Noncyclic Crown-Type Polyethers, Pyridinophane Cryptands, and Their Alkali Metal Ion Complexes: Synthesis, Complex Stability, and Kinetics[1]

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Abstract: Because of their possible relevance as model compounds of cation transport across membranes open chain "crown" ether molecules and pyridinophane cryptands have been synthesized in order to study their interaction with sodium and potassium ions. The stoichiometry and stability of the Na^+ and K^+ complexes were determined spectrophotometrically, and the kinetics of complex formation was investigated by temperature-jump experiments. The two linear quinoline polyether compounds examined possess two nonequivalent binding sites for alkali metal ions in methanol with stability constants between 10^3 and 10^4 M for K_1 and between 10^2 and 10^3 M for K_2. The recombination between metal ion and ligand is one order of magnitude slower than the diffusion-controlled process. This is due to a stepwise replacement of the solvation sphere of the metal ion by the chelating atoms of the multidentate complexone. The pyridinophane cryptand compounds "[2.2.1$_{Py}$]" and "[2.2.1$_{Py}$]diamide" form stable 1:1 complexes with Na^+ and K^+ in aqueous solutions. Two relaxation times were found for the binding process. The kinetic analysis revealed that after the nearly diffusion-controlled encounter and substitution step an isomerization process follows with a frequency of about 10^4 s^{-1}. The differences between the individual rate constants of the different complexes are discussed in terms of ligand structure and cation size. Since the compounds investigated meet the physicochemical requirements of a carrier molecule rather well, physiological experiments were carried out to study the influence of compound I and IV on the motoric frog nerve and on isolated heart cells from rats. In particular it was found that the pyridinophane amide cryptand (IV) strongly interferes with cellular processes of ion translocation.

Since Moore and Pressman[3] reported in 1964 that the antibiotic valinomycin induces the transport of potassium ions through the mitochondrial membrane by complexation, a series of other naturally occurring compounds has been discussed as potential carrier substances on artificial and biological membranes.[4] "Crown" ethers[5] and "cryptates",[6] first synthesized by Pedersen and Lehn, respectively, represent the class of synthetic compounds which is capable of binding alkali and alkaline earth metal ions. As these compounds promise applications in different areas of chemistry and biology,[4,5c,7] the thermodynamics[8] and kinetics[9] of ion complexation as well as the structures and conformational states of both the free ligand and its cation complexes[10] have been investigated by a number of different techniques. Since the elucidation of the mechanism of complex formation of alkali metal ions with synthetic model compounds provides a clue to the understanding of the naturally occurring membrane transport processes,[4,11] we have dealt with a new class of modified polyethers containing heteroaromatic residues.[12] The basic molecular frame of ordinary crown ether molecules consists of a ring of several oxygen atoms connected by ethylene groups. In our studies this main structural pattern was altered in order to study the influence of the following changes on the complexation behavior: After ring opening and subsequent addition of quinoline functions at the terminal oxygens[13] polyether molecules are formed which resemble the noncyclic nigericin antibiotics[14] with respect to their moleular flexibility;[15] on the other hand, the introduction of a pyridine moiety[16] into the polyether compound either by incorporation or by cross-linking makes the complexone more rigid.

In the present paper we report the synthesis and the main spectroscopic properties of linear quinoline crown-type polyethers I and II[17] and pyridinophane cryptands IV and V.[8j,18] The stability constants of several alkali metal ion complexes of these compounds were determined spectrophotometrically. Temperature-jump relaxation studies were performed to elucidate the mechanism of ion complexation. The combined analysis of thermodynamic and kinetic data allows a decision of whether the compounds studied meet the physicochemical requirements for a carrier substance.

Experimental Section

A. Synthetic Section.[19] Analytical and Spectral Data. Melting points were obtained using a "Kofler Mikroheiztisch, Reichert, Wien" and are uncorrected. Elementary analyses were performed by Alfred Bernhardt, Mikroanalytisches Laboratorium, West Germany, and the microanalytical section of the Institut für Organische und Anorganische Chemie Würzburg, West Germany. Infrared spectra (IR) were recorded on a Beckman IR-33 infrared spectrophotometer. Data are reported as follows: position of signal (cm^{-1}); shape of band and intensity, sh = sharp, br = broad, m = moderate, s = strong, ss = very strong; assignment. Nuclear magnetic resonance (NMR) spectra were obtained on a Varian (60 MHz) spectrometer. Chemical shifts are given in parts per million (ppm) upfield to Me_4Si in δ units and coupling constants in cycles per second (Hz). NMR data are reported as follows: chemical shift; multiplicity, s = singlet, m = multiplet, mc = centered multiplet; number of protons; coupling constants; assignment.

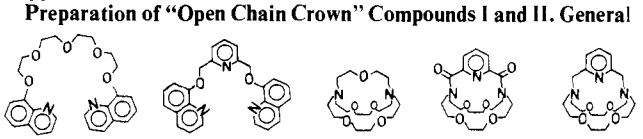
Materials. 1,11-Dibromo-3,6,9-trioxaundecane. This compound was prepared in 42% yield from 3,6,9-trioxa-1,11-undecanediol and PBr_3 (pyridine): colorless oil, bp 123–124 °C (0.2 Torr) [lit.[20] 161–165 °C (7 Torr)].

2,6-Bis(bromomethyl)pyridine was prepared by bromination (48% HBr) of 2,6-bis(hydroxymethyl)pyridine (Chem. Fabrik Weyl AG, D-6800 Mannheim) to give colorless needles (from petroleum ether 50–70: yield 90%, mp 86–89 °C (lit.[21] 62%, mp 84–89 °C).

1,7,10,16-Tetraoxa-4,13-diazacyclooctadecane ("Kryptofix 22") was obtained from Merck, D-6100 Darmstadt.

2,6-Pyridinedicarboxylic acid chloride from EGA-Chemie KG, Keppler + Reif, D-7924 Steinheim.

Preparation of "Open Chain Crown" Compounds I and II. General



(I) (II) (III) (IV) (V)

[2.2.1] [2.2.1$_{Py}$]diamide [2.2.1$_{Py}$]

Table I. Analytical Data and Properties of the Synthesized Complexes of I, II, IV, and V

Starting ligand	Complex with	Stoichiometry ligand/salt	Yield, %	Mp, °C	Anal data (C/H/N/S)[a]	
I	KSCN	1:1	85	154-155	C 59.42, 5.17, 7.70, 5.87	F 59.32, 5.46, 7.57, 5.88
I	NH_4SCN	1:1	63	135 dec	C 61.81, 6.15, 10.68, 6.11	F 61.48, 6.16, 10.54, 6.12
I	RbI	1:1	54	158-160	C 47.25, 4.27, 4.24, -	F 47.42, 4.13, 4.17, -
I	BaI_2	1:1	59	260 dec	C 37.19, 3.36, 3.23, -	F 36.88, 3.59, 3.28, -
I	$Pr(NO_3)_3$	2:3	39	252-253 dec	C 33.26, 3.00, 9.69, -	F 33.10, 3.34, 9.07, -
I	$Nd(NO_3)_3$	2:3	88	220 dec	C 33.08, 3.00, 9.64, -	F 33.29, 3.32, 9.06, -
II	NaSCN	1:1	93	257-258	C 65.81, 4.04, 11.80, 6.76	F 65.50, 4.32, 11.63, 6.76
II	KSCN	1:1	91	197-198	C 63.06, 3.90, 11.41, 6.65	F 63.14, 4.15, 11.16, 6.54
II	NH_4SCN	1:1 ($1H_2O$)	94	130-133	C 64.05, 5.16, 14.36, 6.58	F 64.22, 5.15, 14.36, 6.86
II	$AgNO_3$	1:1 ($2H_2O$)	96	150 dec	C 50.10, 3.87, 9.35, -[b]	F 50.44, 3.74, 9.45, -
II	ZnI_2	3:4 ($3H_2O$)	75	190 dec	C 35.87, 2.53, 5.02, -[c]	F 36.08, 2.76, 4.69, -
II	CdI_2	1:1 ($1H_2O$)	90	254-256	C 38.61, 2.72, 5.40, -	F 38.99, 2.67, 5.60, -
II	$Hg(SCN)_2$	1:1	57	181-182	C 45.66, 2.70, 9.86, 9.03	F 45.47, 2.66, 9.74, 9.10
II	$Fe(ClO_4)_2$	1:1 ($1H_2O$)	54	~180 dec	C 45.07, 3.18, 6.30, -	F 44.78, 3.45, 6.03, -
II	$Ni(ClO_4)_2$	1:1	52	~180 dec	C 46.12, 2.94, 6.45, -	F 45.73, 3.23, 6.11, -
II	$Co(SCN)_2$	1:1	89	240 dec	C 57.04, 3.37, 12.31, 11.28	F 57.35, 3.64, 12.12, 11.08
II	$UO_2(NO_3)_2$	1:1 ($1H_2O$)	70	127-130 dec	C 36.46, 2.82, 8.50, -	F 36.65, 3.04, 8.69, -
IV	$LiClO_4$	1:1	58	270 dec	C 45.63, 5.44, 8.40, -	F 45.63, 5.59, 8.40, -
V	$LiClO_4$	1:1	92	242-244	C 48.39, 6.62, 8.90, -	F 48.17, 6.79, 8.89, -
V	NaSCN	1:1	84	130-135	C 53.79, 7.00, 12.55, -	F 53.91, 7.03, 12.53, -
V	KSCN	1:1	44	134-136	C 51.92, 6.75, 12.11, -	F 51.40, 6.96, 12.02, -

[a] C = calcd, F = found. [b] Ag: calcd, 17.99; found, 17.80. [c] Zn: calcd, 10.41; found, 10.29.

Procedure. 1,11-Dibromo-3,6,9-trioxaundecane (8.00 g, 25 mmol) dissolved in 25 mL of ethanol or 6.62 g (25 mmol) of 2,6-bis(bromomethyl)pyridine dissolved in 100 mL of benzene was added dropwise within 30 min and under stirring to a refluxing solution of 7.27 g (50 mmol) of 8-hydroxyquinoline and 2.81 g of KOH (50 mmol) in 100 mL of ethanol. A colorless precipitate separated (KBr) and the solution became deep red. The mixture was refluxed for 3 h and was then allowed to cool to room temperature. After filtration of the precipitate the solvent was removed by distillation under vacuum, leaving a deep red colored, viscous oil which was taken up in chloroform. In order to separate unreacted 8-hydroxyquinoline, the mixture was extracted several times with dilute NaOH and washed with water. The organic layer was dried over Na_2SO_4 (desiccated) and concentrated by distillation under vacuum to a volume of 20 mL. Chromatography on alumina (Woelm, basic, activity 1) with chloroform gave the pure products.

I: yellowish viscous oil; yield 80%;[22] IR (film) 1580, 1525 (sh, s; quinoline), 1280 (s; CO_{aryl}), 1125 (ss; CO_{alkyl}); NMR ($CDCl_3$) δ 9.06-8.86 (m, 2 H, quinoline), 8.26-8.00 (m, 2 H, quinoline), 7.60-7.00 (m, 8 H, quinoline), 4.66-3.92 (m, sym; 8 H, OCH_2), 3.76 (mc, 8 H, OCH_2). Anal. Calcd for $C_{26}H_{28}N_2O_5$: C, 50.34; H, 3.78; N, 12.36. Found: C, 50.14; H, 3.17; N, 12.39. Picrate of compound I: mp 153-155 °C dec.

II: yellowish bulky crystals; yield 68%; mp 141-143 °C; IR (KBr) 1620, 1600, 1580, 1510 (s; quinoline, pyridine), 1270 (ss; CO_{aryl}), 1120 (ss; CO_{alkyl}); NMR ($CDCl_3$) δ 9.12-8.90 (m, 2 H, quinoline), 8.28-8.00 (m, 2 H, quinoline), 7.76-7.00 (m, 11 H; quinoline, pyridine), 5.64 (s, 4 H, CH_2-benzyl). Anal. Calcd for $C_{25}H_{19}N_3O_2$: C, 76.32; H, 4.87; N, 10.68. Found: C, 76.02; H, 5.05; N, 10.56. Picrate of compound II: yellow crystals, mp 184-186 °C.

Preparation of IV. Pyridine-2,6-dicarboxylic acid chloride (2.04 g, 10 mmol) in 250 mL of benzene and 5.25 g (20 mmol) of 1,7,10,16-tetraoxa-4,13-diazacyclooctadecane ("Kryptofix 22") in 250 mL of dry benzene were synchronously added to 1 L of dry benzene by means of precision dropping funnels within 9 h at 20 °C. The solution was stirred vigorously for an additional 2 h. The precipitate was then filtered off and the benzene solution evaporated at reduced pressure. The remaining oil was crystallized from acetone: 2.88 g (73% yield) of colorless crystals with mp 185-187 °C: IR (KBr) 1635 (s; C=O), 1133, 1124, 1110, 1098 (s; CO); NMR ($CDCl_3$) δ 2.66-5.12 (m; CH_2O, CH_2N), 8.94 (s, pyridine). Anal. Calcd for $C_{19}H_{27}N_3O_6$: C, 58.00; H, 6.91; N, 10.68. Found: C, 57.84; H, 6.99; N, 10.84.

Preparation of V. Boron trifluoride etherate (4.25 g, 30 mmol) in 20 mL of absolute THF was added dropwise to 1.11 g (30 mmol) of sodium borohydride in 20 mL of absolute THF. The mixture was heated at 50 °C for 30 min and the precipitated salt was filtered off by vacuum. At room temperature 1.00 g (2.54 mmol) of IV in 50 mL of absolute THF was added to the filtrate within 30 min. Then the mixture was heated under reflux for 4 h. H_2O (5 mL) was added to the cold solution and a colorless, voluminous precipitate separated. The solvent was removed under vacuum. The remainder was treated with 5 mL of concentrated HCl and 10 mL of H_2O, and the mixture was refluxed for 3 h. Neutralization was achieved using a basic ion-exchange column. The water was distilled off by means of 1-butanol, the remaining fair brown oil was dissolved in diethyl ether and dried with molecular sieve (3 Å). Recrystallization from diethyl ether yielded 290 mg (33%) of colorless platelets with mp 95-96 °C: IR (KBr) 1570 (m, pyridine), 1110 (ss, CO); NMR ($CDCl_3$) δ 2.75 (t, CH_2N), 2.49-2.60 (m, CH_2O), 2.73 (s, CH_2-benzyl), 6.93-7.03, 7.39, 7.45, 7.48, 7.63 (pyridine). Anal. Calcd for $C_{19}H_{31}N_3O_4$: C, 62.44; H, 8.55; N, 11.42. Found: C, 62.46; H, 8.42; N, 11.26.

Preparation of Crystalline Complexes of I, II, IV, and V. The following general procedure[23] allows the synthesis of stoichiometric crystalline complexes with alkali, alkaline earth, ammonium, and heavy metal salts, such as KSCN, NH_4SCN, NaSCN, RbI, BaI_2, $Ba(SCN)_2$, $Pr(NO_3)_3$, $Nd(NO_3)_3$, $AgNO_3$, ZnI_2, CdI_2, $Hg(SCN)_2$, $Fe(ClO_4)_2$, $Co(SCN)_2$, $Ni(ClO_4)_2$, and $UO_2(NO_3)_2$. Equimolar amounts (0.20 mmol) of the corresponding salt dissolved in 0.5 mL of methanol (RbI affords a volume of 5 mL) and of ligand I, II, IV, or V in 10 mL of ethyl acetate were combined with stirring and heating under mild reflux for 0.5 h. If a precipitate was not formed immediately, crystallization was induced by cooling the solution or by adding a few drops of petroleum ether (bp 50-70 °C), respectively.

The precipitates of the corresponding complexes were collected by filtration, washed with ethyl acetate, and dried under vacuum. Usually the complexes separate analytically pure; if not, the precipitate was dissolved in a small amount of methanol, the solution was heated, and ethyl acetate was added, until the solution became turbid.

Yields, physical properties, and analytical data of the isolated complexes are given in Table I; IR data are summarized in Table II.

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

All spectrophotometric measurements were performed using PMQ II, DMR 10, or DMR 22 (Zeiss). Stoichiometries and binding constants were obtained at 25 °C by measuring the absorbance changes due to complex formation.

UV spectra of the free ligands and their complexes were recorded in order to ascertain the optimum wavelength for the quantitative

Table II. Selected Infrared Data of the Complexes

Complex	IR, cm^{-1}	
	Signals due to the ligand skeleton	Signals due to the complexed salt
KSCN·I	1265 (s), 1100 (ss; CO), 950 (s)	2060 (sh, ss; SCN^-)
NH_4SCN·I	1265 (s), 1100 (ss; CO), 950 (m)	3200 (br; NH_4^+), 2070 (sh, ss; SCN^-)
RbI·I	1265 (m), 1100 (ss; CO), 950 (m)	*a*
BaI_2·I	1250 (m), 1090 (ss; CO), 950 (m)	*a*
$3Pr(NO_3)_3$·2I	1100 (m; CO)	1480, 1310 (br, ss; NO_3^-)
$3Nd(NO_3)_3$·2I	1090 (s; CO)	1480, 1300 (br, ss; NO_3^-)
NaSCN·II	1260 (s), 1105 (ss; CO)	2060 (ss; SCN^-)
KSCN·II	1260 (s), 1105 (ss; CO)	2060 (sh, ss; SCN^-)
NH_4SCN·II·$1H_2O$	1260 (m), 1110, 1100 (s; CO)	3500 (br; OH), 3200 (br; NH_4^+), 2060 (sh, ss; SCN^-)
$AgNO_3$·II·$2H_2O$	1265 (s), 1110 (s; CO)	3500 (br; OH), 1380 (br, ss; NO_3^-)
$4ZnI_2$·3II·$3H_2O$	1250 (s), 1125, 1110 (s; CO)	3500 (br; OH)
CdI_2·II·$1H_2O$	1265 (s), 1120 (ss; CO)	3480 (br; OH)
$Fe(ClO_4)_2$·II·$1H_2O$	1260 (m), 1120 (hidden; CO)	3420 (br; OH), 1140, 1120, 1080 (br, ss; ClO_4^-)
$Ni(ClO_4)_2$·II	1120 (hidden; CO)	1145, 1120, 1080 (br, ss; ClO_4^-)
$Co(SCN)_2$·II	1260 (m), 1120 (m; CO)	2080 (ss; SCN^-)
$UO_2(NO_3)_2$·II·$1H_2O$	1110 (s; CO)	3200 (br; OH), 1500, 1300 (br, ss; NO_3^-)
$LiClO_4$·IV	1640 (ss; C=O), 1120 (s; CO)	1090 (ss; ClO_4^-)
$LiClO_4$·V	1595, 1572 (m; aromatic), 1300 (s; CO)	1090 (ss; ClO_4^-)
NaSCN·V	1585, 1570 (m; aromatic), 1110 (s; CO)	2060 (s; SCN^-)
KSCN·V	1585, 1570 (w; aromatic), 1108 (s; CO)	2055 (s; SCN^-)

[a] No characteristic change in signal shape and position.

Table III. Concentrations of Complexones and Metal Ions Used in the Determination of K_{app}

Compd	Cation	Binding site	c_{ligand}, μM	$c_{Metal\ ion}$, mM
I	Na^+	1	50	0.1-2.0
		2	50	3.4-5.6
I	K^+	1	50	0.2-1.6
		2	50	6.0-10.0
I	Mg^{2+}	1	0.5	$(9.5\text{-}11.5) \times 10^{-3}$
		2	0.5	$(13.5\text{-}16.0) \times 10^{-3}$
		3	0.5	$(21\text{-}26) \times 10^{-3}$
		4	0.5	$(36\text{-}4.4) \times 10^{-3}$
II	Na^+	1, 2	9.8	0.07-0.80
II	K^+	1	9.8	0.1-4
		2	9.8	7-16
IV	Na^+	1	3.2	$(15\text{-}80) \times 10^{-3}$
	K^+	1	1.6	$(4\text{-}9) \times 10^{-3}$
V	Na^+	1	4.9	$(5\text{-}50) \times 10^{-3}$
	K^+	1	4.9	$(5\text{-}50) \times 10^{-3}$

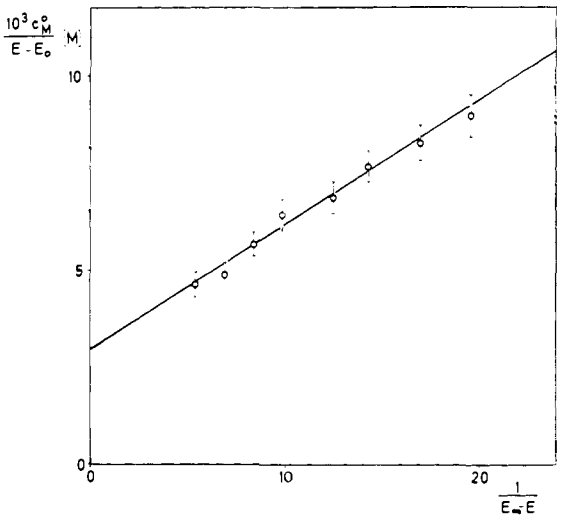


Figure 1. Determination of the stability constant K_{app} of the first binding site of compound I for K^+ in methanol. Double reciprocal plot according to eq 1. The concentration of the ligand was 5×10^{-5} M, the concentration of KCl was varied between 0.2×10^{-3} and 1.6×10^{-3} M (wavelength, 242 nm; thickness of layer, 1 cm; T = 25 °C).

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[24] 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 (average concentration: $c_L^0 = 2 \times 10^{-3}$ M). The metal ion was added in aliquots of $c_M = 0.1 c_L^0$.

The apparent stability constant, K_{app}, defined by $K_{app} = c_{LM}/(c_L c_M)$ was determined by linear regression analysis according to

$$\frac{c_M^0}{E - E_0} = \frac{c_L^0}{E_\infty - E_0} + \left(\frac{1}{K_{app}} \frac{1}{E_\infty - E}\right) \quad (1)$$

plotting $c_M^0/(E - E_0)$ vs. $1/(E_\infty - E)$;[25] c_M^0 and c_L^0 are the initial concentrations of ligand and metal ions, respectively, E is the extinction of the solution, E_0 and E_∞ are the extinctions of the complexone and its cation complex. The initial concentration of the ligand was at least one order of magnitude lower than the reciprocal stability constant K_{app}^{-1} for all compounds with more than one binding site: $c_L^0 < 0.1 c_{K_{app}^{-1}}$. The metal ion was added in excess: $c_M^0 \approx c_M$, $c_M^0 \gg c_L^0$ (Table III). In order to minimize titration errors, one solution was used for three measuring points only. An example for the determination of K_{app} is given in Figure 1, which represents the titration of the first binding site of compound I for potassium ions. The ionic strength never exceeded the value of 10^{-2} M. Up to these concentrations the Debye-Hückel limiting law is valid in aqueous and methanolic[26] solutions. Thermodynamic stability constants were evaluated using the product of activity coefficients.

Fast kinetic measurements were performed using a temperature-jump relaxation apparatus.[27] All measurements refer to a final temperature of 25 °C. Concentrations of free reactants which are needed for the evaluation of the kinetic parameters refer to this temperature. The wavelength for observation were 240 nm for the quinoline polyethers and 265 nm for the pyridinophane cryptands. The concentration of the reactants was varied between 1×10^{-5} and 5×10^{-4} M; under these conditions only the 1:1 binding equilibrium was affected to a measurable extent. Even for the system Na^+/ligand II with rather similar stability constants for the first and second binding site, sufficiently low concentrations of ligand and metal ion could be chosen such that the contribution of the second binding equilibrium to the relaxation process was negligibly small. The ionic strength was adjusted to 0.08 M by addition of $N(CH_3)_4OH$ for all systems involving

Table IV. Stability Constants and Rate Constants of Complexes of the Open-Chain Crown Ethers I and II in Methanol at 25 °C

Compd	Cation	Stoichiometry	Thermodynamic stability constants		Rate constants	
			$\log K_1$	$\log K_2$	k_{12}, M^{-1} s^{-1}	k_{21}, s^{-1}
I	Na^+	1:1; 1:2	3.22 ± 0.01	2.49 ± 0.01		
	K^+	1:1; 1:2	3.51 ± 0.02	2.14 ± 0.02	$(1.1 \pm 0.3) \times 10^8$	$(4 \pm 1) \times 10^3$
	Mg^{2+}	1:1; 1:2	4.99 ± 0.01	4.83 ± 0.01		
		1:3; 1:4	4.63 ± 0.01 ($\log K_3$)	4.40 ± 0.04 ($\log K_4$)		
II	Na^+	1:1; 1:2	3.92 ± 0.02	3.80 ± 0.02	$(4 \pm 1) \times 10^8$	$(2.5 \pm 0.4) \times 10^4$
	K^+	1:1; 1:2	2.75 ± 0.06	2.00 ± 0.01		

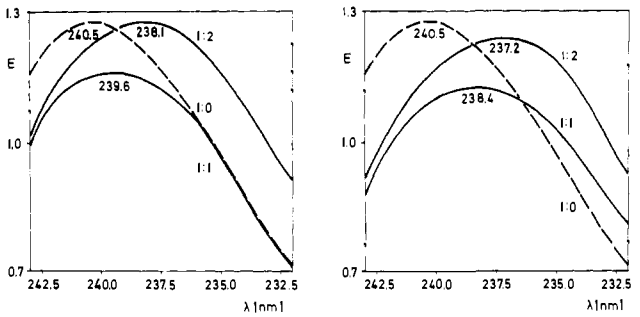


Figure 2. UV spectra of the absorption maxima of compound I and its sodium and potassium complexes in methanol at 25 °C. The concentration of the ligand was 5×10^{-5} M, the concentrations of the salt were 3×10^{-3} M for the 1:1 complex and 2×10^{-2} M for the 1:2 complex (thickness of layer, 1 cm): (a) left, the sodium complexes, isosbestic point 239.3 nm; (b) right, the potassium complexes, isosbestic points 236.4, 238.5 nm.

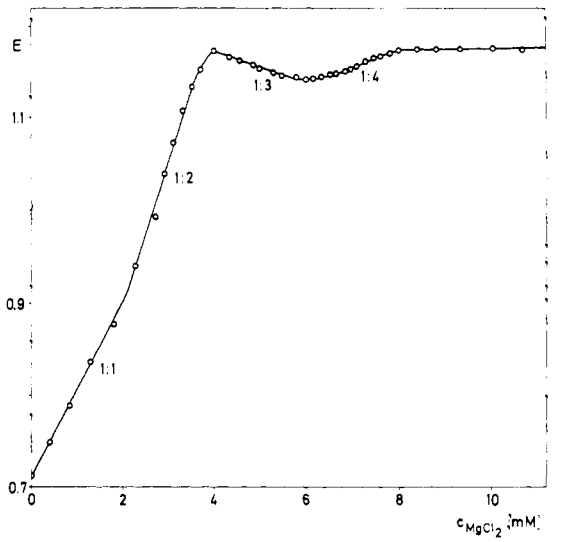


Figure 3. Stoichiometric titration of the binding sites of compound I for Mg^{2+} in methanol. The concentration was 2×10^{-3} M for the ligand plus amounts of the stock solution of 2×10^{-2} M $MgCl_2$ (wavelength, 345 nm; thickness of layer, 5 cm; T = 25 °C).

[2.2.1$_{Py}$] and $N(CH_3)_4Br$ for all the other systems investigated.

The numerical analysis of the oscilloscope traces was carried out using an analog simulation technique. The multiplier signal of a single temperature-jump experiment was stored in a digital transient recorder and displayed continuously by one beam of a double-beam oscilloscope. The second beam of the oscilloscope displayed the simulated time course calculated by an analog computer. The following expression for the time dependence of the intensity $I(t)$ of the signal was fitted to the experimental curves:

$$I(t) = A_I \exp(-t/\tau_I) + A_{II} \exp(-t/\tau_{II}) + Bt + C \qquad (2)$$

The exponentials describe two relaxation processes with the relaxation times τ_I and τ_{II} and the amplitudes A_I and A_{II}. The term Bt takes into account a small linear time dependence of the baseline due to cooling effects in the sample cell after the temperature jump, and the parameter C fits the time-independent part of the intensity. The individual rate constants were evaluated from the concentration dependence of the relaxation times using a weighted least-squares method in the case of a one-step mechanism and a weighted nonlinear least-squares method in case of a two-step mechanism. All digital computations were carried out on a Prime 300 computer. In the iteration procedure the following data were used: The initial metal ion and ligand concentrations, the stability constant, estimated values of k_{12}, k_{21}, and $k_{23} + k_{32}$, and the relaxation times τ_I and τ_{II} in the case of systems involving [2.2.1$_{Py}$], τ_{II} alone in the case of systems involving [2.2.1$_{Py}$]diamide. An extensive statistical analysis was carried out in order to show the confidence of the fitted data.[28]

Results and Discussion

A. Noncyclic Complexones. The complexation behavior of the open-chain crown compounds I and II in methanol with alkali and alkaline earth metal ions can be followed by absorption changes in the UV spectra. The stepwise binding of sodium as well as of potassium ions induces a bathochromic shift of the absorption maximum of the ligand and a decrease of its absorption coefficient (Figure 2). In methanol the 1:1 and 1:2 complexes of Na^+ and K^+ with the quinoline polyether I are of similar stability (Table IV). This independence of the stability constant upon the ionic radius as reflected by the relatively low discrimination factor $K_1^{Na^+}/K_1^{K^+} = 0.5$ is a consequence of the flexibility of the tetraethylene glycol chain, which can easily adapt itself to the different ions. On the other hand, the introduction of a heterocyclic pyridine bridge into the ether chain renders the ligand more rigid and results in a better discrimination of the cations by the ligand II ($K_1^{Na^+}/K_1^{K^+} = 12$).

In order to obtain more detailed information about the contributions of the 8-oxyquinoline residues to the complex formation, the magnesium ion functions as a valuable probe, since it it known that Mg^{2+} forms very stable chelates with 8-hydroxyquinoline,[29] whereas its tendency of complexation toward crown ethers containing only oxygens as heteroatoms is very weak.[8a,b] From the stoichiometric titration (Figure 3) it is evident that compound I possesses four binding sites for Mg^{2+} in methanol. The stability constants listed in Table IV show that the magnesium complexes with ligand I in methanol are considerably more stable than the corresponding alkali complexes. Also the UV spectra of the various complex species in Figure 4 show remarkable differences. Above 320 nm the 1:1 and 1:3 complexes absorb more strongly than the 1:2 and 1:4 complexes. At the maximum of the quinoline absorption at 305 nm, the absorbance of the 1:1 complex exceeds that of all the other species, whereas below 260 nm, where the oxygen of the ether absorbs, it is the 1:2 complex which shows the strongest absorption. In addition, positions and magnitudes of the absorption minima between 260 and 270 nm are different. From these observations it can be concluded that the four binding sites of compound I for Mg^{2+} are not equivalent and that the conformation of the polyether molecule itself is changed upon complexation. For a more detailed elucidation of the structures of the different cation complexes NMR studies are in preparation.

Table V. Stability Constants and Rate Constants for Complexes of the Pyridinophane Cryptands IV and V in Water at 25 °C

Compd	Cation	Thermodynamic stability constant log K	Rate constants			
			k_{12}, M^{-1} s^{-1}	k_{21}, s^{-1}	k_{23}, s^{-1}	k_{32}, s^{-1}
IV	Na^+	4.58 ± 0.03	(3 ± 0.5) × 10^8	(1.5 ± 0.5) × 10^4	(1.4 ± 0.3) × 10^4	(1.4 ± 0.3) × 10^4
	K^+	5.25 ± 0.02	(5 ± 0.5) × 10^8	(3 ± 0.5) × 10^3	(5 ± 2) × 10^3	(1.8 ± 0.3) × 10^4
V	Na^+	4.89 ± 0.03				
	K^+	4.78 ± 0.03	(3 ± 0.5) × 10^8	(7 ± 2) × 10^3	(8 ± 2) × 10^3	(2 ± 0.5) × 10^4

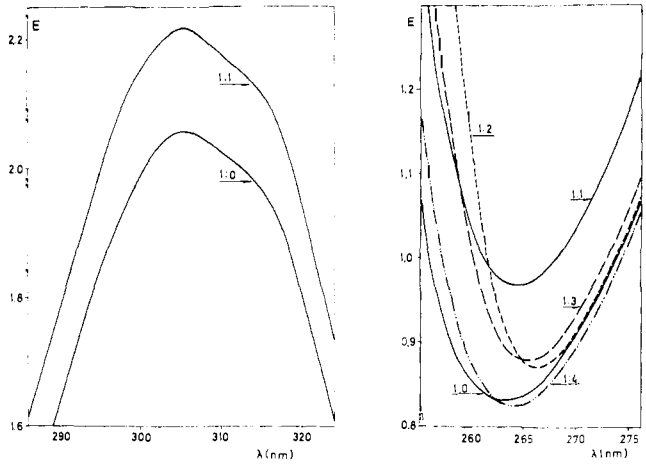


Figure 4. UV spectra of compound I and its Mg^{2+} complexes. The concentration was 1 × 10^{-3} M for the ligand plus stoichiometric amounts of Mg^{2+} (T = 25 °C; thickness of layer, 1 cm; solvent, CH_3OH): (a) absorption maximum of the quinoline moiety; (b) absorption minima between 260 and 270 nm.

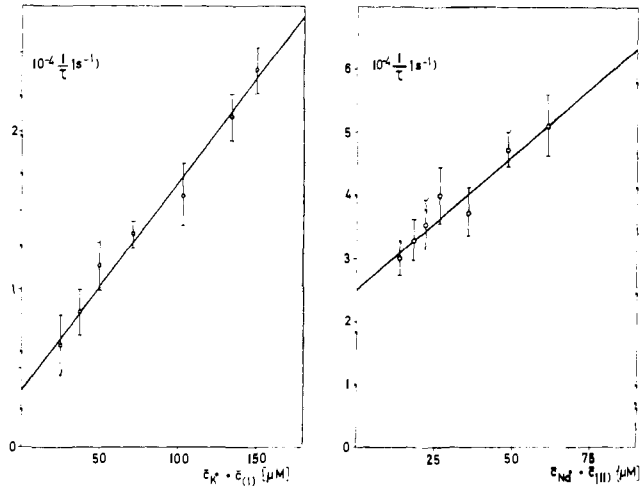


Figure 5. Dependence of the reciprocal relaxation time on the sum of the concentrations of the free reactants for the binding of the first K^+ ion to ligand I and of the first Na^+ ion to ligand II. The error bars of the individual points for $1/\tau$ indicate the experimental error obtained for approximately five temperature jumps with the same solution.

The kinetics of complex formation of potassium ions with compound I and of sodium ions with compound II in methanol were studied by temperature-jump relaxation experiments. Similar experiments on the complexation of K^+ with ligand II and Na^+ with ligand I could not be carried out, since due to the lower stability of these complexes the concentrations of the reactants had to be selected such that the relaxation times were always faster than the resolution of the instrument. Both systems studied exhibit one concentration-dependent relaxation process in the time range between 10^{-4} and 10^{-5} s. For a bimolecular reaction mechanism

$$M^+ + L \underset{k_{21}}{\overset{k_{12}}{\rightleftharpoons}} (LM)^+ \qquad (3)$$

the reciprocal relaxation time is given by

$$1/\tau = k_{12}(\overline{c_L} + \overline{c_M}) + k_{21} \qquad (4)$$

The plots of $1/\tau$ vs. $(\overline{c_M} + \overline{c_L})$ (Figure 5) reveal that the measured data are compatible with the proposed mechanism. The numerical values of the rate constants are listed in Table IV.

The values of the rate constants k_{12} for the recombination between Na^+ and ligand II, and K^+ and ligand I with 4 × 10^8 M^{-1} s^{-1} and 1 × 10^8 M^{-1} s^{-1} are relatively high; they are, however, more than one order of magnitude lower than the value of 5 × 10^9 M^{-1} s^{-1} expected for a diffusion-controlled recombination of alkali ions with uncharged ligands in methanol.[26a] The reduced rate 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 multidentate complexone. In order to account for the high overall rates every single substitution process has to occur with time constants of the order of 10^9 s^{-1}. Values of this order of magnitude have been reported for recombination of alkaline ions with simple chelating agents as NTA and EDTA.[30] The results on the open-chain ligands agree well with similar studies on various macrotetrolide systems reported by Eigen and Winkler.[26a,31]

B. Pyridinophane Cryptands. The pyridinophane ligands IV and V are analogues of the "[2.2.1]" cryptate III.[6] Introducing the pyridine moiety into the cryptand restricts the mobility of the diaza polyether ring by fixation of the bridgehead nitrogens. Nevertheless, their complexes with sodium and potassium ions in aqueous solution are of similar stability as the corresponding complexes with the more flexible [2.2.1] cryptate[6c] (Table V), whereas the degree of selectivity is less pronounced. At a first glance it seems to be surprising that the larger potassium ion is more strongly bound by the diamide than by the less rigid diamine, whereas the affinity of the sodium ion to both ligands stays almost the same. This apparent inconsistency can be elucidated by kinetic studies. UV spectra of [2.2.1$_{Py}$] and its 1:1 complex with K^+ are presented in Figure 6. We examined the kinetic behavior of the Na^+ and K^+ complexes of [2.2.1$_{Py}$] and of [2.2.1$_{Py}$]diamide in aqueous solutions. In all four systems investigated two relaxation processes were observed within the time range of 10^{-4}–10^{-5} s.

In the case of the amide systems the faster relaxation time τ_I was not measurable any more at higher concentrations of reactants because of the insufficient time resolution of the instrument. In the same concentration range, the slower relaxation time $1/\tau_{II}$ levels off in all systems (Figure 7). The finding of two relaxation times and the typical saturation behavior of $1/\tau_{II}$ suggests at least a two-step mechanism for the complex formation. The most simple mechanism consistent with the data is the following one:

$$M + L \underset{k_{21}}{\overset{k_{12}}{\rightleftharpoons}} ((ML)^+)' \underset{k_{32}}{\overset{k_{23}}{\rightleftharpoons}} ((ML)^+)'' \qquad (5)$$

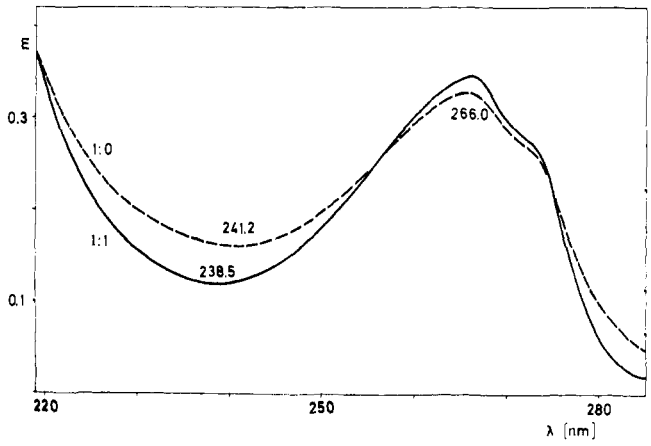


Figure 6. UV spectra of [2.2.1$_{Py}$] and its K^+ complex in aqueous solutions of 1×10^{-2} M $N(CH_3)_4OH$ at 25 °C ($c_{[2.2.1_{Py}]} = 9 \times 10^{-5}$ M, $c_{K^+} = 1 \times 10^{-3}$ M; thickness of layer, 1 cm; isosbestic points, 256, 276 nm).

The expression for both relaxation times are[27a,32]

$$\frac{1}{\tau_{1,2}} = -\frac{(\alpha_{11} + \alpha_{22})}{2}\left[1 \mp \sqrt{1 - \frac{4(\alpha_{11}\alpha_{22} - \alpha_{12}\alpha_{21})}{(\alpha_{11} + \alpha_{22})^2}}\right] \quad (6)$$

with $\alpha_{11} = -k_{12}(c_L + c_M)$, $\alpha_{12} = k_{21}$, $\alpha_{21} = k_{12}(c_L + c_M) - k_{32}$, and $\alpha_{22} = -(k_{21} + k_{23} + k_{32})$. The rate constants for the $K^+/[2.2.1_{Py}]$ interaction were evaluated by fitting them to the data of the relaxation times $1/\tau_1$ and $1/\tau_2$ by the computer method mentioned above. In case of the system $Na^+/[2.2.1_{Py}]$ it was not reasonable to carry out an extended numerical analysis because of the unfavorably small amplitudes of the relaxation processes.

For the systems involving [2.2.1$_{Py}$]diamide the rate constants were calculated using only the data of the slower relaxation time $1/\tau_{II}$ (for further details cf. Riesner et al.[28]). With these values the graph $1/\tau_I$ vs. c_f was simulated. The coincidence of the measured data and of the simulated $1/\tau_I$ plot, which was observed for both systems, demonstrates the validity of the iteration process and the consistency of the data with the proposed mechanism.

In Figure 7 the reciprocal relaxation times obtained for the different systems are plotted vs. the sum of the free concentrations of ligand and metal ion. The rate constants are summarized in Table V.

All corresponding rate constants of the cryptate complexes are of the same order of magnitude, suggesting basically the same molecular mechanism for the formation of the three complexes investigated. The first step of the mechanism includes the diffusion-controlled recombination of the reactants and the stepwise substitution of the water molecules of the inner hydration sphere by the cryptand. This conclusion follows from the values of the rate constants of recombination, which are at least one order of magnitude smaller than those for a diffusion-controlled process (v.s.). The overall rate of the complex formation is determined by structural changes of the ligand, which occur with a frequency of about 10^4 s^{-1}, succeeding the combined encounter and substitution step. This slowing down of the overall reaction rate by four orders of magnitude can be attributed either to the adjustment of the ether oxygens into the interior of the ligand toward the incorporated metal ion by rotations around the C-C bonds or to a shift of the exo-endo equilibrium of the ligand toward the endo conformations.[6] Due to steric restrictions this structural change can become rather slow.

From the comparison of the rate constants k_{23} and k_{32} (Table V) it turns out that the intermediate state $[(LM)^+]'$ is equally or slightly more occupied than the final state; this result is probably a consequence of the rigid aromatic bridge which renders the ligand less flexible and makes the adaptation to the metal ion more difficult as compared to the [2.2.1]cryptate.

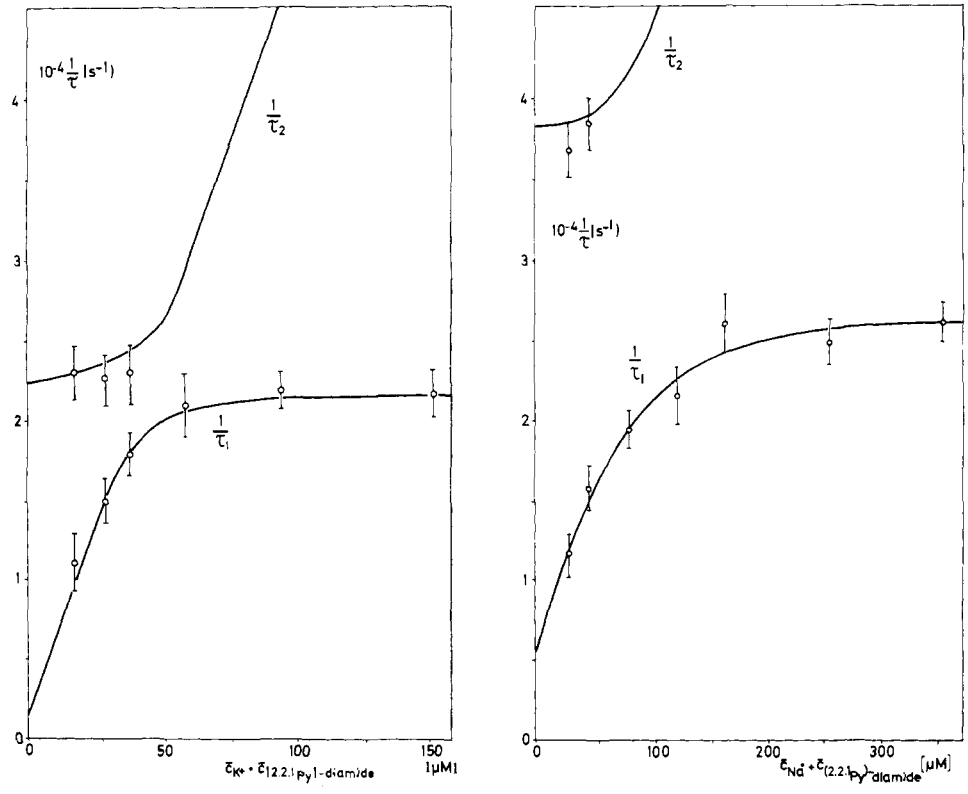


Figure 7. Dependence of the reciprocal relaxation times on the sum of the concentrations of the free reactants for the binding of K^+ and Na^+ to pyridinophane cryptand (**IV**). Individual points for $1/\tau_1$ and $1/\tau_2$ are derived from temperature-jump experiments. The drawn lines represent the best fit for $1/\tau_1$ and $1/\tau_2$ using the rate constants given in Table V.

In case of the potassium complex of [2.2.1$_{Py}$]diamide the steric hindrance introduced by the aromatic bridge is such that only 30% of the complex exists in the final state $[(LM)^+]''$, i.e., in the actual "cryptate conformation"; whereas the sodium complex isomerizes somewhat more easily into the final state ($k_{23}^{Na^+} > k_{23}^{K^+}$). As was pointed out earlier, the potassium complex of the [2.2.1$_{Py}$]diamide is more stable than the sodium complex. Comparing the individual rate constants of the corresponding reactions steps, the difference in the stability of the two complexes is particularly exhibited in the dissociation rate of the first step (k_{21}) with all the other rate constants staying very similar. The kinetic analysis shows that the intermediate state is more favored for the larger potassium ion than for the sodium ion. Although the structure of $[(LM)^+]'$ cannot be fully explained, the differences between the two rate constants k_{21} may be due to various degrees of desolvation of the two metal ions; in addition electrostatic interactions between the positively charged ion and the polarized bonds of the carbonyl residues may contribute to a different extent to the stability of the intermediate state. These arguments are supported by comparing the complexation behavior of potassium with the amide and amine ligands, respectively. The diamine [2.2.1$_{Py}$] has no electronegative carbonyl oxygens at the surface of the molecule. Therefore, the association rate (k_{12}) to the intermediate state decreases, the dissociation rate (k_{21}) increases. Since [2.2.1$_{Py}$] is more flexible than [2.2.1$_{Py}$]diamide and possesses moreover two nucleophilic nitrogens, the final conformation $[(ML)^+]''$ should be favored. Indeed, the rate constant k_{23} is slightly increased as compared to the diamide.

The high rate of complex formation $k_{on} \approx k_{12}k_{23}/(k_{21} + k_{23}) \approx 10^8\ M^{-1}\ s^{-1}$ as well as the two-step mechanism reflecting an ion binding step and a consecutive conformational change meet the kinetic requirements of complex formation postulated by Eigen and his co-workers[26a,30a,31,33] for a carrier molecule very well. After the very fast substitution of the water molecules, which are bound in the inner hydration sphere of the metal ion, the coordination atoms of the chelate are rearranged in order to allow the optimum fit to the encaged metal ion. The high rate of complex formation characterizes the time needed for the acceptance of a metal ion by the carrier. The rate constant of dissociation $k_{off} \approx k_{21}k_{32}/(k_{21} + k_{23}) \approx 10^4\ s^{-1}$ determines the time of delivery of the metal ion after passing the membrane. The value of 10^{-4} s for the dissociation is of the order of the fastest ion transport processes observed on motoric axon membranes.[34] If the stability of the complexes was too high, the rate of dissociation would be reduced to a value unacceptable for a carrier molecule, as in the case of the "original cryptates", which despite their ability of ion transport through apolar media[35] are less suitable as carrier models because of their low rates of dissociation ($k_{off} \approx 30\ s^{-1}$).[9b]

Physiological Addendum.[36] Since the ligands investigated may have potential carrier activities, their influence on ion translocation processes across biological membranes was checked by incubating exitable tissues with quinoline polyether or pyridinophane cryptand solutions. The concentration range used was $0.1-10 \times 10^{-6}$ g of complexone/mL of medium. The following alterations in membrane excitability and energy metabolism were found: the bis(8-quinolinyl)tetraethylene glycol ether (I) hyperpolarizes the motoric frog nerve[37] and reduces the beating frequency of isolated heart cells[38] (negative chronotropic effect). Whereas the quinoline polyether is reversibly bound at the cell surface, the cryptand molecule [2.2.1$_{Py}$]diamide (IV) is incorporated. This complexone facilitates depolarization of the nerve axon. Keeping in mind that the contraction of a muscle cell represents an ATP requiring process, the incubation of heart cells with the amide cryptate yielded an unexpected result: after the compound has been taken up, the beating frequency increases (positive chronotropic effect), and simultaneously, after an initial phase of higher ATP levels, the ATP consumption decreases by 50% below the values found for untreated heart cells.

According to the results presented in this paper, it can be concluded that the quinoline polyether I forms alkali ion complexes of poor selectivity. The on and off rates of $1 \times 10^8\ M^{-1}\ s^{-1}$ and $5 \times 10^{-3}\ s^{-1}$, respectively, meet the kinetic demands for a carrier molecule; however, the positive charges of the quinoline nitrogens prevent permeation of the lipophilic membrane. Although bound at the cell surface, the quinoline polyether represents no carrier molecule.

On the other hand the amide cryptate IV is a well-suited model compound for a biological carrier: almost uncharged at physiological pH, the molecule is incorporated by the cell membrane, forming complexes with sodium and potassium ions of comparably high stability. Exchange of ions at the cell surface depends on relative concentrations of sodium and potassium ions: in the interior of the cell potassium ions are present in the complexed form, whereas in the exterior of the cell the same holds for the sodium ions.

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(37) 8-Hydroxyquinoline alone induces a small depolarization.
(38) Heart cells of 1- to 2-day old Wistar rats were isolated by trypsination as described by Harary and Farley (*Exp. Cell Res.*, **29**, 451 (1963)). Cell culturing was performed in a modified nutrient medium SM 20 (W. Halle and A. Wollenberger, *Am. J. Cardiol.*, **25**, 292 (1970)).

A Quantitative Study of the Photostimulated Reaction of Iodobenzene with Diethyl Phosphite Ion[1]

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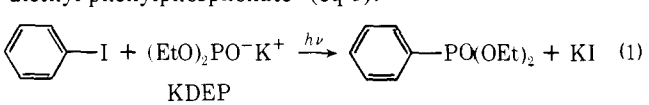
Abstract: The photostimulated reaction of iodobenzene with potassium diethyl phosphite (KDEP) in Me_2SO solution to form diethyl phenylphosphonate occurs with raw quantum yields at 313 nm considerably in excess of unity, frequently 20-50. Reaction rate is proportional approximately to the 0.84 power of light intensity. The dependence of quantum yield on KDEP concentration may be interpreted either on the basis that the photons absorbed by iodobenzene or the photons absorbed by a charge-transfer complex of iodobenzene with diethyl phosphite ion are responsible for initiation. Each of these alternatives is compatible with a different initiation mechanism. The quantum yield under conditions such that all the light is absorbed is independent of iodobenzene concentration. These facts are consistent with a radical chain mechanism with initiation as in steps 8 and 9, 8 and 10, or according to Scheme II, propagation according to Scheme I, and termination mainly via step 16 or 17 with a minor contribution from step 18.

In liquid ammonia solution, iodobenzene undergoes facile photostimulated reaction with diethyl phosphite ion to form diethyl phenylphosphonate[2] (eq 1).



(1)

This reaction is one of a family of photostimulated nucleophilic substitution reactions of unsubstituted phenyl halides and related substrates. Other nucleophiles that behave similarly are arenethiolate ions,[3] ketone enolate ions,[4,5] picolyl anions,[6] and the enolate ion of *tert*-butyl acetate.[7]

All these reactions are believed to occur by the $S_{RN}1$ mechanism. This mechanism, which involves radical and radical anion intermediates and electron transfer steps, was first proposed for certain nucleophilic substitutions at saturated carbon by Kornblum[8] and Russell[9] and their associates. Kim and Bunnett[10] recognized it as a mechanism of aromatic substitution in 1970, and proposed the symbol $S_{RN}1$. The propagation steps of the mechanism are represented, for the reaction of present interest, in Scheme I.

Scheme I

$$[PhI]^- \cdot \xrightarrow{k_2} Ph \cdot + I^- \quad (2)$$

$$Ph \cdot + (EtO)_2PO^- \xrightarrow{k_3} [PhPO(OEt)_2]^- \cdot \quad (3)$$

$$[PhPO(OEt)_2]^- \cdot + PhI \xrightarrow{k_4} PhPO(OEt)_2 + [PhI]^- \cdot \quad (4)$$

A radical chain mechanism also must have initiation and termination steps, - but for the $S_{RN}1$ mechanism there has been little evidence as to what they are. For light-stimulated reactions, initiation has usually been represented as a photostimulated electron transfer from nucleophile to substrate, either in a charge-transfer complex or by photoejection and then electron recapture.[2-6] In that case the substrate radical anion would enter the propagation cycle at step 2. An alternative possibility is initiation by photolysis of the C-I bond,[11,12] forming phenyl radical which enters the cycle at step 3.

A quantitative study of the reaction of iodobenzene with diethyl phosphite ion was undertaken for the purpose of getting