Cation Complexing Properties of Synthetic Macrocyclic Polyether–Diester Ligands Containing the Pyridine Subcyclic Unit

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Abstract: Ten new macrocyclic polyether-diester compounds containing a pyridine subcyclic unit substituted in the 4 position with chloro or methoxy groups have been prepared. These compounds along with their unsubstituted pyridine analogues form strong complexes with alkylammonium and some metal cations. Complexation with alkylammonium and potassium cations was accompanied by significant chemical-shift changes in the ^{1}H NMR spectra. Relative free energies of activation ($\Delta G^{\ddagger}$) for the dissociation of the alkylammonium complexes were determined from their temperature-dependent ^{1}H NMR spectra. Complexes of the methoxy-substituted ligands with all the alkylammonium ions studied had a greater $\Delta G^{\ddagger}$ than those of the chloro-substituted ligands. Formation constants as well as ΔH and $T\Delta S$ values were determined by a calorimetric technique for the reaction of Na^+, K^+, Rb^+, Ag^+, NH_4^+, and Ba^{2+} with the ligands of 18 ring members containing pyridine and 4-chloropyridine subcyclic groups. The complexes formed between the alkali metal cations and these ligands were almost as stable as those formed with 18-crown-6 and pyridino-18-crown-6 (**1**). The pyridino ligands were also found to be effective carriers of Ag^+ across a $CHCl_3$ liquid membrane separating aqueous phases.

Introduction

There has been much interest in synthetic macrocyclic polyethers in recent years because of their ability to selectively complex both metal[2] and organic ammonium[3,4] cations. Various modifications have been made to the basic crown ether structure in an attempt to enhance the selectivity of these ligands and the stabilities of complexes formed. Among these modifications are the substitution of ligand donor atoms such as sulfur and nitrogen for one or several of the polyether oxygens and the inclusion of ester linkages in the polyether ring. In this paper we report the synthesis and complexation properties of several new macrocyclic polyether-diester compounds containing the pyridine nitrogen donor atom (compounds **2–15,** Figure 1).

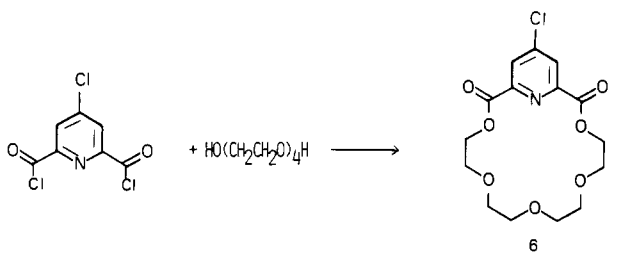
The evaluation of pyridine nitrogen as a macrocyclic donor atom is desirable for at least two reasons. First, Cram and co-workers have shown that crown ligand **1**, which incorporates a pyridine subcyclic unit, forms complexes with alkylammonium cations which are more stable thermodynamically than those formed with 18-crown-6.[4] Since ammonium ion binds to 18-crown-6 by hydrogen bonding to alternate donor atoms,[5] it was postulated that the pyridine nitrogen of **1** forms a stronger hydrogen bond with the ammonium hydrogen than does an ether oxygen. Such macrocylic ammonium ion complexes are currently being studied as models for enzyme–substrate binding[6-11] and use of pyridine nitrogen donor atoms could increase the strength of this binding. Second, we have shown[12] that incorporation of the pyridine nitrogen atom into the ring of macrocyclic polyether–diester compound **16** to form **2** restores metal cation complex stability lost upon inclusion of the ester groups into 18-crown-6.

Macrocylic ligands containing pyridine nitrogen groups have not been studied extensively because the incorporation of pyridine groups into unsubstituted crown rings (e.g., compound **1**) is difficult synthetically. However, the preparation of macrocyclic polyether-diester compounds containing a pyridine subcyclic unit is relatively simple.[12,13] Compound **2**, for example, was prepared in 78% yield from readily available starting materials.[13] The ease of their preparation coupled with the potentially high stabilities of their alkylammonium and metal cation complexes makes these compounds excellent candidates as binding sites in synthetic enzymatic receptor molecules and as ligands for the many applications for metal cation complexation.[2,14,15]

Preliminary publications[12,16] have compared the metal cation complexation of compound **2** with pyridino polyether **1,** 18-crown-6, and macrocyclic diester compounds **16**[17] and **17**.[16] A preliminary report of the temperature-dependent ^{1}H NMR spectral study of the complexation of the new pyridino diester ligands has also been published.[18] We here report the details of these studies. Also included are the results of metal cation transport studies using chloroform membranes containing compounds **2, 6, 7, 10,** and **13** as carriers. These studies illustrate the relative effectiveness of these ligands as membrane carriers compared to parent crown ether ligands.

Results and Discussion

Preparation of Ligands. The substituted pyridino ligands were prepared by reacting the appropriately substituted 2,6-pyridinedicarbonyl chloride with the appropriate glycol.[13] For example, compound **6** was prepared from 4-chloro-2,6-



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pyridinedicarbonyl chloride and tetra(ethylene glycol). As can be seen in Table I, the yields of the new 4-substituted compounds were very good for all compounds except the 15-membered rings. These results are more remarkable when one considers that the starting materials either can be purchased or are readily prepared. Table I also lists other macrocyclic compounds containing the pyridine subcyclic unit.

The preparation of 4-chloro-2,6-pyridinedicarbonyl chloride was done in one step from the commercially available 4-oxo-1,4-dihydro-2,6-pyridinedicarboxylic acid (chelidamic acid) using 3 equiv of phosphorus pentachloride; however, an attempt to isolate the product at this point gave a very low yield. The desired diacid chloride was obtained in much higher yield

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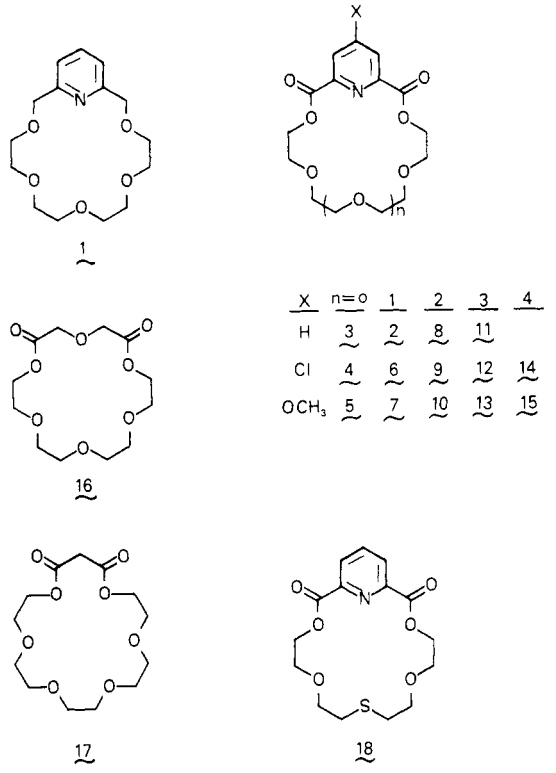
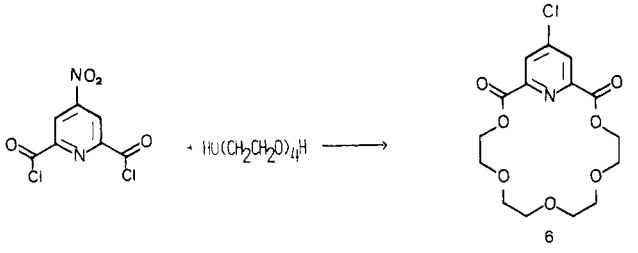


Figure 1. Structural formulas for compounds **1–18**.

by the three-step sequence given in the Experimental Section. We desired to prepare macrocyclic compounds substituted on the pyridine ring with a variety of groups for further complexation studies. Several attempts to convert the 18-membered 4-chloropyridino macrocyclic compound (**6**) to other 4-substituted macrocyclic derivatives in a manner similar to that described[20] for diethyl 4-chloro-2,6-pyridinedicarboxylate were unsuccessful. Thus, it was necessary to convert the starting 4-chloro-2,6-pyridinecarboxylic acid to other 4-substituted analogues. Macrocyclic compounds **5, 7, 10, 13,** and **15** were readily prepared from the 4-methoxy-2,6-pyridinedicarbonyl chloride. However, when the 4-nitro diacid chloride was reacted with tetra(ethylene glycol), the 4-chloro macrocyclic compound **6** was isolated. The chloride ion liberated in

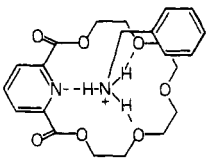


the reaction replaced the 4-nitro group. The fact that the nitro group was not replaced when 4-nitro-2,6-pyridinedicarbonyl chloride was prepared from the diacid using thionyl chloride but was replaced during the cyclization step gives support to the supposition that the good yields observed for these cyclization reactions are due to a template effect.[13] The proton liberated during the reaction with the first carbonyl chloride becomes weakly bonded to the pyridine nitrogen and is probably the template which causes the second hydroxy group to be in the correct position for cyclization. The subsequent complexation of the proton by the macrocyclic ring would increase the reactivity of the chloride ion and would allow the substitution of chloride for the nitro group that we observed. Others have observed a considerable amount of dissolved acid in the crude product of **2.** This acid can be removed by sublimation, repeated recrystallization, or drying under vacuum.[21]

The structural formulas proposed for the macrocyclic compounds are consistent with data derived from infrared (IR) and proton nuclear magnetic resonance (^{1}H NMR) spectra (Table II), combustion analyses and molecular weight determinations. The aromatic portion of the ^{1}H NMR spectra of the 4-chloro and 4-methoxy compounds exhibited the expected signals at δ 8.31 ± 0.03 and 7.80 ± 0.06, respectively. The remainder of the ^{1}H NMR signals were as reported for the unsubstituted pyridine macrocyclic compounds:[13] δ 4.55 ± 0.08 ($COOCH_2$), 3.84 ± 0.06 ($COOCH_2CH_2$), and 3.70 ± 0.10 (OCH_2). The ^{1}H NMR signals for the various complexes of these compounds are also listed in Table II.

Complexation Studies. The cation complexation properties of the pyridino macrocyclic diester compounds have been studied using temperature-dependent ^{1}H NMR spectroscopy, calorimetry, and membrane transport of metal cations. These studies will be discussed under separate headings.

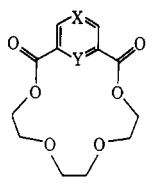
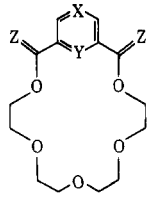
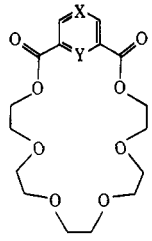
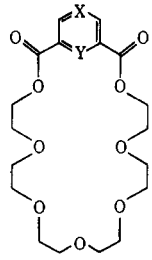
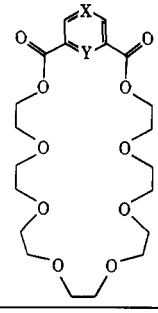
Temperature-Dependent ^{1}H NMR Spectroscopy. Formation of complexes by these compounds with primary alkylammonium cations in an equimolar mixture of the two reactants in methylene-d_2 chloride was observed for all ligands except the 15-membered rings (**3–5**). Complexation for the other ligands was accompanied by significant chemical-shift changes in the ^{1}H NMR spectra (see Table II). For example, the singlet at δ 3.67 ± 0.01 attributable to ether methylene hydrogens for the 18-membered rings (**2, 6,** and **7**) separated into two multiplets of four hydrogens each for all the complexes. These chemical-shift changes, however, were different for the different types of alkylammonium ions. For the benzylammonium perchlorate complexes of **2, 6,** and **7,** one set of signals attributable to the ether methylene hydrogens was shifted upfield (δ 3.67 to 3.55) and the other set downfield (to δ 3.77). The ^{1}H NMR signals for the aromatic hydrogens were also shifted downfield. All ^{1}H NMR signals for the complexes of **2, 6,** and **7** with isopropyl- and *tert*-butylammonium perchlorates were shifted downfield. Thus the upfield shift of one set of ^{1}H NMR signals shows that the complexes of **2, 6,** and **7** with the benzylammonium ion are unusual. Laidler and Stoddart have also shown that other benzylammonium ion complexes are unusual.[8,9] We believe that the ammonium ion is hydrogen bonded to the pyridine nitrogen and to two ether oxygens and that the benzene ring of the benzylammonium ion is over the ether methylene hydrogens in the center of the metacyclophane chain as illustrated below. The benzene ring current could then



cause the observed upfield shift of the methylene hydrogen signal in the ^{1}H NMR. No complexes were observed with dialkylammonium cations.

The temperature dependencies of the ^{1}H NMR spectra for the complexes of the 18- and 21-membered-ring compounds (**2, 6–10** and **18**) with benzyl-, *tert*-butyl-, isopropyl-, and β-phenylethylammonium perchlorates and benzylammonium thiocyanates have been examined (Table III). In every case, the ^{1}H NMR signal attributable to the ester methylene hydrogens (δ 4.55 ± 0.08) separated into a doublet and a multiplet of equal intensities at low temperature (Table III). These signals can be attributed to the hydrogens on one side of the complex (see illustration above) vs. those on the other side when the exchange rate has become slow at low temperatures. The low-temperature peak separations were 136–260 Hz for the 18-membered rings and 43–64 Hz for the 21-membered rings. The complexes for the larger compounds (**11–14**) formed

Table I. A Comparison of the Physical Properties of the Macrocyclic Polyether-Diester Ligands with a Pyridine Subcyclic Unit

	compd	substituents	yield, %	mp, °C	ref
	**3**	X = CH; Y = N	9.6	139-140	*a*
		X = N; Y = CH	1	137-137.5	*a*
	4	X = CCl; Y = N	8.8	126-127	*b*
	5	X = $COCH_3$; Y = N	1	154-154.5	*b*
	**2**	X = CH; Y = N; Z = O	70-78	86.5-87.5	*a, c*
	1	X = CH; Y = N; Z = H_2	29	40-41	*d*
		X = N; Y = CH; Z = O	32.7	112-113	*a*
	6	X = CCl; Y = N; Z = O	91	104-105	*b*
	7	X = $COCH_3$; Y = N; Z = O	54.2	116-117	*b*
	**8**	X = CH; Y = N	24.7	143-144.5	*a*
		X = N; Y = CH	6.9	54.5-55.5	*a*
	9	X = CCl; Y = N	72.3	70-71	*b*
	10	X = $COCH_3$; Y = N	18.5	122-123	*b*
	**11**	X = CH; Y = N	28.5	110-111	*a*
		X = N; Y = CH	7.5	50-51	*a*
	12	X = CCl; Y = N	37.7	65-66	*b*
	13	X = $COCH_3$; Y = N	42.9	72-73	*b*
	**14**	X = CCl; Y = N	45	52-53	*b*
	15	X = $COCH_3$; Y = N	36.5	oil	*b*

[a] Reference 13. [b] This work. [c] Reference 19. [d] Reference 4.

but no separation of the ^1H NMR signals was observed at −100 °C. Only broadening of the ^1H NMR signals was observed for all uncomplexed macrocyclic compounds at low temperatures.

Calculation of kinetic parameters for the formation of the complexes was done using eq 1[22] and 2:

$$k_c = \pi \Delta \nu / 2 \qquad (1)$$

where k_c = exchange rate at coalescent temperature (T_c) and $\Delta\nu$ = ^1H NMR peak separation,

$$\frac{-\Delta G^{\ddagger}_c}{RT_c} = \ln \frac{k_c h}{kT_c} \qquad \text{(Eyring equation)} \qquad (2)$$

where $\Delta G^{\ddagger}_c$ = free energy of activation, h = Planck constant, k = Boltzmann constant, and R = molar gas constant. The observed $\Delta\nu$ and T_c values as well as the calculated k_c and $\Delta G^{\ddagger}_c$ values are shown in Table III. The $\Delta G^{\ddagger}_c$ values where the molar ratio of crown to salt, C:S, is 1:1 can be equated to the free energy of activation ($\Delta G^{\ddagger}_{d+ri}$) for an equilibration of the ammonium salt from one face of the ligand to the other face with both dissociative and ring-inversion components.[8,10,11,23] In solutions where C:S = 2:1, the measured $\Delta G^{\ddagger}_c$ probably involves an equilibration between complexed and uncomplexed ligands and thus can be equated to the free energy of activation of dissociation, $\Delta G^{\ddagger}_d$. The differences in the free-energy values ($\Delta G^{\ddagger}_{d+ri} - \Delta G^{\ddagger}_d$) for the benzylammonium perchlorate complexes of **2, 6,** and **7** (0.7, 0.5, and 1.2, respectively) are similiar to those reported for other systems of restricted rotation[11] but are much less than those reported for less sterically hindered crown compounds.[10] This result is as expected since the pyridine moiety greatly restricts the rotational degrees of freedom for the rest of the macrocyclic ring.

For every salt system studied, the values of $\Delta G^{\ddagger}_c$ for the complexes gave the order OCH_3 > H > Cl for the substituents

Table II. ^{1}H NMR Data for Compounds **2–15** and **18** and Their Alkylammonium and Potassium Cation Complexes[a]

compd	OCH_2	$COOCH_2CH_2$	$COOCH_2$	aromatic	remarks
3	4.02 (s, 4)	3.91 (m, 4)	4.47 (m, 4)	7.91–8.31 (m, 3)	ref 13; no complexes formed
4	4.03 (s, 4)	3.94 (m, 4)	4.50 (m, 4)	8.28 (s, 2)	no complexes formed
5	4.05 (s, 4)	3.94 (m, 4)	4.47 (m, 4)	7.74 (s, 2)	OCH_3 at 4.01; no complexes formed
2	3.68 (s, 8)	3.78 (m, 4)	4.53 (m, 4)	8.02 (t, 1), 8.28 (d, 2)	
		Complex with **2**			
$C_6H_5CH_2NH_3ClO_4$	3.52 (m, 4), 3.77 (m, 4)	3.84 (m, 4)	4.52 (m, 4)	8.21 (t, 1), 8.43 (d, 2)	
$C_6H_5CH_2NH_3SCN$	3.58 (m, 4), 3.82 (m, 4)	3.89 (m, 4)	4.57 (m, 4)	8.25 (t, 1), 8.46 (d, 2)	
i-$C_3H_7NH_3ClO_4$	3.73 (m, 4), 3.83 (m, 4)	3.92 (m, 4)	4.72 (m, 4)	8.27 (t, 1), 8.52 (d, 2)	
t-$C_4H_9NH_3ClO_4$	3.75 (m, 4), 3.87 (m, 4)	3.96 (m, 4)	4.68 (m, 4)	8.28 (t, 1), 8.59 (d, 2)	
$C_6H_5CH_2CH_2NH_3ClO_4$	3.71 (m, 4), 3.76 (m, 4)	3.85 (m, 4)	4.64 (m, 4)	8.13 (t, 1), 8.37 (d, 2)	
KSCN	3.80 (s, 8)	3.90 (m, 4)	4.76 (m, 4)	8.1–8.6 (m, 3)	
6	3.67 (s, 8)	3.79 (m, 4)	4.54 (m, 4)	8.29 (s, 2)	
		Complex with **6**			
$C_6H_5CH_2NH_3ClO_4$	3.53 (m, 4), 3.77 (m, 4)	3.84 (m, 4)	4.54 (m, 4)	8.42 (s, 2)	
$C_6H_5CH_2NH_3SCN$	3.57 (m, 4), 3.77 (m, 4)	3.85 (m, 4)	4.54 (m, 4)	8.39 (s, 2)	
i-$C_3H_7NH_3ClO_4$	3.73 (m, 4), 3.83 (m, 4)	3.92 (m, 4)	4.72 (m, 4)	8.47 (s, 2)	
t-$C_4H_9NH_3ClO_4$	3.76 (m, 4), 3.88 (m, 4)	3.96 (m, 4)	4.68 (m, 4)	8.48 (s, 2)	
$C_6H_5CH_2CH_2NH_3ClO_4$	3.71 (m, 4), 3.77 (m, 4)	3.85 (m, 4)	4.65 (m, 4)	8.34 (s, 2)	
KSCN	3.81 (s, 8)	3.92 (m, 4)	4.76 (m, 4)	8.47 (s, 2)	
NaSCN	3.80 (s, 8)	3.96 (m, 4)	4.72 (m, 4)	8.45 (s, 2)	
$AgNO_3$	3.80 (s, 8)	3.90 (m, 4)	4.68 (m, 4)	8.45 (s, 2)	
7	3.68 (s, 8)	3.78 (m, 4)	4.53 (m, 4)	7.82 (s, 2)	OCH_3 at 3.97
		Complex with **7**			
$C_6H_5CH_2NH_3ClO_4$	3.53 (m, 4), 3.77 (m, 4)	3.83 (m, 4)	4.48 (m, 4)	7.93 (s, 2)	OCH_3 at 4.05
$C_6H_5CH_2NH_3SCN$	3.57 (m, 4), 3.77 (m, 4)	3.84 (m, 4)	4.52 (m, 4)	7.94 (s, 2)	OCH_3 at 4.04
i-$C_3H_7NH_3ClO_4$	3.73 (m, 4), 3.82 (m, 4)	3.90 (m, 4)	4.68 (m, 4)	7.97 (s, 2)	OCH_3 at 4.06
t-$C_4H_9NH_3ClO_4$	3.75 (m, 4), 3.88 (m, 4)	3.96 (m, 4)	4.67 (m, 4)	7.99 (s, 2)	OCH_3 at 4.07
$C_6H_5CH_2CH_2NH_3ClO_4$	3.68 (m, 4), 3.73 (m, 4)	3.82 (m, 4)	4.58 (m, 4)	7.84 (s, 2)	OCH_3 at 3.99
KSCN	3.83 (s, 8)	3.95 (m, 4)	4.75 (m, 4)	7.95 (s, 2)	OCH_3 at 4.05
8	3.57 (s, 4), 3.65 (m, 8)	3.83 (m, 4)	4.54 (m, 4)	8.00 (t, 1), 8.29 (d, 2)	
		Complex with **8**			
$C_6H_5CH_2NH_3ClO_4$	3.66 (s, 4), 3.71 (m, 4), 3.75 (m, 4)	3.85 (m, 4)	4.47 (m, 4)	8.11 (t, 1), 8.37 (d, 2)	
t-$C_4H_9NH_3ClO_4$	3.62 (s, 4), 3.73 (m, 4), 3.77 (m, 4)	3.89 (m,4)	4.70 (m, 4)	8.10 (t, 1), 8.44 (d, 2)	
9	3.57 (s, 4), 3.64 (m, 8)	3.83 (m, 4)	4.56 (m, 4)	8.30 (s, 2)	
		Complex with **9**			
$C_6H_5CH_2NH_3ClO_4$	3.65 (s, 4), 3.70 (m, 4), 3.76 (m, 4)	3.85 (m, 4)	4.48 (m, 4)	8.33 (s, 2)	
t-$C_4H_9NH_3ClO_4$	3.58 (s, 4), 3.67 (m, 4), 3.73 (m, 4)	3.88 (m, 4)	4.69 (m, 4)	8.39 (s, 2)	
10	3.58 (s, 4), 3.66 (m, 8)	3.83 (m, 4)	4.53 (m, 4)	7.81 (s, 2)	OCH_3 at 3.96
		Complex with **10**			
$C_6H_5CH_2NH_3ClO_4$	3.65 (s, 4), 3.68 (m, 4), 3.75 (m, 4)	3.83 (m, 4)	4.47 (m, 4)	7.85 (s, 2)	OCH_3 at 4.01
t-$C_4H_9NH_3ClO_4$	3.61 (s, 4), 3.69 (m, 4), 3.76 (m, 4)	3.88 (m, 4)	4.66 (m, 4)	7.91 (s, 2)	OCH_3 at 4.02
11	3.48 (m, 4), 3.53 (m, 4), 3.63 (m, 8)	3.85 (m, 4)	4.55 (m, 4)	8.00 (t, 1), 8.28 (d, 2)	
		Complex with **11**			
$C_6H_5CH_2NH_3ClO_4$	3.52 (m, 8), 3.61 (m, 4), 3.69 (m, 4)	3.84 (m, 4)	4.55 (m, 4)	8.09 (t, 1), 8.33 (d, 1)	
t-$C_4H_9NH_3ClO_4$	3.61 (s, 8), 3.64 (m, 4), 3.72 (m, 4)	3.90 (m, 4)	4.70 (m, 4	8.17 (t, 1), 8.42 (d, 1)	
12	3.63 (s, 8 H), 3.76 (s, 8 H)	3.95 (m, 4)	4.63 (m, 4)	8.33 (s, 2)	
13	3.46 (m, 4), 3.48 (m, 4), 3.57 (m, 4), 3.62 (m, 4)	3.79 (m, 4)	4.46 (m, 4)	7.72 (s, 2)	OCH_3 at 3.91
		Complex with **13**			
$C_6H_5CH_2NH_3ClO_4$	3.46 (s, 8), 3.54 (m, 4), 3.63 (m, 4)	3.84 (m, 4)	4.47 (m, 4)	7.77 (s, 2)	OCH_3 at 3.94
14	3.52 (m, 12); 3.61 (m, 4), 3.65 (m, 4)	3.84 (m, 4)	4.54 (m, 4)	8.26 (s, 2)	

Table II (*Continued*)

compd	OCH_2	$COOCH_2CH_2$	$COOCH_2$	aromatic	remarks
		Complex with **14**			
$C_6H_5CH_2NH_3ClO_4$	3.58 (m, 16), 3.68 (m, 4)	3.82 (m, 4)	4.52 (m, 4)	8.28 (s, 2)	
15	3.59–3.76 (m, 20)	3.93 (m, 4)	4.60 (m, 4)	7.81 (s, 1)	OCH_3 at 4.03
18	2.82 (t, 4), (SCH_2)				
	3.76 (t, 4)	3.83 (m, 4)	4.52 (m, 4)	8.01 (t, 1), 8.29 (d, 2)	
		Complex with **18**			
$C_6H_5CH_2NH_3ClO_4$	2.86 (t, 4) (SCH_2),				
	3.81 (m, 4)	3.83 (m, 4)	4.42 (m, 4)	8.20 (t, 1), 8.43 (d, 2)	

[a] Spectra were recorded in CD_2Cl_2 at 220 MHz on a Perkin-Elmer R34 spectrometer except for the metal salts and for compounds **3–5, 12,** and **15,** which were recorded in $CDCl_3$ at 90 MHz on a Varian EM390 spectrometer. The numbers are parts per million using Me_4Si as internal standard.

Table III. Temperature-Dependent ^1H NMR Spectral Data and Kinetic Parameters for the Complexation of Primary Alkylammonium Salts with Compounds **2, 6–10,** and **18**[a]

ratio C:S	RNH_3X R	X	compd	temp dependent ^1H NMR signals, δ	T_c, °C (±3)	$\Delta\nu$ (°C) (±2 Hz)	k_c, s^{-1}	$\Delta G^{\ddagger}_c$ kcal/mol
1:1	$C_6H_5CH_2$	ClO_4	**2**	5.12 (d), 4.04 (m)	+10	260 (−60)	577	13.0
			6	5.07 (d), 4.01 (m)	0	233 (−50)	518	12.5
			7	5.03 (d), 3.97 (m)	+25	233 (−45)	547	13.7
			8	4.58 (d), 4.38 (m)	−30	44 (−70)	98	11.6
			9	4.61 (d), 4.33 (m)	−25	57 (−70)	137	12.0
			10	4.56 (d), 4.34 (m)	−15	48 (−60)	108	12.6
			18	4.92 (d), 4.20 (m)	−30	158 (−80)	352	11.3
				3.00 (m), 2.76 (m)	−40	53 (−80)	117	11.3
1:1	$C_6H_5CH_2$	SCN	**2**	5.10 (d), 4.02 (m)	−40	237 (−55)	528	10.6
			6	5.13 (d), 4.01 (m)	−55	247 (−90)	577	9.7
			7	5.10 (d), 4.00 (m)	−30	242 (−80)	567	11.1
1:1	t-C_4H_9	ClO_4	**2**	5.03 (d), 4.39 (t)	−20	141 (−90)	361	11.8
			6	5.02 (d), 4.41 (t)	−30	134 (−70)	332	11.3
			7	4.95 (d), 4.37 (t)	−10	128 (−60)	303	12.3
			8	4.83 (m), 4.61 (m)	−85	48 (−105)	108	9.1
			9	4.82 (m), 4.63 (m)	−90	42 (−105)	93	8.9
			10	4.82 (m), 4.53 (m)	−75	64 (−105)	142	9.5
1:1	i-C_3H_7	ClO_4	**2**	5.21 (d), 4.33 (m)	−10	194 (−70)	430	12.2
			6	5.21 (d), 4.33 (m)	−20	194 (−60)	430	11.7
			7	5.17 (d), 4.28 (m)	−10	196 (−60)	435	12.2
1:1	$C_6H_5CH_2CH_2$	ClO_4	**2**	5.17 (d), 4.32 (m)	−10	187 (−80)	415	12.2
			6	5.17 (d), 4.36 (m)	−10	178 (−80)	396	12.2
			7	5.13 (d), 4.27 (m)	+10	189 (−60)	420	13.2
2:1	$C_6H_5CH_2$	ClO_4	**2**	5.10 (d), 4.02 (m)	−5	238 (−50)	528	12.3
			6	5.12 (d), 4.03 (m)	−10	240 (−60)	557	12.0
			7	5.06 (d), 4.00 (m)	0	233 (−50)	518	12.5

[a] All spectra were recorded at 220 MHz on a Perkin-Elmer R34 spectrometer; ^1H NMR probe was $COOCH_2$ except for compound **18,** where the top figures are for $COOCH_2$ and the bottom are for SCH_2. T_c = coalescence temperature; $\Delta\nu$ = frequency separation for the ^1H NMR probe; k_c = exchange rate constant at T_c (eq 1); $\Delta G^{\ddagger}_c$ = free energy of activation at T_c (eq 2).

on the pyridine moiety (see Table III). This order parallels the basicity of the 4-substituted pyridines where $OCH_3 > H > Cl$.[24] These results clearly indicate that the alkylammonium salt is complexed through a hydrogen bond to the pyridine nitrogen. A similar kinetic stability order for the complexation of aryldiazonium salts by compounds **8–10** was observed by Bartsch and co-workers[25] and investigated by Izatt et al.[26] The data in Table III also shows that the 18-membered ring compounds (**2, 6,** and **7**) form more stable complexes than the compounds with 21-membered rings (**8–10**). Complexes were formed between primary alkylammonium ions and the larger ring compounds (**11–15**) but the $\Delta G^{\ddagger}_c$ values must be less than 8 kcal/mol since a separation of the ^1H NMR signals was not observed at −100 °C. The data for the complexation of benzylammonium perchlorate with a sulfur-containing pyridino polyether diester compound (**18**) are also included in Table III. This compound exhibited a decrease in complex kinetic stability due to a destabilizing effect of the ring sulfur atom.

It is instructive to note that the complexes with benzylammonium perchlorate are more stable kinetically than those with aliphatic ammonium salts. As was mentioned above, enhanced stability for several benzylammonium–crown complexes has also been observed by Laidler and Stoddart.[8,9] They attributed the added kinetic stability to a dipole–induced dipole between the benzene ring and the ligand. They also suggest that the decrease in kinetic stability for the thiocyanate vs. perchlorate (13.0 vs. 10.6 kcal/mol) complexes (see Table III) is a result of the fact that thiocyanate ions are more efficient at "destructuring" the complexes than are the perchlorate ions.[9]

Calorimetry. Table IV lists the results of a titration calorimetric study of the reaction in methanol of **2** and **6** with several inorganic cations. For comparison purposes, the corresponding results for 18-crown-6, **1,** and **16** are listed. Unfortunately neither **7** nor any of the larger ring compounds **8–10** were sufficiently soluble in methanol to allow determination of complexation data.

As noted earlier,[12] substitution of a pyridine nitrogen for an oxygen in 18-crown-6 does not greatly alter the stabilities of

Table IV. Log K, ΔH (kcal/mol), and $T\Delta S$ (kcal/mol) Values for the Interaction of Several Macrocyclic Ligands with Metal Ions in Methanol at 25 °C and $\mu = 0.005$

ligand	value	Na^+	K^+	Rb^+	Ba^{2+}	Ag^+	NH_4^+
2	log K	4.29	4.66	4.24	4.34	4.88	2.93
	ΔH	−6.19	−9.3	−9.07	−6.03	−7.83	−7.75
	$T\Delta S$	−0.34	3.0	−3.3	−0.11	−1.17	−3.8
6	log K	4.14 ± 0.07	4.73 ± 0.08	3.56 ± 0.09	*a*	3.76 ± 0.02	2.86 ± 0.03
	ΔH	−6.03 ± 0.18	−7.97 ± 0.23	−9.23 ± 0.27		−8.04 ± 0.08	−6.78 ± 0.16
	$T\Delta S$	−0.4	−1.5	−4.4		−2.9	−2.9
1	log K	4.09	5.35	4.56	>5.5	>5.5	
	ΔH	−5.44	−9.11	−8.72	−7.72	−8.33	
	$T\Delta S$	0.14	−1.81	−2.50			
18-C-6[b]	log K	4.36	6.06	5.32	7.04	4.58	4.27
	ΔH	−8.36	−13.41	−12.09	−10.41	−9.15	−9.27
	$T\Delta S$	−2.41	−5.14	−4.83	−0.80	−2.90	−3.44
16	log K	2.50	2.79	2.09	3.13	2.50	*c*
	ΔH	−2.27	−5.87	−6.99	−0.4	−1.53	
	$T\Delta S$	1.14	−2.06	−4.14	3.87	1.88	

[a] Ligand decomposition occurred. [b] 18-C-6 = 18-crown-6. [c] No measurable heat other than heats of dilution indicating that ΔH and/or log K are very small.

Table V. Rate[a] of Transport of Various Metal Nitrate Salts (mol/24 h × 10^7) through a Chloroform Membrane Containing 10^{-3} M Ligand

ligand	Li	Na	K	Rb	Cs	Mg	Ca	Sr	Ba	Ag
2	*b*	2.7 ± 0.2	93 ± 11	31 ± 3	1.8 ± 0.5	*b*	1.07 ± 0.17	15 ± 5	*b*	312 ± 26
6		1.6 ± 0.3	71 ± 7	16 ± 3	*b*		*b*	5.8 ± 1.0	*b*	330 ± 60
7	*b*	3.9 ± 0.5	156 ± 46	21 ± 1	2.6 ± 1.0	*b*	2.5 ± 0.5	91 ± 1	3.3 ± 0.3	462 ± 43
10		3.9 ± 0.3	23 ± 4	62 ± 8	42 ± 14	*b*	*b*	*b*	13.6 ± 0.3	770 ± 23
13		8 ± 2	6 ± 2	8 ± 2	111 ± 18	*b*	*b*	*b*	5.2 ± 3.0	366 ± 99
18-C-6	*b*	11.3 ± 0.6	277 ± 30	214 ± 40	67 ± 12	*b*	26.3 ± 1.3	316 ± 22	60 ± 17	223 ± 74
16		*b*	*b*	*b*			*b*	*b*	*b*	*b*

[a] Reported as average of three independent determinations and standard deviations from the average. [b] Measured transport rate corresponds to that of "blank" experiment with no ligand in the membrane (<1 × 10^{-7} mol/24 h).

the complexes of Na^+, K^+, or Rb^+ (compare **1** and 18-crown-6). In contrast, substitution of a pyridine moiety in **16** to give **2** greatly enhances the stabilities of cation complexes (see Table IV). Addition of a chlorine atom to compound **2** to give **6** does not significantly alter the stabilities of the complexes of Na^+, K^+, or NH_4^+ in methanol. However, the Rb^+ and Ag^+ complexes are significantly destabilized. This destabilizing effect by the addition of the 4-chloro group is consistent with the stability order H > Cl reported above from the ^1H NMR experiments. The decreased basicity of the pyridine nitrogen atom resulting from the presence of the 4-chloro group is apparently too small to greatly affect the stabilities of any complexes except that of Ag^+. Thus we conclude that the nitrogen atom plays a more significant role in the binding of Ag^+ by the macrocycle than in binding the other cations studied. This observation is consistent with the known preference of Ag^+ for nitrogen rather than oxygen donor atoms.[27]

Decomposition of compound **6** in the presence of Ba^{2+} (and Sr^{2+}, not listed in Table IV) was noted from the calorimetric studies. This decomposition was followed in deuterated methanol by changes in the ^1H NMR spectrum over a period of 2 days. No decomposition was noted for the K^+ complex of **6** or for the Ba^{2+} complex of **2.** It is likely that the electron-withdrawing effect of the 4-chloro group coupled with the strong polarizing effect of the divalent cations caused a great increase in the rate of transesterification of the ester linkages in **6.**

Membrane Transport. We have measured the transport rate of several cations through a chloroform membrane[28] which contained one of several of the ligands studied and which separates two aqueous phases. The results are found in Table V. Among the three analogous ligands **2, 6,** and **7,** the transport rates of the cations Na^+, K^+, Cs^+, Ca^{2+}, and Sr^{2+} decreased in the order $OCH_3 > H > Cl$ (**7** > **2** > **6**). This observation is consistent with the stability order for organic ammonium ions described above and follows the trend expected based on the basicity of 4-substituted pyridine.[24] It is interesting that this electronic effect altered the rates of transport of these cations through a chloroform membrane such that measurable differences exist between results for the chloro compound **6** and those for unsubstituted compound **2** (Table V) even though the binding constants for these two ligands were very similar (Table IV). This difference for the substituent effects may reflect the different solvents, methanol and chloroform, used in these experiments. Solvation effects in the more polar solvent, methanol, are apparently large enough to overwhelm the small differences in the binding energy terms caused by chloro substitution in the pyridine ring. In both experiments, where a nonpolar solvent was used, membrane transport (chloroform) and ^1H NMR (methylene chloride), the electronic effect of the substituents on the pyridine ring was apparent. The cation Rb^+ did not follow the expected trend ($OCH_3 > H > Cl$) in transport experiments. This cation is too large to enter the cavity of crown-6 ligands and for this reason may not feel those electronic effects in the same way as the other cations studied.

Consistent with the increase in ligand size, ligands **7, 10,** and **13** show transport selectivity for K^+, Rb^+, and Cs^+, respectively. The transport selectivity of **13** for Cs^+ over Rb^+ is unusually high. Table V shows that in general the pyridino diester ligands are not as effective in transporting cations as 18-crown-6. However, they are much more effective than the analogous ligand **16** which does not contain the pyridine moiety.

The pyridino ligands were more effective as carriers of Ag^+ than was 18-crown-6 probably because of the stronger binding

of Ag^+ by the pyridine nitrogen. Again, the methoxy ligand **7** transported Ag^+ faster than did **2** or **6**, the transport rates of which were not significantly different from one another. The larger rings, **10** and **13**, were as effective in transporting Ag^+ as the 18-membered rings **2**, **6**, and **7**.

Experimental Section

All infrared (IR) spectra were obtained on a Perkin-Elmer Model 457 spectrophotometer. The proton nuclear magnetic resonance (^1H NMR) spectra were obtained on a Varian EM-390 spectrophotometer in deuteriochloroform or on a Perkin-Elmer R-34 spectrometer in methylene-d_2 chloride using tetramethylsilane as an internal standard and are reported in Table II. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn., or M-H-W Laboratories, Phoenix, Ariz. The molecular weight determinations were by osmometry on a Hitachi Perkin-Elmer 115 molecular weight apparatus. Melting points were determined on a Thomas-Hoover capillary-type melting-point apparatus and are uncorrected.

Starting Materials. The starting materials were either purchased (tri(ethylene glycol) (Baker), tetra(ethylene glycol) (Aldrich), penta(ethylene glycol) (Columbia), and chelidamic acid (Aldrich)) or prepared in our laboratory (hexa(ethylene glycol),[29] hepta(ethylene glycol),[29] and the diacid chlorides as indicated below).

4-Chloro-2,6-pyridinedicarbonyl chloride was prepared by refluxing a mixture of chelidamic acid (100 g, 0.5 mol) and phosphorus pentachloride (418 g, 2.0 mol) in chloroform for 72 h. The resulting acid chloride could not be purified at this point, so it was hydrolyzed by adding it to cold water. The crude diacid was collected on a filter and washed several times with ice-cold water to remove the phosphoric acid. The resulting crude 4-chloro-2,6-pyridinedicarboxylic acid was refluxed with an excess of thionyl chloride and a few drops of dimethylformamide. After the excess thionyl chloride was removed under vacuum, the crude acid chloride was recrystallized from hexane, 70 g (59%), mp 96–98 °C (lit. 97–98 °C).[30] The acid chloride was sublimed at 95 °C (1 mm) immediately before use in the preparation of each macrocyclic compound.

4-Methoxy-2,6-pyridinedicarbonyl chloride was prepared in a manner similar to that reported by Markees and Kidder.[31] 4-Chloro-2,6-pyridinedicarbonyl chloride from the reaction of phosphorus pentachloride was converted to the dimethyl ester with anhydrous methanol and methoxylated with sodium methoxide. The resulting dimethyl 4-methoxy-2,6-pyridinedicarboxylate was hydrolyzed and then treated with excess thionyl chloride in dimethylformamide. Recrystallization from hexane gave the 4-methoxy diacid chloride, 51 g (44%), mp 99–100 °C (lit. 97–99 °C).[31]

4-Nitro-2,6-pyridinedicarboxylic acid was prepared by treating the crude 4-chlorodicarboxylic acid as prepared above with aqueous ammonia (28.7% NH_3) in a bomb at 150 °C for 24 h. The resulting 4-amino-2,6-pyridinedicarboxylic acid (60 g, 0.33 mol) was dissolved in 100 mL of concentrated sulfuric acid and slowly added to a solution of 175 mL of 30% hydrogen peroxide and 350 mL of fuming sulfuric acid at 10 °C. After stirring for several hours at 10 °C, the reaction mixture was allowed to come to room temperature and stir for 2 days. The reaction mixture was carefully diluted to 1 L keeping the temperature below 25 °C. The light yellow 4-nitro-2,6-pyridinedicarboxylic acid precipitated upon dilution and was collected on a filter and dried to yield 48 g (69%). A small sample was recrystallized from water, mp 206 °C dec, ^1H NMR (TFA) δ 9.32 (s, 2 H).

Anal. Calcd for $C_7H_4N_2O_6 \cdot H_2O$: C, 36.53; H, 2.62. Found: C, 36.77; H, 2.48.

4-Nitro-2,6-pyridinedicarbonyl chloride was prepared by treating the 4-nitro-2,6-pyridinedicarboxylic acid (35 g, 0.165 mol) with an excess of $SOCl_2$ containing a few drops of dimethylformamide until a clear solution was obtained. Upon removal of the excess $SOCl_2$, a yellow powder was obtained (25 g, 61%). Recrystallization of the diacid chloride from hexane gave light yellow crystals, mp 127–128.5 °C, ^1H NMR δ 9.07 (s, 2 H, aromatic H).

General Procedure for the Preparation of Macrocyclic Compounds. The appropriate diacid chloride and glycol, each dissolved in 200 mL of benzene unless otherwise specified, were simultaneously dripped from separate addition funnels into 1 L of rapidly stirring benzene. The reaction mixture was allowed to stir for at least 2 days at approximately 50 °C unless otherwise specified. After the reaction was complete, the solvent was removed under reduced pressure. The resulting viscous residue was extracted with hot hexane in a liquid–liquid extractor wherein the viscous liquid residue was heated. Specific details concerning the further purification of each product are given below.

16-Chloro-3,6,9,12-tetraoxa-18-azabicyclo[12.3.1]octadeca-1(18),14,16-triene-2,13-dione (4). 4-Chloro-2,6-pyridinedicarbonyl chloride (15.05 g, 0.063 mol) and tri(ethylene glycol) (9.48 g, 0.063 mol) were used. After extraction, the product (1.76 g, 8.8%) was further purified by sublimation at 150 °C (1 mm) and recrystallization from methanol to give white needles, mp 126–127 °C, IR (KBr) 1725 cm^{-1}.

Anal. Calcd for $C_{13}H_{14}ClNO_6$: C, 49.46; H, 4.47; mol wt, 315.71. Found: C, 49.21; H, 4.39; mol wt, 317.

19-Chloro-3,6,9,12,15-pentaoxa-21-azabicyclo[15.3.1]heneicosa-1(21),17,19-triene-2,16-dione (6). 4-Chloro-2,6-pyridinedicarbonyl chloride (18.23 g, 0.0764 mol) and tetra(ethylene glycol) (14.85 g, 0.0764 mol) were used. Upon removal of the solvent, the residue crystallized. After extraction, the product (25 g, 91%) was recrystallized from ethanol to give white needles, mp 104–105 °C, IR (KBr) 1725 cm^{-1}.

Anal. Calcd for $C_{15}H_{18}ClNO_7$: C, 50.08; H, 5.04; mol wt, 359.76. Found: C, 49.94; H, 4.92; mol wt, 367.

The sodium thiocyanate complex of compound **6** was prepared by adding equimolar amounts of **6** and the salt to acetonitrile. The precipitate was filtered and dried: mp 187–188 °C; IR (KBr) 2080 and 1730 cm^{-1}.

Anal. Calcd for $C_{15}H_{18}ClNO_7 \cdot NaSCN$: C, 43.56; H, 4.12. Found: C, 43.70; H, 4.08.

The potassium thiocyanate complex of compound **6** was prepared as above; mp 206 °C dec; IR (KBr) 2070 and 1725 cm^{-1}.

Anal. Calcd for $C_{15}H_{18}ClNO_7 \cdot KSCN$: C, 42.06; H, 3.97. Found: C, 41.87; H, 3.92.

The silver nitrate complex of compound **6** was prepared by adding equimolar amounts of **6** and the salt to acetonitrile. The solvent was removed and the residue dissolved in chloroform and filtered. Addition of ether precipitated the product which was filtered and dried: mp 200 °C dec; IR (KBr) 1720 and 1380 cm^{-1}.

Anal. Calcd for $C_{15}H_{18}ClNO_7 \cdot AgNO_3$: C, 34.02; H, 3.43. Found: C, 33.83; H, 3.24.

22-Chloro-3,6,9,12,15,18-hexaoxa-24-azabicyclo[18.3.1]tetracosa-1(24),20,22-triene-2,19-dione (9). 4-Chloro-2,6-pyridinedicarbonyl chloride (13.25 g, 0.056 mol) and penta(ethylene glycol) (13.24 g, 0.056 mol) were used. After extraction, the product (16.0 g, 72.3%) was recrystallized from ethanol to give white crystals, mp 70–71 °C, IR (KBr) 1727 cm^{-1}.

Anal. Calcd for $C_{17}H_{22}ClNO_8$: C, 50.56; H, 5.49; mol wt, 403.82. Found: C, 50.74; H, 5.60; mol wt, 405.

25-Chloro-3,6,9,12,15,18,21-heptaoxa-27-azabicyclo[21.3.1]heptacosa-1(27),23,25-triene-2,22-dione (12). 4-Chloro-2,6-pyridinedicarbonyl chloride (11.48 g, 0.0481 mol) and hexa(ethylene glycol) (13.59 g, 0.0481 mol) were used. After extraction, the product (8.12 g, 37.7%) was recrystallized from a 50/50 mixture of hexane and ethanol to give white crystals, mp 65–66 °C, IR (KBr) 1720 cm^{-1}.

Anal. Calcd for $C_{19}H_{26}ClNO_9$: C, 50.95; H, 5.85; mol wt, 447.87. Found: C, 50.90; H, 5.89; mol wt, 456.

28-Chloro-3,6,9,12,15,18,21,24-octaoxa-30-azabicyclo[24.3.1]-triaconta-1(30),26,28-triene-2,25-dione (14). 4-Chloro-2,6-pyridinedicarbonyl chloride (12.62 g, 0.0529 mol) and hepta(ethylene glycol) (17.27 g, 0.0529 mol) were used. After extraction, the product (11.7 g, 45%) was recrystallized from hexane to give white, fluffy needles, mp 52–53 °C, IR (KBr) 1720 cm^{-1}.

Anal. Calcd for $C_{21}H_{30}ClNO_{10}$: C, 51.27; H, 6.15; mol wt, 491.92. Found: C, 51.27; H, 5.99; mol wt, 486.

16-Methoxy-3,6,9,12-tetraoxa-18-azabicyclo[12.3.1]octadeca-1(18),14,16-triene-2,13-dione (5). 4-Methoxy-2,6-pyridinedicarbonyl chloride (25.00 g, 0.107 mol) and tri(ethylene glycol) (16.00 g, 0.107 mol) were used. The benzene-soluble portion of the reaction mixture was recrystallized twice from methanol to give white needles (0.14 g, <1%), mp 154–154.5 °C, IR (KBr) 1725 cm^{-1}.

Anal. Calcd for $C_{14}H_{17}NO_7$: C, 54.02; H, 5.50. Found: C, 53.83; H, 5.57.

19-Methoxy-3,6,9,12,15-pentaoxa-21-azabicyclo[15.3.1]heneicosa-1(21),17,19-triene-2,16-dione (7). 4-Methoxy-2,6-pyridinedicarbonyl chloride (18.00 g, 0.0769 mol) and tetra(ethylene glycol) (14.94 g, 0.0769 mol) were used. After extraction, the product (14.8 g, 54.2%) was recrystallized from ethanol to give white crystals, mp 116–117 °C, IR (KBr) 1725 cm^{-1}.

Anal. Calcd for $C_{16}H_{21}NO_8$: C, 54.08; H, 5.96; mol wt, 355.34. Found: C, 53.98; H, 5.86; mol wt, 356.

The potassium thiocyanate complex of compound **7** was prepared by adding equimolar amounts of **7** and the salt to acetonitrile. The solvent was removed and the residue dissolved in chloroform and filtered. Addition of ether precipitated the product which was filtered and dried: mp 169.5–170 °C; IR (KBr) 2060 and 1725 cm^{-1}.

Anal. Calcd for $C_{16}H_{21}NO_8$·KSCN: C, 45.12; H, 4.68. Found: C, 45.11; H, 4.51.

22-Methoxy-3,6,9,12,15,18-hexaoxa-24-azabicyclo[18.3.1]tetracosa-1(24),20,22-triene-2,19-dione (10). 4-Methoxy-2,6-pyridinedicarbonyl chloride (17.10 g, 0.0731 mol) and penta(ethylene glycol) (17.41 g, 0.0731 mol) were used. After extraction, the product (5.40 g, 18.5%) was recrystallized twice from ethanol to give white platelets, mp 122–123 °C, IR (KBr) 1715 cm^{-1}.

Anal. Calcd for $C_{18}H_{25}NO_9$: C, 54.13; H, 6.31; mol wt, 399.40. Found: C, 53.94; H, 6.42; mol wt, 399.

25-Methoxy-3,6,9,12,15,18,21-heptaoxa-27-azabicyclo[21.3.1]-heptacosa-1(27),23,25-triene-2,22-dione (13). 4-Methoxy-2,6-pyridinedicarbonyl chloride (15.00 g, 0.0641 mol) and hexa(ethylene glycol) (18.10 g, 0.0641 mol) were used. After extraction, the product (12.2 g, 42.9%), which was a viscous oil, crystallized upon standing. Recrystallization from ethanol/hexane gave a white, crystalline product, mp 72–73 °C, IR (KBr) 1720 cm^{-1}.

Anal. Calcd for $C_{20}H_{29}NO_{10}$: C, 54.17; H, 6.59; mol wt, 443.45. Found: C, 53.99; H, 6.62; mol wt, 444.

28-Methoxy-3,6,9,12,15,18,21,24-octaoxa-30-azabicyclo[24.3.1]-triaconta-1(30),26,28-triene-2,25-dione (15). 4-Methoxy-2,6-pyridinedicarbonyl chloride (15.00 g, 0.0641 mol) and hepta(ethylene glycol) (20.92 g, 0.0641 mol) were used. After extraction, the product (11.4 g, 36.5%) was a viscous oil which would not crystallize. The product oil was dissolved in $CHCl_3$, treated with Norit, and dried under vacuum, IR (neat) 1720 cm^{-1}.

Anal. Calcd for $C_{22}H_{33}NO_{11}$: mol wt, 487.50. Found: mol wt, 489. Satisfactory C and H analyses were not obtained.

Attempted Synthesis of 19-Nitro-3,6,9,12,15-pentaoxa-21-azabicyclo[15.3.1]heneicosa-1(21),17,19-triene-2,16-dione. 4-Nitro-2,6-pyridinedicarbonyl chloride (22.48 g, 0.0903 mol) and tetra(ethylene glycol) (17.54 g, 0.0903 mol) were used. The general procedure for the preparation of macrocyclic compounds was followed. During the course of the reaction, an orange color appeared in solution due to the presence of dissolved NO_2 gas. Workup of the reaction gave compound **6** in a good yield.

Temperature-Dependent ^1H NMR Spectra. The ^1H NMR spectrum of the macrocyclic compound (about 20 mg) in methylene-d_2 chloride was first obtained. Then the solution was mixed with an equimolar amount of the alkylammonium salt (or half-molar in the case of the 2:1 complex) and another ^1H NMR spectrum was obtained. The probe temperature was then lowered until one or more sets of peaks separated (usually −45 to −105 °C; see Table III). Successive ^1H NMR spectra were taken while raising the temperature to about 20 °C above the coalescence temperature. The spectral data and kinetic parameters are listed in Table III.

Determination of Log K, ΔH, and $T\Delta S$ in Methanol. Log K, ΔH, and $T\Delta S$ values for the interaction of several ligands with the cations shown in Table IV were determined in methanol (Fisher reagent, <0.05% H_2O) at 25 °C by isoperibol titration calorimetry in a 25-mL reaction vessel as described previously.[32] The sources and purities of metal salts used have been outlined elsewhere.[32] Concentrations of methanolic ligand solutions were given by thermometric titration to an end point against KCl.

Cation Transport Measurements. The rates of transport of metal nitrate salts through chloroform membranes containing the carriers listed in Table V were determined using a method described previously.[28] A 3-mL stirred chloroform membrane containing 1.0 mM ligand separated a 1.0 M source phase solution of metal nitrate (0.5 M in the case of $CsNO_3$, 0.33 M in the case of $Ba(NO_3)_2$) and a distilled water receiving phase. All results were normalized to those for a 1.0 M source phase. The moles of cation transferred into the receiving phase in 24 h was determined by ion chromatography (Rb, Cs, and Ba) or by atomic absorption spectroscopy (all other cations).

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References and Notes

(1) On leave, fall 1978, The University, Sheffield, England.
(2) Lamb, J. D.; Izatt, R. M.; Christensen, J. J. In "Chemistry of Macrocyclic Compounds", Melson, G., Ed.; Plenum Press: New York, 1979.
(3) (a) Izatt, R. M.; Izatt, N. E.; Rossiter, B. E.; Christensen, J. J.; Haymore, B. L. *Science* **1978,** *199,* 944–946. (b) Izatt, R. M.; Lamb, J. D.; Izatt, N. E.; Rossiter, B. E.; Christensen, J. J. *J. Am. Chem. Soc.,* **1979,** *101,* 6273–6276.
(4) (a) Newcomb, M.; Timko, J. M.; Walba, D. M.; Cram, D. J. *J. Am. Chem. Soc.* **1977,** *99,* 6392–6398. (b) Cram, D. J.; Cram, J. M. *Science* **1974,** *183,* 803–809.
(5) Negano, O.; Kobayashi, A.; Sasaki, Y. *Bull. Chem. Soc. Jpn.* **1978,** *51,* 790–793.
(6) Behr, J. P.; Lehn, J. M.; Vierling, P. *J. Chem. Soc., Chem. Commun.* **1976,** 621–623.
(7) Behr, J. P.; Lehn, J. M. *J. Chem. Soc., Chem. Commun.* **1978,** 143–146.
(8) Laidler, D. A.; Stoddart, J. F. *J. Chem. Soc., Chem. Commun.* **1977,** 481.
(9) Laidler, D. A.; Stoddart, J. F. *Tetrahedron Lett.* **1979,** 453–456.
(10) Metcalfe, J. C.; Stoddart, J. F.; Jones, G. *J. Am. Chem. Soc.* **1977,** *99,* 8317–8318.
(11) Beckford, H. F.; King, R. M.; Stoddart, J. F.; Newton, R. F. *Tetrahedron Lett.* **1978,** 171–174.
(12) Izatt, R. M.; Lamb, J. D.; Asay, R. E.; Maas, G. E.; Bradshaw, J. S.; Christensen, J. J.; Moore, S. S. *J. Am. Chem. Soc.* **1977,** *99,* 6134–6136.
(13) Bradshaw, J. S.; Asay, R. E.; Maas, G. E.; Izatt, R. M.; Christensen, J. J. *J. Heterocycl. Chem.* **1978,** *15,* 825–831.
(14) Izatt, R. M., Christensen, J. J., Eds. "Progress in Macrocyclic Chemistry", Vol. 1; Wiley-Interscience: New York, 1979.
(15) Melson, G., Ed. "Thermodynamics of Cation-Macrocycle Interactions"; Plenum Press: New York, 1979.
(16) Izatt, R. M.; Lamb, J. D.; Maas, G. E.; Asay, R. E.; Bradshaw, J. S.; Christensen, J. J. *J. Am. Chem. Soc.* **1977,** *99,* 2365–2366.
(17) Maas, G. E.; Bradshaw, J. S.; Izatt, R. M.; Christensen, J. J. *J. Org. Chem.* **1977,** *42,* 3937–3941.
(18) Bradshaw, J. S.; Maas, G. E.; Izatt, R. M.; Lamb, J. D.; Christensen, J. J. *Tetrahedron Lett.* **1979,** 635–638.
(19) Frensch, K.; Vögtle, F. *Tetrahedron Lett.* **1977,** 2373–2374.
(20) Merkees, D. G. *J. Org. Chem.* **1963,** *28,* 2530–2533.
(21) Parish, W. W.; Stott, P. E., Parish Chemical Co., Provo, Utah 84601, unpublished results.
(22) Sutherland, I. O. *Annu. Rep. NMR Spectrosc.* **1971,** *4,* 71–235.
(23) Hodgkinson, L. C.; Leigh, S. J.; Sutherland, I. O. *J. Chem. Soc., Chem. Commun.* **1976,** 639–640.
(24) Grandberg, I. I.; Gaizora, G. K.; Kost, A. N. *Khim. Geterotsikl. Soedin.* **1966,** 561; *Chem. Abstr.* **1967,** *66,* 10453*b*.
(25) Bartsch, R. A. In ref 14, Vol. 2, in press.
(26) Izatt, R. M.; Lamb, J. D.; Rossiter, B. E.; Izatt, N. E.; Christensen, J. J.; Haymore, B. L. *J. Chem. Soc., Chem. Commun.* **1978,** 386–387.
(27) Cotton, F. A.; Wilkinson, G. "Advanced Inorganic Chemistry"; Interscience: New York, 1972; p 1048.
(28) Christensen, J. J.; Lamb, J. D.; Izatt, S. R.; Starr, S. E.; Weed, G. C.; Astin, M. S.; Stitt, B. D.; Izatt, R. M. *J. Am. Chem. Soc.* **1978,** *100,* 3219–3220.
(29) Bradshaw, J. S.; Reeder, R. A.; Thompson, M. D.; Flanders, E. D.; Carruth, R. L.; Izatt, R. M.; Christensen, J. J. *J. Org. Chem.* **1976,** *41,* 134–136.
(30) Markees, D. G. *J. Org. Chem.* **1958,** *23,* 1030–1033.
(31) Markees, D. G.; Kidder, G. W. *J. Am. Chem. Soc.* **1956,** *78,* 4130–4133.
(32) Izatt, R. M.; Terry, R. E.; Nelson, D. P.; Chan, Y.; Eatough, D. J.; Bradshaw, J. S.; Hansen, L. D.; Christensen, J. J. *J. Am. Chem. Soc.* **1976,** *98,* 7626–7630.