performed using PMQ II, DMR 10, or DMR 22 (Zeiss). Fluorescence measurements were carried out using a Schoeffel RRS 1000 spectrofluorimeter. Stoichiometry and binding constants were obtained at 25 °C by measuring the changes of the optical signals due to complex formation. The temperature of the cuvette was controlled within 0.1 °C by thermostated cell holders. UV spectra and excitation and emission spectra (uncorrected) of the free ligands and their alkali metal ion complexes were recorded in order to ascertain the optimum wavelengths for the quantitative determinations. The titrations were carried out at constant concentration of polyether by varying the concentration of the salt in question. For the determination of the complex stoichiometry the initial concentration of the ligand $c_L{}^0$ was chosen at least one order of magnitude higher than the estimated value of the reciprocal equilibrium constant. Because of the rather low solubility of alkali metal salts in methanol ($\simeq$50 mM) this condition could only be satisfied as long as all the individual binding constants were larger than K_i = 200 M^{-1}. In all other cases the stoichiometry as well as the binding constant had to be evaluated from the slope of the same titration curve as described below.

The apparent stability constant K_{app}, defined by $K_{app} = c_{LM}/(c_L \times c_M)$, was determined directly from the experimental binding curve plotting the normalized extinction E/E_L or the normalized fluorescence F/F_L vs. the quotient of the initial concentrations of metal ion and ligand $c_M{}^0/c_L{}^0$. The binding curve for the case of the extinction measurements is given by the equation

$$\frac{E_\cdot}{E_L} = 1 + \frac{E_{LM} - E_L}{E_L} T \tag{1}$$

An identical equation holds for fluorescence measurements. E_L (F_L) and E_{LM} (F_{LM}) are the extinctions (fluorescence signals) of the free ligand and its cation complex. The titration function T represents the algebraic solution for the equilibrium concentrations in dependence of the variation of the initial concentrations $c_M{}^0$ with $c_L{}^0$ being constant. In case of a 1:1 binding equilibrium T is

$$T = \frac{1}{2}\left(1 + \frac{1}{Kc_L{}^0} + \frac{c_M{}^0}{c_L{}^0}\right)\left[1 - \left(1 - \frac{4\,\frac{c_M{}^0}{c_L{}^0}}{\left(1 + \frac{1}{Kc_L{}^0} + \frac{c_M{}^0}{c_L{}^0}\right)^2}\right)^{1/2}\right] \tag{2}$$

The binding constant K_{app} and the stoichiometry n were evaluated using a nonlinear least-squares analysis;[15] the calculations were carried out on a Prime computer 300. Starting from approximate values of K_{app}, n, E_L (F_L), and E_{LM} (F_{LM}) the best fit of data was obtained by systematic variation of the four parameters according to the curve-fitting procedure developed by Powell[14] (subroutine VA 05A, Harwell subroutine library). The confidence limits of the individual data and the correlation matrix as a criterion of the interrelation of the parameters were calculated in order to check the validity of the iteration.

Five to ten titrations were carried out for the determination of one association constant. The initial concentration of the ligand $c_L{}^0$ was at least one order of magnitude lower than the reciprocal stability constant $K_{app}{}^{-1}$: $c_L{}^0 < 0.1 c_{K_{app}^{-1}}$. The metal ion was added in excess: $c_M{}^0 \gg c_L{}^0$; $c_M{}^0 \simeq c_M$. Thermodynamic stability constants were evaluated using the product of the activity coefficients.[16]

Reaction enthalpies and rate constants were determined by the analysis of temperature-jump relaxation experiments.[2b,17] All measurements refer to a final temperature of 25 °C. The ionic strength was adjusted to 0.08 M by addition of $N(CH_3)_4Br$.

For the determination of the rate constants the concentration of the reactants was varied between 1×10^{-5} and 5×10^{-4} M; under these conditions only 1:1 binding equilibria were present to a measurable extent. Relaxation times were determined from the experimental curves by an analogue simulation technique as described previously.[5a] The individual rate constants were evaluated from the concentration dependence of the relaxation times using a weighted least-squares method.

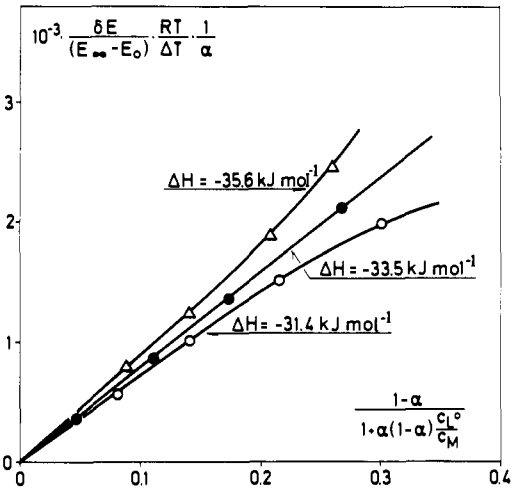


Figure 1. Typical example of the iteration procedure for the evaluation of the reaction enthalpy according to eq 7 (K^+ complex of ligand 1V, methanolic solution of 0.08 M $N(CH_3)_4Br$, T = 298 K, λ 305 nm).

The enthalpy of the complex formation ΔH was obtained from the relaxation amplitude, which is related to the shift of concentrations of the 1:1 equilibrium according to[17,18]

$$\delta c_{complex} = \frac{\partial c_{complex}}{\partial \ln K}\frac{\partial \ln K}{\partial T}\delta T = \Upsilon \frac{\Delta H}{RT}\frac{\delta T}{T} \tag{3}$$

The amplitude factor can be expressed by the degree of association $\alpha = c_{LM}/c_L{}^0$, calculated from the known stability constant according to

$$\Upsilon = \frac{\alpha(1-\alpha)}{1 + \alpha(1-\alpha)(c_L{}^0/c_M)} c_L{}^0 \tag{4}$$

Since the perturbation of the equilibrium is monitored spectrophotometrically, the expression for the enthalpy is as follows:

$$\frac{\delta E_{chem}}{E_{LM} - E_L} = \frac{\alpha(1-\alpha)}{1 + \alpha(1-\alpha)(c_L{}^0/c_M)}\frac{\delta T}{T}\frac{\Delta H}{RT} \tag{5}$$

δE_{chem} is the change of signal due to complex formation. If as in most cases the relaxation processes were faster than the resolution of the instrument, the signal δE_{chem} due to the chemical reaction could not be separated from the temperature dependence of the extinction δE_0. The major contributions to this nonspecific effect are the temperature dependence of the extinction coefficients and concentration changes of the ligand due to the thermal expansion of the solvent:

$$\delta E_0 = c_L \delta\epsilon_L + c_{LM}\delta\epsilon_{LM} - (c_L\epsilon_L + c_{LM}\epsilon_{LM})(\delta V/V) \tag{6}$$

The temperature dependence of the extinction of ligand and complex, respectively, was measured in static control experiments. The values of δE_0 of the different complexes amounted to 8–30% of the experimental signal δE_{total}. Since the limit of error of $\Delta\delta E_0/\delta E_0$ varied from 1 to 3%, the error of the evaluation of the relaxation amplitude ($\delta E_{chem} = \delta E_{total} - \delta E_0$) was small compared to the signal to noise ratio of 10–50 of the optical signal. The temperature-jump experiments were standardized in order to obtain reproducible reference signals and signal to noise ratios. The concentration of the absorbing complexone was held constant, and the concentration of the metal ion in question was varied.

The reaction enthalpy was evaluated by plotting the expression

$$\frac{\delta E_{chem}}{\delta E_{LM} - \delta E}\frac{RT^2}{\Delta T}\frac{1}{\alpha} = A$$

vs.

$$\frac{1-\alpha}{1 + \alpha(1-\alpha)(c_L{}^0/c_M)} = B$$

$$A = \Delta H B \tag{7}$$

using a nonlinear weighted iteration program. The initial values of

Table II. Thermodynamic Stability Constants (log K_s) of Alkali Metal Ion Complexes in Methanol at 25 °C (K_s in L mol^{-1})[a]

compound	stoichiometry	log K_s with cation				
		Li^+	Na^+	K^+	Rb^+	Cs^+
I	1:1	2.37 ± 0.07	3.22 ± 0.01	3.51 ± 0.02	3.06 ± 0.06	2.6 ± 0.1
	1:2	<1.0 (K_2)	2.49 ± 0.02 (K_2)	2.14 ± 0.02 (K_2)		
II	1:1	<1.0	1.43 ± 0.08	1.59 ± 0.05	1.93 ± 0.06	1.75 ± 0.04
IV	1:1	3.45 ± 0.04	3.41 ± 0.05	3.24 ± 0.04	3.19 ± 0.05	<1.7
V	1:1	<0	0.7 ± 0.2	1.58 ± 0.05	0.5 ± 0.1	<0
VI	1:1	<0.7	1.51 ± 0.06	1.87 ± 0.03	1.79 ± 0.02	1.58 ± 0.03
VII	1:1	1.2 ± 0.2	3.65 ± 0.02	2.75 ± 0.06	2.4 ± 0.1	1.6 ± 0.2
	1:2			2.00 ± 0.01 (K_2)		
VIII	1:1		0.5 ± 0.2	<0		
IX	1:1	1.9 ± 0.1	0.7 ± 0.1			
X	1:1	2.18 ± 0.08	3.69 ± 0.05	2.58 ± 0.05	2.05 ± 0.02	1.57 ± 0.06
	1:2		2.37 ± 0.06 (K_2)			
valinomycin[b]	1:1	<0.7	1.1	4.9	5.3	4.4
nonactin[c]	1:1	<0.3	2.4	4.2	4.2	3.2
nigericin[d]	1:1		4.0	5.7		
18-crown-6 (XII)[e]	1:1		4.3	6.1		4.6
dibenzo-30-crown-10 (XIII)[f]	1:1		2.1	4.6	4.6	2.2
(2.2.2) XIV[g]		2.6	>8.0	>7.0	>6.0	4.4
XV[h]	1:1	<1.3	2.5	2.3	2.2	
XVI[h]	1:1	1.9	2.2	2.0	2.0	
XVII[j]	1:1		1.8	≃1.0		
tetraglyme[k]	1:1		1.28	1.72		1.45
pentaglyme[k]	1:1		1.47	2.20		1.85
hexaglyme[k]	1:1		1.60	2.55		2.17

[a] Thermodynamic stability constants were obtained for the ligands I, II, IV, VI, VII, and X; in all other cases the apparent stability constants log K_{app} are listed. [b] Reference 23. [c] Reference 24. [d] References 24 and 27. [e] Reference 25. [f] References 25 and 29. [g] Reference 26. [h] Reference 6d. The values were obtained in ethanol at 30 °C. [j] Reference 28. [k] $CH_3(OC_2H_5)_nOCH_3$, n = 4, 5, 6; ref 20a.

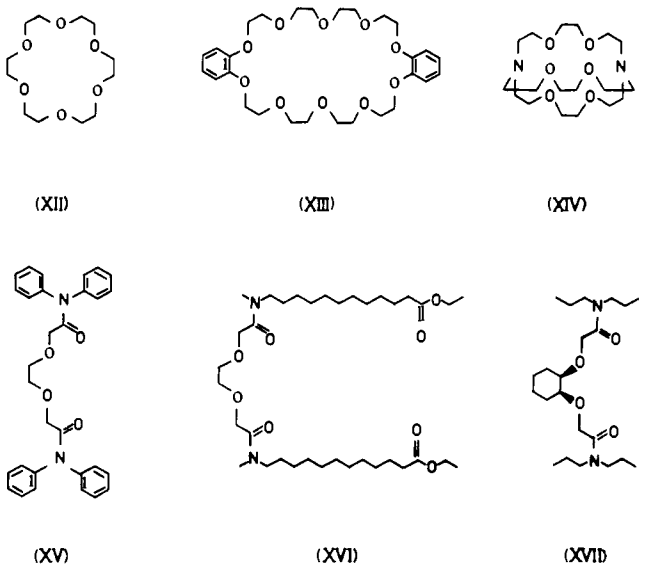
the iteration are the degree of association α and the equilibrium concentration of metal ion evaluated from the spectrophotometrically determined association constant. The reaction enthalpy was obtained by fitting to a straight line through the origin of the coordinate system varying ΔH, α, and c_M within the confidence limits of the static determinations. An example of the plots is given in Figure 1. The validity of the method was checked for some complexes using van't Hoff plots which were obtained from spectrophotometric titrations at different temperatures. The data agree well within 0.5-1 kJ mol^{-1}. If the temperature dependence of the reaction enthalpy was larger than 0.1 kJ K^{-1} mol^{-1}, the heat capacity ΔC_p^0 could be determined from variation of the heights of the amplitudes of the temperature jumps. The increase of temperature in the temperature-jump cell due to the voltage discharge of the capacitor was calibrated within ±2% using the dye cresol red.

Results and Discussion

A. Stability and Selectivity of Complex Formation.[20] The stability constants of the alkali metal ion complexes of ligands I-X are listed in Table II. They are mean values with the standard deviation of the mean. The differences in the accuracy of the constants reflect the different magnitudes of the optical signals.

Depending on the various functional groups of the ligands the association constants range over four orders of magnitude. The stability of complexes arise from the two major structural features of the ligands: the glyme units with their water-like bond angles provide the basic requirements for complexation, and the aromatic residues are the structural elements which control the strength of complexation by π-electron interactions,[21] steric influences, and hydrophobic interactions, and by supplying additional donor groups.

The ligands I-VI are derivatives of tetraethylene glycol. The individual ligands differ with respect to their aromatic end groups which act as additional donors for the chelation of the metal ions. These donors control the stability of the alkali metal ion complexes. This can be visualized by comparison of the association constants of ligands V, VI, and I (Figure 2A). Weak end group donors are stepwise substituted by strong ones. Compound V with its two phenyl groups only possesses



the five ether oxygens as coordination centers. Since π-electron–metal-ion interactions or sandwich-like end to end interactions of the phenyl groups certainly stabilize pseudocyclic conformations only to a small extent, the sterically and electrostatically most favorable configuration of the oxygen atoms defines the size of the coordination sphere, into which potassium ions fit best (K = 38 M^{-1}). Of all the six derivatives of tetraethylene glycol the bisphenyl ligand V exhibits the highest peak selectivity for potassium. Sodium and rubidium ions are bound poorly (K = 5 and 3 M^{-1}, respectively); the binding constants for lithium and cesium are below the limit of detection (K < 1 M^{-1}).

The substitution of one benzene by quinoline leads to ligand VI. The stability constants increase, especially for the larger cations rubidium and cesium; the selectivity of complex formation for potassium, however, is much less pronounced. 8-Oxyquinoline is a strong, rigid donor. Therefore it can be considered as the center of nucleation of the binding process.

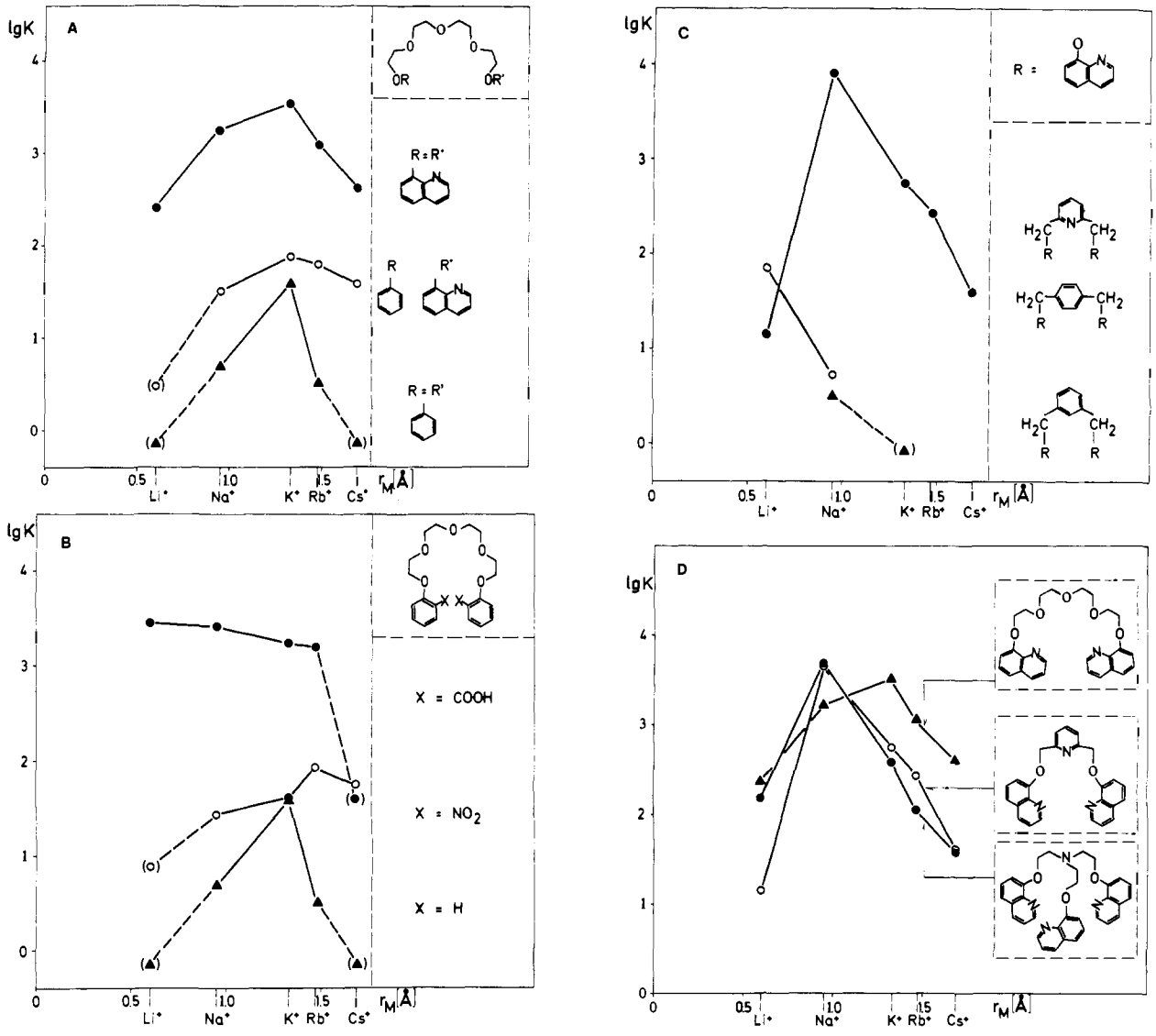


Figure 2. Stability constants of the alkali metal ion complexes of the noncyclic crown-type polyethers in methanol at 298 K as a function of the ionic radius: (A) compounds V, VI, and 1, stepwise substitution of weak end group donors by strong ones; (B) compounds V, II, and IV, variation of the donor X in ortho position of the end group; (C) compounds VII, VIII, and IX, compounds containing aromatic chain segments; (D) compounds 1, VII, and X, change of topology.

Subsequently, the metal ion is encircled by the ether chain which because of its flexibility easily adapts to different cation sizes. The compound I contains two quinoline groups at the terminal positions. As compared to ligand VI complex stability is increased by a factor of 10–50, because the metal ion is better shielded from the solvent and the counterions. The partial stacking of the quinolines stabilizes the pseudocyclic conformation of the complex as was shown by X-ray analysis.[19] The cation is surrounded by a helical configuration of the ligand. All seven heteroatoms take part in complexation. The stability of the first binding site ranges from 2.4×10^2 M^{-1} for Li^+ to 3.2×10^3 M^{-1} for the K^+ complex. A second nonequivalent binding site was found for Li^+, Na^+, and K^+; the binding affinities are about one order of magnitude lower (Table I).[5]

Additional coordination centers of the aromatic end groups have a considerable influence on the stability of complexes. In Figure 2B the association constants of complexones with various donors X in the ortho position of the aromatic residue are compared (X = H, NO_2, COOH). Because of the absence of particular donor groups the bisphenyl ligand V is a weak complexing agent (vide supra). The introduction of two nitro groups as donors favors the binding of sodium, rubidium, and cesium ions by a factor of 5–50, whereas the stability of the potassium complex remains constant. Rubidium ions are bound with the highest stability constant of $K = 90$ M^{-1}. The preference of compound II for large cations can be explained by the fact that the electrostatic repulsion of the nitro groups promotes the formation of a large pseudocycle.

The terminal *o*-benzoic acids of complexone IV contribute more strongly to complexation than the *o*-nitrobenzenes. Ligand IV binds alkali metal ions with stability constants larger than 10^3 M^{-1}. The stability constants of the complexes are comparable to those of the oxyquinolyl compound I. The selectivity of complex formation, however, is entirely different. The stability of the 1:1 complexes decreases monotonously with increasing ionic radius (Figure 2B), whereas all other ligands investigated show peak selectivity. Obviously the incorporation of the metal ion into the pseudocycle given by the optimum fit of the coordinating atoms of the ligand cannot be the only reaction responsible for the binding process. The charge neutralization of the benzoate anions by the metal ions represents another possible driving force for the uptake of the metal ion. Referring to this question, it has to be investigated if deprotonation occurs by complexation.

The experimental results are different for the solid state and the solution, respectively. The IR spectra of the crystalline KSCN or $Ca(SCN)_2$ complexes, for example, show that in the solid state the ligand is not negatively charged.[22b] Instead, the

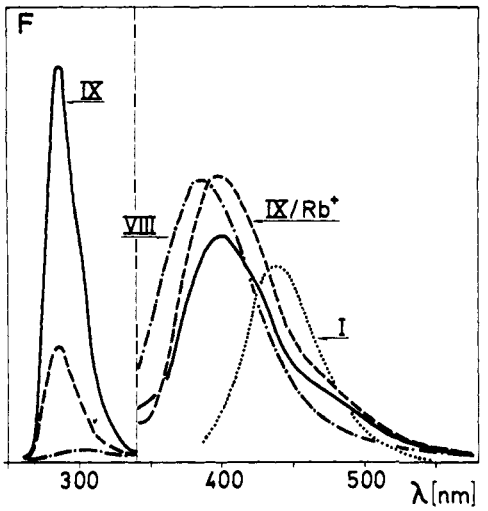


Figure 3. Normalized fluorescence emission spectra of the ligands I, VIII, and IX and its alkali metal ion complexes in methanol at 298 K: (A) concentration of ligand IX 4.7×10^{-5} M, concentration of RbCl 2.5×10^{-3} M, λ_{ext} 265 nm; (B) concentration of ligand VIII 3×10^{-5} M, concentration of KCl 4×10^{-2} M, λ_{ext} 275 nm; (C) concentration of ligand I 2.3×10^{-4} M, concentration of KCl 2.5×10^{-2} M, λ_{ext} 300 nm.

cyclization of the complexone is performed by intramolecular hydrogen bonds between the carbonyl and the hydroxy residues of the end groups. Titrations in methanol-water mixtures indicate that in solution both the protonated and the deprotonated forms of the ligand take part in complexation. The binding of potassium ions was determined in methanol-water mixtures (99/1, 95/5, 50/50 vol %) containing 1 M acid and base, respectively. Already small amounts of water considerably reduce the complex stability. In 1 M triethylamine the association constant decreases from 1.3×10^3 M^{-1} in 1% water (v/v) to 6×10^2 M^{-1} in 5% water (v/v), and in 1 M HCl from 180 to 50 M^{-1}, correspondingly. In equivolumetric mixtures of water and methanol complex formation could not be detected anymore. The binding constant in alkaline solution is one order of magnitude larger than that in acidic solution. This demonstrates that the benzoate anion is a stronger complexing group than the neutral benzoic acid; the neutralization of charges is more efficient with respect to complex stability than the ring formation by hydrogen bonds. From the extrapolation of the values of log K in water-containing solution to pure methanol it becomes evident that the stability constant obtained in dry methanol coincides with the values determined in alkaline solution. This leads to the conclusion that even in dry methanol having a residual water concentration of maximum 5 mM the uptake of the metal ion is combined with a delivery of protons. Complex formation is due to the chelation of the coordination centers and to the salt-like interactions between the metal ion and the benzoates. The contribution of the first effect is largest for potassium and rubidium; that of the second effect decreases with increasing ionic radius. The opposite dependence of the effects on the ionic radius can explain the low discrimination of compound IV between the alkali metal ions and the relatively high stability of the lithium and sodium complexes. We assume that the smaller cations fill the space between the two carboxyl groups, whereas the larger cations occupy the interior cavity.

The derivatives of tetraethylene glycol I–VI do not complex selectively, because the flexible ether chain can adapt itself to cations of different size. The insertion of aromatic bridges reduces the flexibility of the ligands. Accordingly, the selectivity of complex formation improves. This is illustrated by comparison of the binding constants of the complexones I–VI with those of the compounds VII,[5] VIII, and IX (Table II). These three complexones contain aromatic chain segments and two 8-oxyquinoline units as strong donor end groups. The small size of the interior cavity favors the binding of lithium and sodium ions (Figure 2C).

Ligand VIII mimics bond lengths and bond angles of glyme compounds, since the benzene ring in the middle of the molecule is meta substituted. A crystalline potassium complex of 2:3 stoichiometry could be obtained (Table I); however, complex formation in solution is characterized by binding constants within the limits of detection ($K_{M^+} < 5$ M^{-1}). This ligand resembles two oxyquinolines held together by the *m*-xylene bridge in an unfavorable steric position relative to each other rather than a crown compound with its regular sequence of coordinating centers and ethylene units. This argument is supported by comparing the complexation behavior of ligand VIII with that of ligand VII, which contains pyridine instead of benzene. The stability constants are increased by three orders of magnitude. The additional coordinating atom in a regular position completes the alternating sequence of ether oxygens and heteroaromatic nitrogens. The pyridino compound VII binds alkali metal ions as well as the analogous compound I, but selectively is more pronounced. The peak stability was found for sodium ions with $K = 4.5 \times 10^3$ M^{-1}.

As mentioned above, the X-ray analysis of the Rb^+ complex of ligand I[19] demonstrates that the π electrons of the end groups greatly enhance the stability of the pseudocircular conformation of the complex. The contribution of π electrons with respect to interactions with the bound metal ion depends on the configuration of the ligand; e.g., the π electrons of the phenylene residue of the meta-substituted compound VIII contribute only to a minor extent to intramolecular complexation, because the charge cloud of the benzene is aligned perpendicularly to the central plane of coordination. Ligand IX, however, contains a para-substituted phenylene moiety in the middle of the molecule. The water-like bond lengths and bond angles are distorted, but on the other side the para substitution allows strong charge-induced dipole interactions between cation and aromatic residue. The binding constants evaluated from fluorescence titrations show that electrostatic attractions overcompensate for the loss of stability due to the deformation of the coordination shell. The stability of the lithium and sodium complexes increase by a factor of 10 as compared to ligand VIII.

The influence of the geometric arrangement of the aromatic residues on complexation shows up in the fluorescence behavior of the ligands I, VIII, and IX and their metal ion complexes (Figure 3). The spectra of the tetraethylene glycol derivative I and of the meta-substituted phane VIII remain unchanged upon the addition of salt up to the concentration where saturation occurs. The fluorescence of the para-substituted phane IX, however, responds sensitively to metal ion concentrations of even less than 1 mM. Exciting at the maximum of the phenylene absorption at 260 nm, alkali metal ions quench the fluorescence of the benzene up to 90% and increase the fluorescence of the quinolines up to 25%. Fluorescence titrations at the maximum of the benzene absorption show that in the range from 0.1 to 20 mM of salt the individual alkali metal ions behave very differently. The addition of lithium ions yields a typical binding curve, but the addition of potassium, rubidium, and cesium ions results in a linear decay of fluorescence. In the case of sodium ions both effects overlap. Since the concentrations of salt are too small to induce nonspecific quench processes, the different fluorescence behavior must reflect different modes of binding. We assume that in the case of lithium we observe the uptake of the metal ion into the inner circle of the ligand constituted by the four coordination centers and the benzene, whereas in the case of the larger cations we observe interactions outside of the circle, e.g., 1:1 adducts or sandwich complexes of 1:2 or higher stoichiometry between the cation and the phenylene residues.

Conformational flexibility of the ligand and selectivity of complex formation counteract each other. The topological aspects of this statement are visualized in Figure 2D. Three open-chain ligands were chosen which all have quinolines as end groups. Therefore, the maximum values of the stability constants for the metal ion, which fit best to the respective ligand, are quite similar. Compound I discriminates poorly between cations of different size because of its flexible ether chain (vide supra). The pyridine ligand VII complexes approximately four times more selectively than compound I, because the steric hindrance introduced by aromatic bridges limits the conformational flexibility of the ligand. Stability and selectivity of complex formation slightly improve once again, if in addition the complexed cation is more efficiently shielded from solvent and counterion. In analogy to the transition from cyclic crown ethers to bicyclic cryptands the so-called tripodand excludes bound cations more extensively from the solvent than the nearly planar pyridine compound VII. The short name tripodand stands for a three-armed neutral ligand with each arm bearing donor atoms.[22a,c-e] Complexone X shows the largest selectivity and peak stability of all compounds investigated. Sodium ions are bound with the maximum association constant of $K = 5 \times 10^3\ M^{-1}$. A second nonequivalent binding site was found for sodium to be $K = 240\ M^{-1}$ (Table II). It is suggested that small ions are totally encircled by the seven donor atoms of the tripodand X; the larger cations, however, do not fit well into such a small spherical cage. Therefore, the coordinating branches of the molecule have to spread out, and the desolvation of the larger metal ions by the coordinating atoms cannot be performed completely.

In conclusion, the ten open-chain polyethers discussed here bind alkali metal ions with association constants ranging from 10^0 to $5 \times 10^3\ M^{-1}$, which correspond to the lower range of values obtained for cyclic complexones.[2] The list of reference compounds in Table II shows that the peak binding constants for the cyclic depsipeptides like valinomycin[23] and for the macrotetrolide antibiotics like nonactin[24] exceed those for the synthesized noncyclic complexones by a factor of 10–1000. Crown ethers have maximum stability constants of $10^6\ M^{-1}$,[25] macrobicyclic cryptands even values up to $10^{10}\ M^{-1}$.[26] On the other hand, those open-chain antibiotics, which can neutralize the charge of the bound metal ion by a dissociable carboxyl group, are stronger complexing agents than the compounds I–X; e.g., nigericin and monensin bind alkali metal ions 10–100 times better.[24,27] Comparing neutral noncyclic ionophores, the complexation strength particularly of compounds I, IV, VII, and X seems to be remarkably high. The derivatives of 3,7-dioxaazelaic acid diamide XV[6d] and XVI[6d] and of *cis*-1,2-cyclohexanebisoxyacetic diamide XVII[28] are synthetic noncyclic neutral ionophores, which were synthesized by Simon et al. in order to be used as selective complexones in liquid membranes of ion-sensitive electrodes. They form alkali metal ion complexes in ethanol at 30 °C with a maximum stability of $300\ M^{-1}$. Even if the considerable decrease of stability due to the change of solvent from ethanol to methanol is neglected, it is obvious that these ligands are weaker complexones for alkali metal ions than the glyme analogues and the ligands containing aromatic chain segments presented in this paper. The real glymes $CH_3(OC_2H_5)_nOCH_3$ with $n = 4, 5, 6$ form alkali metal ion complexes in methanol with stability constants between 20 and 50 M^{-1} for sodium ions and between 50 and 400 M^{-1} for potassium ions which correspond to the range of values found for the weak complexing aromatic analogues II, V, and VI. The values obtained for the stability constants and for the selectivity ratios $K(K^+)/K(Na^+)$ increase with the number of coordinating sites.[20a]

B. Thermodynamics of Complex Formation.[30] The complex stability results from the superposition of several different, partly counteracting increments of free energy: the binding energy given by the interaction of the polar groups of the complexone with the cation, the energy of the conformational change of the ligand as a consequence of complex formation, and the energies of desolvation of metal ion and ligand. The free energy of complexation comprises enthalpic and entropic terms. The recombination of a charged ligand with a metal ion of the hard A type to form a complex of electrostatic nature is preferentially entropy driven; the recombination of an uncharged ligand with a metal ion of the soft B type to form a complex of covalent nature is preferentially enthalpy driven.[31] This empirical rule cannot be applied to a prediction of the complexation behavior of alkali metal ions with noncyclic crown-type polyethers, because alkali metal ions belong to the A group of hard, unpolarizable cations, and all the noncyclic ligands studied belong to the group of uncharged ligands. Therefore we need experimental data to answer the question whether the complex stability is of enthalpic or entropic origin.

The enthalpies of reaction were evaluated from the relaxation amplitudes of temperature-jump experiments as described in the Experimental Section. The various influences of cation size and ligand structure on the thermodynamics of complex formation were separated by variation of the alkali metal ion keeping the ligand fixed and vice versa. The reaction enthalpies of the binding of the five alkali metal ions were determined for the strongest complexing agents (I, IV, and X). The numerical values of $\Delta G°$, $\Delta H°$, $\Delta S°$, and $\Delta C_p{}^0$ at 25 °C are listed in Table III. As a typical example of the relation between ligand structure and thermodynamics the potassium complexes of the compounds I, II, IV, and VI were investigated. These complexones differ with respect to the strength of coordination of the terminal donors (Table IV). Reaction enthalpies of compounds VII–IX could not be determined because of the unfavorable signal to noise ratios of the relaxation amplitudes. For a comparison of the open-chain ligands with the cyclic and bicyclic complexones Table IV includes thermodynamic data of complexation of the antibiotic nonactin,[32] the crown ethers 18-crown-6[25b] and dibenzo-30-crown-10,[29] and the (2.2.2)-cryptand.[33]

A survey of the data shows that the complex stability of the noncyclic ligands is entirely of enthalpic origin accompanied by an unfavorable decrease of entropy. The ΔH values of the noncyclic compounds (between −20 and −70 kJ mol^{-1}) are comparable to the values obtained for cyclic complexones in methanol; however, for some complexes the decrease of entropy can become remarkably high. The largest negative entropies of complexation were found for the lithium and sodium complexes of the aromatic tetraethylene glycol ethers and for the rubidium and cesium complexes of the tripodand X with maximum values of nearly $-200\ J\ K^{-1}\ mol^{-1}$.

Figure 4 illustrates the influence of the cation size on $\Delta G°$, $\Delta H°$, and $\Delta S°$ of the three ligands I, IV, and X. The glyme analogues I and IV and the tripodand X show opposite behavior with respect to the dependence of enthalpy and entropy on cation size. In case of the complexones I and IV the heat of reaction and the loss of entropy decrease with increasing ionic radius. Ligand X, however, behaves like the cyclic complexones (Table III). The values of $\Delta H°$ and $\Delta S°$ become more negative with increasing ionic radius. These experimental results need to be discussed in the light of the different intrinsic contributions to enthalpy and entropy.

The complexation enthalpy can be split into contributions from the cation and the ligand. The interaction of the metal ions with the solvent molecules of the first solvation shell is partly or totally substituted by the interaction with the polar groups of the ligands. Furthermore, the difference of the solvation enthalpies of the ordered solvent molecules outside of the complex and outside of the first solvation shell of the free metal ion, respectively, has to be taken into consideration. The

Table III. Thermodynamics of Alkali Metal Ion Complex Formation in Methanol at 25 °C ($\Delta G°$, $\Delta H°$ in kJ mol^{-1}, $\Delta S°$, $\Delta C_p{}^0$ in J K^{-1} mol^{-1})

compd		Li^+	Na^+	K^+	Rb^+	Cs^+
I	$\Delta G°$	-13.4 ± 0.6	-18.4 ± 0.5	-20.1 ± 0.4	-17.6 ± 0.8	-15 ± 1
	$\Delta H°$	-63 ± 2	-36 ± 1	-21 ± 1	-20 ± 1	-25 ± 1
	$\Delta S°$	-170 ± 10	-59 ± 5	-3 ± 5	-7 ± 7	-33 ± 4
	$\Delta C_p{}^0$	$(4 \pm 2)\ 10^2$	$(1.2 \pm 0.8)\ 10^2$			
IV	$\Delta G°$	-19.7 ± 0.5	-19.7 ± 0.4	-20.1 ± 0.4	-18.4 ± 0.4	-11 ± 1
	$\Delta H°$	-41 ± 1	-68 ± 2	-33.3 ± 0.6	-25.1 ± 0.4	-24 ± 1
	$\Delta S°$	-70 ± 3	$-(1.6 \pm 0.2)\ 10^2$	-22 ± 1	-23 ± 3	$-(4 \pm 2)\ 10$
	$\Delta C_p{}^0$	$(1.1 \pm 0.3)\ 10^3$	$(3.8 \pm 0.3)\ 10^3$	$(6.7 \pm 0.6)\ 10^2$	$(0.6 \pm 1.0)\ 10^2$	$(1.3 \pm 1)\ 10^2$
X	$\Delta G°$	-13 ± 1	-20.9 ± 0.3	-14.6 ± 0.4	-11.7 ± 0.5	-8.8 ± 0.4
	$\Delta H°$	-19 ± 3	-35 ± 2	-50 ± 1	-66 ± 2	-50 ± 8
	$\Delta S°$	$-(2 \pm 1)\ 10$	-46 ± 4	-119 ± 6	-184 ± 4	$-(1.4 \pm 0.3)\ 10^2$
	$\Delta C_p{}^0$				$(6 \pm 1)\ 10^2$	$(8 \pm 4)\ 10^2$
nonactin[a]	$\Delta G°$		-16	-26		
	$\Delta H°$		-11	-44		
	$\Delta S°$		15	-61		
18-crown-6 (XII)[b]	$\Delta G°$		-25	-35		
	$\Delta H°$		-35	-56		
	$\Delta S°$		-34	-73		
dibenzo-30-crown-10 (XIII)[c]	$\Delta G°$		-12	-26	-26	-24
	$\Delta H°$		-17	-49	-53	-47
	$\Delta S°$		-14	-75	-90	-76
(2.2.2) XIV[d]	$\Delta G°$		-41	-56	-48	-20
	$\Delta H°$		-44	-79	-82	-50
	$\Delta S°$		-11	-80	-115	-99

[a] Reference 32. [b] Reference 25b. [c] Reference 29. [d] Values were obtained in CH_3OH/H_2O (95/5 vol %), ref 33.

Table IV. Thermodynamics of K^+ Complexing by Aromatic Glyme Analogues in Methanol at 25 °C

	complexone			
	I	II	IV	VI
$\Delta G°$, kJ mol^{-1}	-20.1 ± 0.3	-9.2 ± 0.4	-20.1 ± 0.4	-10.5 ± 0.4
$\Delta H°$, kJ mol^{-1}	-21 ± 1	-29 ± 1	-33.3 ± 0.6	-59 ± 2
$\Delta S°$, J K^{-1} mol^{-1}	-3 ± 5	-67 ± 2	-22 ± 1	$-(1.6 \pm 0.2)\ 10^2$

changes of the enthalpy of the ligand by complexation are mainly due to the changes of solvation, intramolecular ligand-ligand repulsions, the stacking of the aromatic residues, and the steric deformation of the ligand induced by the bound metal ion.

In methanol the electrostatic interaction between the metal ion and the coordinating sites of the ligand represents one of the most important driving forces of the complexation enthalpy, because the counteracting interaction with the solvent molecules is relatively small as compared to the corresponding interactions in aqueous solution. If the solvent molecules are not too tightly bound, the uptake of the small cations by the ligand should be favored. The tripodand X, however, prefers the large cations as far as the enthalpy is concerned. This may be due to the fact that the binding of the small ion leads to an unfavorable conformation of the ligand characterized by inter-binding-site repulsions and deformations of the molecular frame; e.g., the amine bonds of the tripodand might be distorted by tension.

In contrast, ligand I prefers the small ions, because the electrostatic attraction is the dominant increment of the negative complexation enthalpy. Because of the high flexibility of the open-chain compound sterically unfavorable conformations can be avoided. Furthermore, the stacking energy of the terminal aromatic moieties contributes to the negative ΔH values. In addition, particularly in the case of the smaller cations, the desolvation may not take place completely.

In principle, the same arguments hold for the dicarboxylic acid IV; however, as discussed in the preceding section A, the complexation is coupled with the deprotonation of the ligand. The anomalous dependence of the enthalpy on ionic radius with the peak value for the sodium complex and the very large values of the molar heat capacity of more than 1 kJ K^{-1} mol^{-1} for the lithium and sodium complexes confirm the results of the spectrophotometric titrations which were interpreted as being produced by the superposition of two reactions.

The complex formation of the glyme analogues and of the tripodand is enthalpically favored, but entropically disfavored. As in the discussion of the enthalpy values a more thorough understanding of the entropy values is achieved considering the various intrinsic contributions. The total $\Delta S°$ is composed of changes of the solvation entropies of metal ion and ligand, of the internal entropy of the ligand, and of the entropy of the solvent due to the different arrangement of solvent molecules in the environment of a free metal ion and of a large, apolar complex ion, respectively. The change of the total number of particles accompanied by changes of the individual translational entropies considerably contributes to the complexation entropy.

This contribution often determines the dependence of the complexation entropy on the ionic radius. The degrees of freedom within the solution are increased by the release of the solvent molecules of the first solvation shell. This increase of entropy on ligand binding is largest for the small cations because of the larger influence on the arrangement of solvent molecules. Therefore, the total entropy of complexation is expected to be most positive or least negative for lithium and to become more negative with increasing ionic radius. It can be seen from Table III that this prediction is fulfilled for the cyclic[25b,29,32] and bicyclic complexones[33] and the noncyclic tripodand.

The nearly linear ligands I and IV, however, show the opposite dependence of the complexation entropy on the ionic radius. Thus, in the case of the glyme analogues the release of the solvation shell has to be overcompensated for by the other contributions to the complexation entropy. The metal ion may

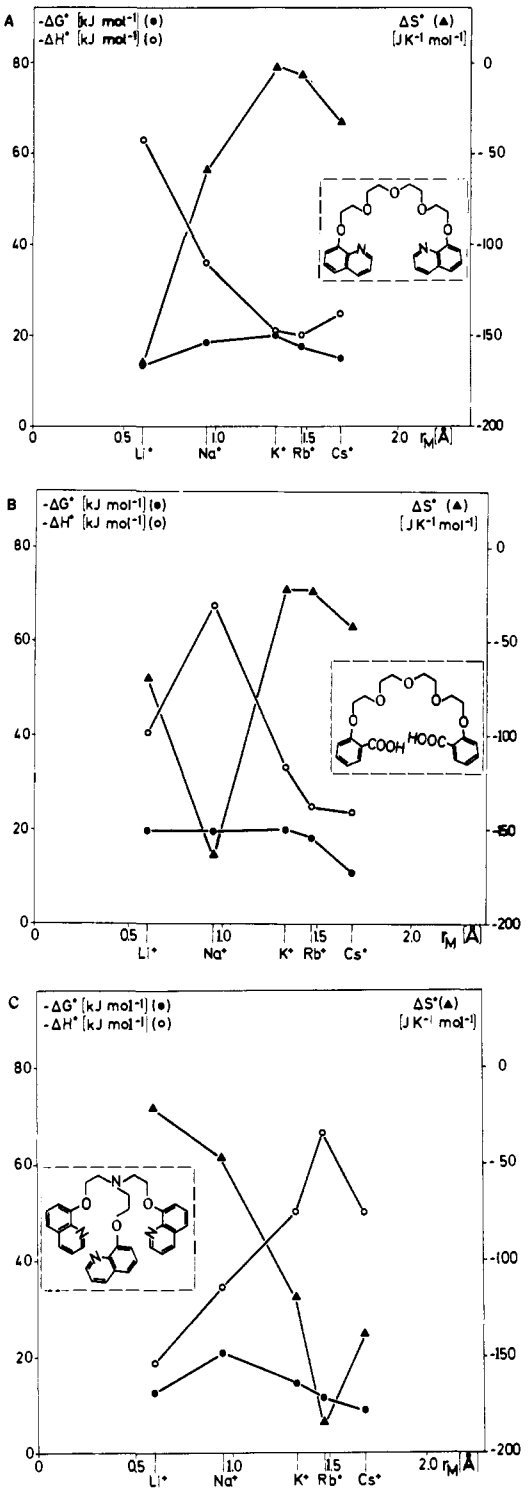


Figure 4. Free energies $\Delta G°$, enthalpies $\Delta H°$, and entropies $\Delta S°$ of the alkali metal ion complex formation of the ligands I (A), IV (B), and X (C) as a function of the ionic radius (methanolic solutions at 298 K).

not be completely desolvated. In our opinion, however, this behavior is mainly attributed to the change of the solvation and internal entropies of the ligand due to complex formation. The change of the topology of the ligand from a linear conformation in the uncomplexed state to a helical conformation in the complexed state leads to a large loss of entropy. The number of the degrees of freedom of the ligand is severely reduced because of the stiffening of the molecular frame and the adjustment of the coordinating atoms to the encaged metal ion. This conclusion is supported by the experimental finding that the decrease of entropy due to complexation is smallest for the uptake of those cations which do not induce steric deformations

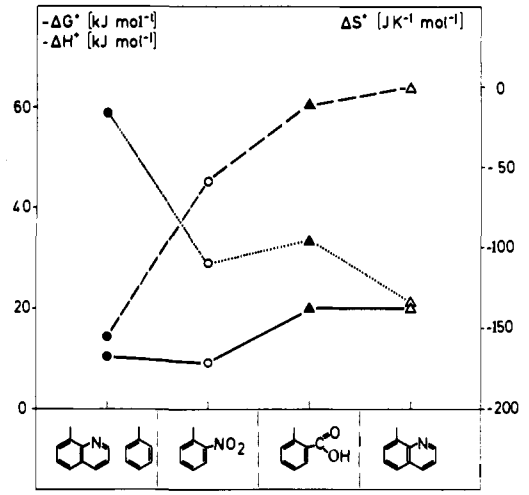


Figure 5. Free energies $\Delta G°$ (—), enthalpies $\Delta H°$ (·····), and entropies $\Delta S°$ (- - -) of complexation of potassium ions by the glyme analogues I, II, IV, and VI in methanol at 298 K.

of ligand structure. Potassium and rubidium ions fit well into the sterically optimum cavity of ligand I. In these cases both the free and the complexed state are nearly equally favored with respect to entropic terms. Thus, the peak stability of the potassium complex of ligand I is a consequence of the absence of a destabilizing loss of entropy; correspondingly the lability of the lithium complex is due to the entropically unfavorable conformational change of the ligand.

The tripodand **X** is much more restricted in its conformational flexibility than the compounds I and IV. Thus, the differences of the solvation and of the internal entropies of the ligand between the free and the complexed state are comparably small, and, instead, the difference of the translational entropy due to the release of the solvation shell controls the dependence of the complexation entropy on the ionic radius.

Figure 5 demonstrates the strong influence of ligand structure on complexation entropy in case of the glyme analogues. The addition and/or variation of the donor groups in ortho position of the terminal aromatic moieties shift the complexation entropies of the potassium complexes over nearly two orders of magnitude.

C. Kinetics of Complex Formation. The kinetics of alkali metal ion complex formation was studied for the strongest complexing agents (I, IV, VII, and X) by temperature-jump relaxation experiments. In case of the dicarboxylic acid IV and the tripodand X the relaxation times were always faster than the resolution of the instrument of 10^{-5} s. The experiments on the complexation of Li^+, Na^+, K^+, and Rb^+ with the glyme analogue I and of Na^+, K^+, and Rb^+ with the pyridine compound VII showed a single concentration-dependent relaxation process in the time range between 10^{-4} and 10^{-5} s. For a bimolecular reaction mechanism

$$M^+ + L \underset{k_{off}}{\overset{k_{on}}{\rightleftharpoons}} [LM]^+ \qquad (8)$$

the reciprocal relaxation time is given by

$$1/\tau = k_{on}(\bar{c}_L + \bar{c}_M) + k_{off} \qquad (9)$$

The plots of $1/\tau$ vs. $(\bar{c}_M + \bar{c}_L)$ (Figure 6) reveal that the measured data are compatible with the proposed mechanism. The numerical values of the rate constants are listed in Table V. In case of the systems Rb^+/ligand I, K^+/ligand VII, and Rb^+/ligand VII it was not reasonable to carry out an extensive numerical analysis, since the relaxation time and the time of resolution of the apparatus could not be clearly separated.

The values of the rate constant k_{on} for the recombination of metal ion and ligand between 3×10^7 and 4×10^8 M^{-1} s^{-1}

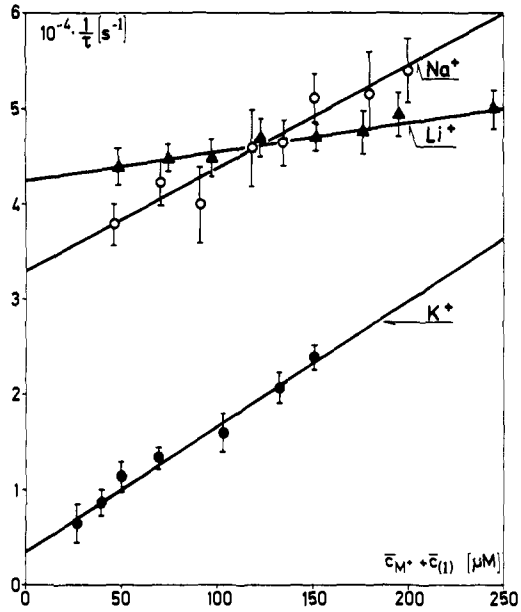


Figure 6. Dependence of the reciprocal relaxation time on the sum of the concentrations of the free reactants for the binding of the first Li^+, Na^+, and K^+ ion to ligand 1 in methanol at 298 K. The error bars of the individual points $1/\tau$ indicate the experimental error obtained for approximately five temperature jumps with the same solution.

Table V. Rate Constants of Alkali Metal Ion Complex Formation in Methanol at 25 °C

compd	cation	k_{on}, M^{-1} s^{-1}	k_{off}, s^{-1}
I	Li^+	(3 ± 2) 10^7	(4.3 ± 0.2) 10^4
	Na^+	(1.0 ± 0.5) 10^8	(3.4 ± 0.6) 10^4
	K^+ [a]	(1.1 ± 0.3) 10^8	(4 ± 1) 10^3
	Rb^+		$\simeq 10^5$
VII	Na^+ [a]	(4 ± 1) 10^8	(2.5 ± 0.4) 10^4
	K^+		$> \simeq 10^5$

[a] Reference 5a.

are relatively high; they are, however, lower than the value of around 10^9–10^{10} M^{-1} s^{-1} expected for a diffusion-controlled recombination of alkali metal ions with complexones in methanol.[2b] An example of a diffusion-controlled reaction is the recombination of the negatively charged open-chain antibiotic nigericin with sodium ions in methanol ($k_{on} \simeq 10^{10}$ M^{-1} s^{-1}).[24] The reduced rate of about 10^8 M^{-1} s^{-1} in case of the ligands I and VII is a consequence of the stepwise replacement of the solvent molecules in the inner coordination sphere of the metal ion by the chelating atoms of the multidentated complexone.[34] In order to account for the high overall rates every single substitution process has to occur with a time constant of the order between 10^8 and 10^9 s^{-1}.

Generally the rate of solvent substitution decreases with decreasing ionic radius of the metal ion, because the solvent molecules of the inner solvation shell are more tightly bound owing to the stronger electrostatic interaction. This behavior is exemplified by the glyme analogue I (Figure 7). Moreover, Figure 7 shows that the stability of the complexes increases with decreasing k_{off} values, e.g., the most stable potassium complex dissociates with the smallest frequency. The dependence of the association and dissociation rate constants of ligand I on the ionic radius corresponds to the results on the cyclic complexones valinomycin[35] and dibenzo-30-crown-10[29] obtained by Grell and Chock.

D. Synopsis. Referring to Figure 2 it becomes evident that the rigidity and the mode of linkage of the chain segments, the donor properties of the aromatic and heteroaromatic chain segments in the middle of the molecule, the coordinating

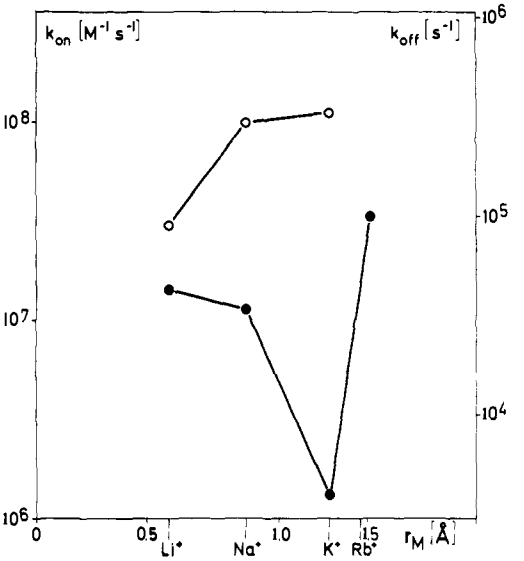


Figure 7. Dependence of the formation rates k_{on} (○) and of the dissociation rates k_{off} (●) of the alkali metal ion complexes of ligand 1 as a function of the ionic radius.

strength of the donors in the ortho position of the aromatic end groups, and the symmetric and the asymmetric substitution of end-group donors, respectively, are the structural units of the open-chain polyethers with aromatic end groups which control the stability of alkali metal ion complexes. The stability constants in methanol range over about four orders of magnitude. The influence of the length of the glycol chain on complex stability is discussed elsewhere.[7,20a,22b] The thermodynamic analysis revealed that the complex stability arises from the large negative enthalpies which compensate for the entropically unfavorable change of topology due to the transition from the linear conformation in the uncomplexed to the circular conformation in the complexed state. According to the high flexibility of the ligands the discrimination between metal ions of different ionic radius is low. The selectivity of complex formation is entirely reflected in the dissociation rates; the formation rates, however, monotonically increase with increasing ionic radius.

E. Possible Applications of the Noncyclic Complexones as Lipophilizers.[36] The open-chain polyethers discussed here can be obtained in high yields by nucleophilic substitution of 1,ω-di- and trihalogen compounds and of 1,ω-ditosylates, respectively, with the alkali salts of aromatic monohydroxy compounds. The syntheses are easily performed, because the expensive and time-consuming cyclization step is omitted. Therefore, processing in large batches is possible. However, the time- and cost-saving synthetic approach is not the only argument which favors the application of the noncyclic ligands as phase-transfer catalysts[2] and as solubilizing agents for salts in nonpolar organic solvents.[2,37] The complexones are soluble in almost all organic solvents; only in water is the solubility poor. The thermodynamic data show that the variation of the aromatic donors shifts the complex stability in methanol over four orders of magnitude. Therefore, if one needs a complexone of distinct coordinating strength, the required compound is easily "tailored" by choice of the appropriate aromatic moiety. Besides, kinetic restrictions for the use of these complexones do not exist. Metal ion and complex equilibrate within less than 10^{-4} s. The noncyclic polyethers with aromatic end groups can substitute for the common cyclic complexones with respect to the use as ion lipophilizers in organic chemistry.[38]

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