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Five new proton-ionizable macrocyclic ligands containing a pyrimidone-subcyclic unit, **6-10**, were prepared from the previously prepared pyrimidinocrown ethers **1-5** (see Figure 1 and Scheme 1). One of the new proton-ionizable crown ethers is chiral. The proton-ionizable pyrimidinocrown ethers were prepared in high yields by treating the appropriate methoxy-substituted pyrimidinocrown with 5 M sodium hydroxide in a 50% alcohol-water mixture. Complexation properties of four of the pyrimidine-derived macrocycles were studied by various nmr techniques. Pyrimidono-18-crown-6 (**9**) forms a strong complex with benzylammonium perchlorate and also forms a complex with benzylamine. (*S,S*)-Dimethyl-substituted pyrimidino- and pyrimidono-18-crown-6 ligands **4** and **9** form stronger complexes with the (*R*)-form of α -(1-naphthyl)ethylammonium perchlorate than with the (*S*)-form. (*S,S*)-Dimethyl-substituted pyrimidono-18-crown-6 (**9**) also forms a stronger complex with (*R*)- α -(1-naphthyl)ethylamine than with the (*S*)-form. The crystal structure for compound **7** is reported.

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Introduction.

Among the synthetic macrocyclic ligands, crown ethers which contain their donor atoms (mainly oxygen) incorporated in a cyclic backbone have contributed abundantly to modern coordination chemistry because of their ability to selectively complex both metal and organic ammonium cations [2]. Enantiomeric recognition, as a special case of molecular recognition, involves the differentiation of one enantiomer of a guest from the other by a chiral host. Molecules which possess the capacity to selectively detect enantiomers are of interest to researchers in organic, biological, pharmaceutical, and analytical chemistry [3]. Examples of enantiomeric discrimination can be found in many natural processes such as enzyme-substrate interactions, immunological responses, the mechanism of drug action, and the storage and retrieval of genetic information. Recent successes in imitating biochemical phenomena using small synthetic compounds has shown that biological behavior can be engineered into simple molecules. To a large extent, research activity in this area is driven by the desire to understand the ability of molecules to discern one another through molecular interactions that form stable organized structures. Crown ethers have demonstrated an ability to bind cationic guests selectively [4,5]. This has created interest in them as enzyme models [3].

For the past three decades, work in our laboratory has been directed toward the systematic determination of the parameters that affect complex stability, and to understand that stability in terms of thermodynamic and kinetic data for complex formation [5-7]. In our studies, various structural changes have been made to the basic crown ether structure in an attempt to enhance the selectivity of these

ligands and the stability of complexes formed with both metal and organic cations. Some of these modifications involve the substitution of ligand polyether oxygen donor atoms by sulfur and/or nitrogen atoms. Other substitutions have involved the insertion of aromatic and/or heterocyclic ring systems into the macroring [6-8].

Crown ethers containing a proton-ionizable group is an area of interest for many researchers [9]. The majority of these ligands have the proton-ionizable moiety as a part of the macroring. The proton-ionizable macrocyclic ligands increase the cation-crown complex stability and allow a selective proton-coupled transport of metal ions through various membrane systems [10-13] without the need for an anion to accompany the macrocycle-ion complex. The transport of these metal cations, in many cases, is pH dependent so that transport can be turned on or off by adjusting the pH [9,11,14]. Proton-ionizable ligands having the 4-pyridone subcyclic unit have been used as carriers in the transport of metal ions in some ligand membrane systems [11-13].

Enantiomeric recognition of organic amines and ammonium salts by chiral macrocyclic ligands is an area of molecular recognition that is receiving attention at the present time [5,15,16]. Our interest in enantiomeric recognition has, until now, focused on the interaction of chiral crowns containing pyridine derivatives as a part of the macroring with chiral organic ammonium salts [5,17,18]. In certain cases these chiral pyridine-containing crowns have demonstrated considerable enantiomeric recognition.

Macrocyclic ligands containing the pyrimidine subcyclic unit have not been studied extensively because the incorporation of pyrimidine groups into the crown ether ring is

difficult. Pyrimidinocrown ethers 1-5 (Figure 1) were prepared by treating 4-methoxy-5-methyl-2,6-pyrimidinedimethanol with the appropriate oligoethylene glycol ditosylate, to form 1-3 and 5, or the corresponding pyrimidinedimethanol ditosylate and the chiral dimethyl-substituted tetraethylene glycol to form 4 as reported [19]. This paper reports on the synthesis of the pyrimidone-containing macrocycles 6-10 (Figure 1) and complexation of organic ammonium salts and amines by pyrimidine-derived ligands 2, 4, 7, and 9.

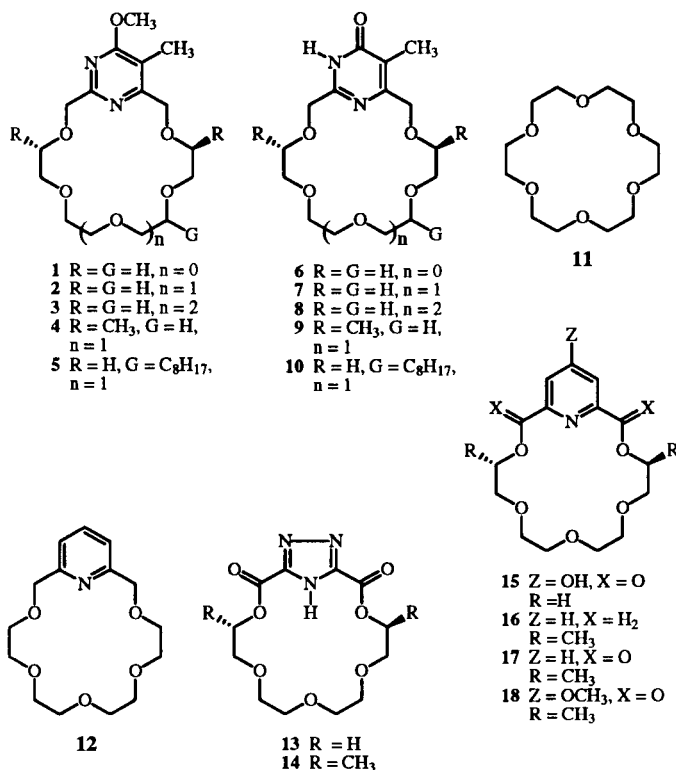


Figure 1. Macroyclic Ligands Used in this Study.

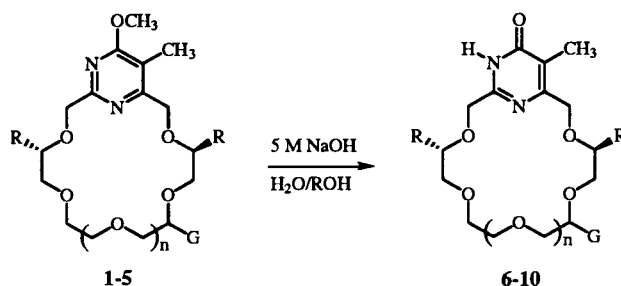
Results and Discussion.

Synthesis and Structure.

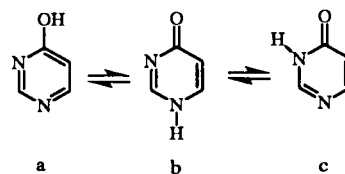
Proton-ionizable pyrimidonocrown ethers 6-10 were synthesized by refluxing the corresponding methoxy-substituted pyrimidinocrown ethers 1-5 in a 5 M sodium hydroxide solution made from a 1:1 mixture of water and an alcohol for 48 hours (Scheme I). The proton-ionizable pyrimidonocrown ethers were isolated in 80-95% yields as solids. Conversion of the methoxy group to hydroxy which tautomerizes to the pyrimidone subcyclic unit with a pK_a of about 8.5 [20] provides a crown ether capable of reacting with organic amines.

The structures proposed for these new proton-ionizable macrocyclic compounds are consistent with data obtained from ¹H nmr and mass spectra, the X-ray crystal structure of

Scheme 1. Preparation of Pyrimidonocrown Ethers



7, and combustion analyses. Many heterocyclic aromatic compounds can exist in two or more tautomeric forms. Although preliminary ir spectral studies of the unsubstituted pyrimidones suggested that they existed as pyrimidinols, better experimental evidence has since reversed that notion [21]. Many of the investigations of the tautomeric forms of the pyrimidones have been done using N- and O-substituted derivatives. Prototropic tautomerism in the pyrimidones gives rise to the 4-hydroxypyrimidine (a), 1H-pyrimidone (b), and 3H-pyrimidone(c) forms shown below.



The amide tautomeric form c has been shown to be strongly favored in the solid state and in solution over the vinylogous amide form b [22]. Recent studies have confirmed the predominance of the amide type tautomers over the 4-hydroxypyrimidine form [23]. The ¹H nmr spectra of the pyrimidonocrown ethers show the existence of tautomeric forms. For example, the ¹H nmr spectrum of macrocycle 7 has singlet signals at $\delta = 1.98$ ppm and 2.05 ppm corresponding to the methyl substituent on the pyrimidone ring and two broad concentration dependent singlets between $\delta = 12$ ppm and 9 ppm which are exchangeable with deuterium oxide. The area under the plot of the N-H signal at $\delta \sim 12$ ppm changes in proportion to the change in the area under the plot of the methyl singlet at $\delta = 1.98$ ppm. The area integrations of these two signals were always smaller than those of the signals at $\delta \sim 10$ ppm and $\delta = 2.05$ ppm. These results suggest that these are tautomeric forms for the pyrimidonocrown ethers in solution. The transient ionizable position of the pyrimidone-18-crown-6 places the methyl group on the pyrimidone ring in different chemical environments giving rise to the two singlets at $\delta = 1.98$ ppm and 2.05 ppm in the ¹H nmr spectrum of 7. The ¹H nmr spectrum of macrocycle 7

in deuterium oxide or when complexed with benzylamine exhibits only one signal for the methyl group attached to the pyrimidone ring. The solid structure of this macrocycle exists in the favored amide form (c) as discussed below.

Solid State Crystal Study.

The conformation of pyrimidonocrown ether **7** along with the atom labels are shown in Figure 2. The positional and equivalent isotropic thermal parameters of the nonhydrogen atoms are listed in Table 1. The bond lengths and angles of the

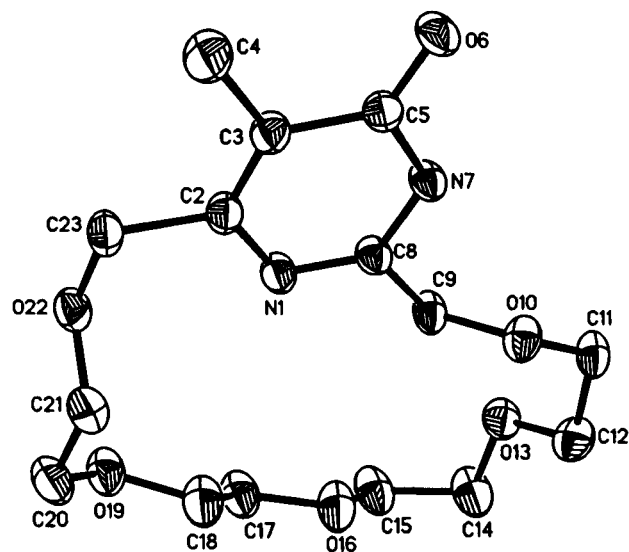


Figure 2. X-ray Crystal Structure of Pyrimidono-18-Crown-6 (**7**)

molecule are contained in Table 2. The values for these distances and angles are normal. The most unique feature of the molecule is the elliptical shape of the polyether ring cavity. This shape is indicated by the following interatomic distances: O22...C12, 7.565 Å and N1...C18, 3.727 Å. This elongated shape is also indicated by the four consecutive *trans* torsion angles in the macrocyclic ring: C14-C15-O16-C17, C15-O16-C17-C18, O16-C17-C18-O19, and C17-C18-O19-C20. The unusual torsion angle in this sequence is about the C17-C18 bond (169.6°). Generally O-C-C-O torsion angles in this type of molecule have values close to 60°.

Another interesting feature of the solid state structure of compound **7** is the fact that the molecules exist as dimers with two hydrogen bonds joining the aromatic portions of the molecules in a manner similar to base pairing found in nucleic acids. This is not unexpected because of the structural similarity of the aromatic group in the ligand to uracil and other bases found in nucleotides. The dimer and associated hydrogen bonding are shown in Figure 3 with the two molecules related by a center of symmetry. The hydrogen bond data are: H7...O6A, 2.01 Å; N7...O6A, 2.860 Å

Table 1
Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Coefficients ($\text{\AA}^2 \times 10^3$) for the Non-hydrogen Atoms of **7**

	x	y	z	U(eq)[a]
N1	159(2)	3618(2)	3664(1)	41(1)
C2	531(2)	2390(3)	4652(2)	38(1)
C3	-680(3)	2245(3)	5490(2)	38(1)
C4	-272(3)	943(3)	6586(2)	57(1)
C5	-2459(2)	3385(3)	5324(2)	36(1)
O6	-3688(2)	3351(2)	5988(1)	49(1)
N7	-2736(2)	4586(2)	4321(1)	38(1)
C8	-1445(2)	4671(3)	3545(2)	37(1)
C9	-1974(3)	6044(3)	2492(2)	44(1)
O10	-3138(2)	7626(2)	2792(1)	45(1)
C11	-4286(3)	8826(3)	1960(2)	47(1)
C12	-3435(3)	9631(3)	962(2)	53(1)
O13	-2520(2)	8407(2)	296(1)	53(1)
C14	-1456(3)	8931(4)	-596(2)	68(1)
C15	256(3)	7443(4)	-654(2)	62(1)
O16	1066(2)	7033(2)	335(1)	62(1)
C17	2587(3)	5472(3)	439(2)	58(1)
C18	3163(3)	5083(3)	1574(2)	60(1)
O19	4483(2)	3390(2)	1777(1)	55(1)
C20	5203(3)	2919(3)	2805(2)	55(1)
C21	4008(3)	2751(3)	3817(2)	47(1)
O22	3538(2)	1368(2)	3851(1)	45(1)
C23	2413(3)	1134(3)	4777(2)	48(1)

[a] Equivalent isotropic U defined as one third of the trace of the orthogonalized U_{ij} tensor

Table 2
Bond Lengths and Angles for **7**

1	2	3	1 - 2 (Å)	1 - 2 - 3 (°)
C2	N1	C8	1.380 (2)	116.5 (2)
N1	C2	C3		123.8 (2)
C23	C2	N1	1.526 (3)	116.2 (2)
C3	C2	C23	1.368 (3)	119.9 (2)
C2	C3	C4		124.0 (2)
C2	C3	C5		118.7 (2)
C4	C3	C5	1.509 (3)	117.3 (2)
C3	C5	O6	1.440 (3)	125.6 (2)
C3	C5	N7		114.3 (2)
O6	C5	N7	1.236 (2)	120.1 (2)
C5	N7	C8	1.381 (2)	123.0 (2)
N1	C8	N7	1.298 (2)	123.5 (2)
N1	C8	C9		120.3 (2)
N7	C8	C9	1.360 (3)	116.2 (2)
C8	C9	O10	1.505 (3)	107.7 (2)
C9	O10	C11	1.415 (2)	114.4 (2)
O10	C11	C12	1.429 (2)	114.0 (2)
C11	C12	O13	1.498 (3)	109.5 (2)
C12	O13	C14	1.408 (3)	114.8 (2)
O13	C14	C15	1.425 (3)	109.5 (2)
C14	C15	O16	1.493 (3)	108.5 (2)
C15	O16	C17	1.416 (3)	113.0 (2)
O16	C17	C18	1.419 (3)	107.0 (2)
C17	C18	O19	1.493 (4)	108.3 (2)
C18	O19	C20	1.408 (3)	113.3 (2)
O19	C20	C21	1.412 (2)	115.3 (2)
C20	C21	O22	1.506 (3)	109.1 (2)
C21	O22	C23	1.415 (4)	112.4 (2)
O22	C23	C2	1.408 (3)	115.1 (2)

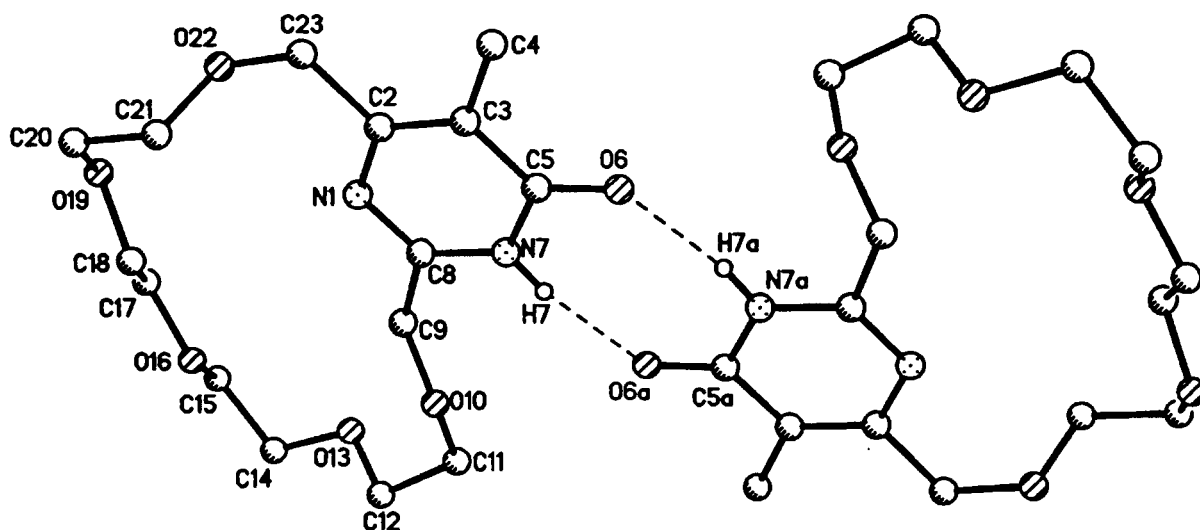


Figure 3. X-ray Crystal Structure of the Dimer of 7 Showing the Hydrogen Bonding.

and the angle N7-H7...O6A, 170° . The macrocycle is nearly planar. A least-square plane was calculated for the six donor atoms of the macrocycle and the average deviation of a hetero atom from that plane is 0.318 \AA . The dihedral angle between that least-square plane and the least-square plane of the six atom aromatic ring of the ligand is 4.1° . The average deviation of an atom in the aromatic group from its plane is 0.010 \AA .

Complexation Studies.

In this study, two kinds of quantities associated with host-guest interactions were investigated, ΔG_c^\ddagger and $\log K$. ΔG_c^\ddagger is the activation energy at the coalescence temperature for the dissociation of a host-guest complex. ΔG_c^\ddagger values have been widely used to quantitate interactions between macrocyclic ligands and organic ammonium cations [24, 25]. The temperature dependencies of the ^1H nmr spectra for the complexes of the pyrimidino- and pyrimidono-18-crown-6 ligands with benzylammonium perchlorate and benzylamine were determined using the ^1H nmr signal attributable to the methylene hydrogens situated between the pyrimidine (pyrimidone) ring and an adjacent oxygen of the polyether ring as reported for the similar pyridino- and pyridonocrown ethers [26-28]. Table 3 shows the coalescence temperatures (T_c) and ΔG_c^\ddagger values for the dissociation of the complexes of these pyrimidino- and pyrimidonocrown ether ligands along with the complexes of other crown ethers. It is apparent from these ΔG_c^\ddagger values that the macrocyclic ligands containing an aromatic or heteroaromatic ring moiety form kinetically more stable complexes with benzylammonium perchlorate than does the polyether 18-crown-6 (11).

The complex of 2 with benzylammonium perchlorate is kinetically stable compared to the complexes of pyridine-

Table 3

ΔG_c^\ddagger Values for the Interactions of Various Macrocycles with Benzylammonium Perchlorate and Benzylamine as Determined by a Variable Temperature ^1H nmr Method in Deuteriomethylene chloride.

Ligand	Cations [a]	ΔG_c^\ddagger (kcal/mole)	T_c ($^\circ\text{K}$)	ref
2	Bz-NH ₃ ⁺	13.4	258	[b]
7	Bz-NH ₂	10.5	213	[b]
11	Bz-NH ₃ ⁺	8.4	173	29
12	Bz-NH ₃ ⁺	11.9	238	30
13	Bz-NH ₃ ⁺	10.4	219	31
	Bz-NH ₂	14.0	288	31
14	Bz-NH ₂	12.7	267	31
15	Bz-NH ₃ ⁺	14.1	308	28
	Bz-NH ₂	12.3	263	28
16	Bz-NH ₃ ⁺	11.7	244	27
17	Bz-NH ₃ ⁺	13.4	265	27

[a] Bz-NH₃⁺ = benzylammonium perchlorate, Bz-NH₂ = benzylamine.
[b] This work.

derived macrocycles listed in Table 3. This complex is also kinetically more stable than the complex of triazoloderived crown ether 13 (ΔG_c^\ddagger 10.4). The value of ΔG_c^\ddagger for proton-ionizable pyrimidonocrown 7 with benzylamine is 10.5 kcal/mol which makes this complex less stable kinetically than benzylamine complexes with 13 and 15.

Complexes formed with pyrimidino-18-crown-6 ligand 4 and pyrimidono-18-crown-6 ligand 7 were accompanied by significant chemical shift changes in their ^1H nmr spectra. These shifts in the ^1H nmr signals upon complexation were used to determine the $\log K$ values for the formation of these complexes as reported [29,30,32]. The $\log K$ values are given in Table 4. Some specific chemical shifts are of interest. The

signal at $\delta = 4.56$ attributable to the methylene hydrogens located between the pyrimidone ring and the ether oxygen of uncomplexed **7** moved upfield to $\delta = 4.29$ upon complexation with benzylamine. In complexes involving pyrimidino-18-crown-6 ligand **2** and pyrimidono-18-crown-6 ligand **7**, the signals for substituents attached to the pyrimidine (pyrimidone) ring exhibit upfield shifts (shielding) in their ^1H nmr spectra. The methylene hydrogens of the oligoether

Table 4

Log K Values for the Interactions of Pyrimidino- and Pyrimidonocrown Ethers with Several Primary Organic Ammonium Perchlorates as Determined by a ^1H nmr Method at 25°C [a]

Ligand	Cation [b]	Solvent [c]	Log K	Δ Log K
2	Bz-NH ₃ ⁺	1M/1C	5.72	
		M	4.27	
7	Bz-NH ₃ ⁺	1M/1C	3.74	
		1M/1C	3.31	
4	(<i>R</i>)-NapEt-NH ₃ ⁺	1M/1C	5.18	
	(<i>S</i>)-NapEt-NH ₃ ⁺	1M/1C	4.23	0.95
	(<i>R</i>)-NapEt-NH ₃ ⁺	M	3.73	
	(<i>S</i>)-NapEt-NH ₃ ⁺	M	3.35	0.38
	(<i>R</i>)-PhEt-NH ₃ ⁺	M	3.51	
	(<i>S</i>)-PhEt-NH ₃ ⁺	M	3.21	0.30
	(<i>R</i>)-PhEtOH-NH ₃ ⁺	M	2.94	
	(<i>S</i>)-PhEtOH-NH ₃ ⁺	M	2.75	0.19
	(<i>S</i>)-PhEtOH-NH ₃ ⁺	M	2.75	0.19
9	(<i>R</i>)-NapEt-NH ₃ ⁺	1M/1C	3.41	
	(<i>S</i>)-NapEt-NH ₃ ⁺	1M/1C	3.05	0.36
	(<i>R</i>)-NapEt-NH ₂	1M/1C	2.47	
	(<i>S</i>)-NapEt-NH ₂	1M/1C	2.07	0.40

[a] Varian Gemini-200 and 500 MHz spectrometers were used to record all ^1H nmr Spectra. [b] Bz-NH₃⁺ and BzNH₂ are in Table 3, NapEt-NH₃⁺ = the (*R*)- or (*S*)-isomer of α -(1-naphthyl)ethylammonium perchlorate, NapEt-NH₂ = α -(1-naphthyl)ethylamine, PhEt-NH₃⁺ = the (*R*) or (*S*)-isomers of α -(1-phenylethyl) ammonium perchlorate. PhEtOH-NH₃⁺ = the hydrogen perchlorate salt of 2-amino-2-phenylethanol. [c] M = perdeuteriomethanol, C = deuteriochloroform.

macroring of these ligands when complexed exhibit downfield shifts (deshielding) in their ^1H nmr spectra. These spectral results suggest that the aromatic ring of the guest aromatic ammonium ion is interacting with the pyrimidine (pyrimidone) ring of the host. The aromatic ring current could then be the source of the observed chemical shifts of the signals for the various hydrogens. The magnitude of these chemical shifts appear to correlate with the magnitude of the log K values. For example, upfield shifts of the methyl substituent bound to the pyrimidine ring of chiral macrocycle **4** exhibited an upfield shift of 0.40 ppm in its complex in methanol- d_4 with the (*R*)- α -(1-naphthylethyl)-ammonium perchlorate ((*R*)-NapEtNH₃⁺) (log $K = 3.73$, Table 4) vs. an upfield shift of 0.34 in its complex with (*S*)-NapEtNH₃⁺ (log $K = 3.35$). The magnetic shielding and deshielding of proton signals was also observed for the pyridine-containing crown ethers [33].

Effect of Host Structure on Complexation.

It is of interest to note how structural modifications in the host are manifested in the strength of its interaction with the guest as determined by log K values. Conversion of the pyrimidine methoxy group into the pyrimidone carbonyl group removes aromatic character from the pyrimidine ring and lowers the log K values of the host-guest system from 5.72 to 3.74 for the 2-Bz-NH₃⁺ and 7-Bz-NH₃⁺ interactions (Table 4). Since one of the origins for enantiomeric recognition is expected to be steric repulsion between the substituents at the stereocenters and the substituent groups of the ammonium cation [27], it is expected that complex stability as determined by log K should decrease as the steric repulsion increases in the macroring. The data in Table 4 support this expectation. Optically active (*S,S*)-dimethylpyrimidinocrown **4** forms a weaker complex with enantiomeric NapEt-NH₃⁺ or α -(1-phenylethyl)ammonium perchlorate (PhEt-NH₃⁺) than optically inactive pyrimidinocrown **2** with benzylammonium perchlorate (Bz-NH₃⁺).

Table 5 lists the Δ log K values as determined by the ^1H nmr titration spectral method for various chiral macrocycle-chiral primary ammonium salt interactions at 25° . The chiral ligands included in Table 5 have methyl groups attached to two stereocenters. This keeps the bulkiness of the substituents at the stereocenters constant. The Δ log K values range from 0.95 for the complexes of (*S,S*)-**4** with the enantiomeric forms of NapEt-NH₃⁺ in a 1:1 deuteriomethanol-deuteriochloroform mixture, to 0.36 for the NapEt-NH₃⁺ complexes of (*S,S*)-**9** in the same solvent system. The lack of aromatic character in the pyrimidone ring of (*S,S*)-**9** could

Table 5

Δ Log K Values for the Interactions of Various Macrocycles with Enantiomeric Organic Ammonium Perchlorate Salts [a]

Ligand	Cations [b]	Solvent [c]	Δ Log K	ref	
<i>(S,S)</i> - 4	NapEt-NH ₃ ⁺	IM/IC	0.95	[d]	
	NapEt-NH ₃ ⁺	M	0.38	[d]	
	PhEt-NH ₃ ⁺	M	0.30	[d]	
<i>(S,S)</i> - 9	NapEt-NH ₃ ⁺	IM/IC	0.36	[d]	
	<i>(S,S)</i> - 16	NapEt-NH ₃ ⁺	IM/IC	0.54	29
		NapEt-NH ₃ ⁺	M	0.40	29
<i>(S,S)</i> - 17	PhEt-NH ₃ ⁺	IM/IC	0.33	29	
	NapEt-NH ₃ ⁺	IM/IC	0.60	30	
	NapEt-NH ₃ ⁺	M	0.41 [e]	27	
<i>(R,R)</i> - 17	PhEt-NH ₃ ⁺	M	0.33	29	
	NapEt-NH ₃ ⁺	IM/IC	0.60	29	
	NapEt-NH ₃ ⁺	M	0.42	32	
<i>(S,S)</i> - 18	NapEt-NH ₃ ⁺	IM/IC	0.80	29	
	NapEt-NH ₃ ⁺	M	0.45 [e]	29	
	PhEt-NH ₃ ⁺	M	0.19 [e]	29	

[a] Determined by ^1H nmr method at 25° . Varian Gemini-200 and 500 MHz spectrometers were used to record all ^1H nmr Spectra unless otherwise noted. [b] See footnote a of Table 4 for the cation structures. [c] M = perdeuteriomethanol, C = deuteriochloroform. [d] This work. [e] Determined by a calorimetric method.

play a role in the low $\Delta \log K$ value for its complexes with NapEt-NH₃⁺. It is also of interest to note the consistency in the $\Delta \log K$ values listed for all complexes with NapEt-NH₃⁺ in deuteriomethanol. In these cases, the $\Delta \log K$ values range from 0.45 for the NapEt-NH₃⁺ complexes of (*S,S*)-**18** to 0.38 for the NapEt-NH₃⁺ complexes of (*S,S*)-**4**. It is obvious that enantiomeric recognition by pyrimidine-derived (*S,S*)-**4** compares favorably to the popular pyridine-derived crown ethers in both solvent systems.

Effect of Cation Structure on Complexation.

The effect of the structure of the organic ammonium cation was evaluated using the interaction of (*S,S*)-**4** with the enantiomeric forms of NapEt-NH₃⁺, PhEt-NH₃⁺, and the hydrogen perchlorate salt of 2-amino-2-phenylethanol (PhEtOH-NH₃⁺). Both NapEt-NH₃⁺ and PhEt-NH₃⁺ form stable complexes with (*S,S*)-**4** in methanol-d₄ ($\log K > 3$, Table 4). Even though NapEt-NH₃⁺ has a more extended π system and hence a better chance for π - π interactions with the pyrimidine ring of the macrocyclic ligand, (*S,S*)-**4** displays good enantiomeric recognition for both NapEt-NH₃⁺ ($\Delta \log K = 0.38$) and PhEt-NH₃⁺ ($\Delta \log K = 0.30$). Thus, while π - π interactions of the host and guest aromatic systems may play an important role in enantiomeric recognition in some systems, it may not be absolutely necessary to cause good chiral recognition [29].

It is interesting that (*S,S*)-**9** interacted reasonably well with the free amines, (*R*)- and (*S*)-NapEt-NH₂ (Table 4).

Table 6

Summary of Crystal Data and Experimental Conditions for 7

Formula	C ₁₅ H ₂₄ N ₂ O ₆
Formula weight	328.4
F(000)	352
Crystal size, mm	0.28 x 0.40 x 0.45
μ , mm ⁻¹	0.103
Space group	PI
Crystal system	Triclinic
a, Å	8.641(1)
b, Å	8.699(2)
c, Å	12.547(2)
a, deg.	74.24(1)
b, deg.	79.91(1)
g, deg.	64.44(1)
Volume, Å ³	817.1
Z	2
Density, calc, Mg/m ³	1.335
2 θ range, deg.	4.0 to 55.0
Independent data	3775 ($R_{\text{int}} = 1.6\%$)
Observed data ($F > 8\sigma(F)$)	2062
Data/parameter	8.8:1
R	3.84%
Rw	5.94%
Weighting scheme	$w^{-1} = \sigma^2(F) + 0.0020 F^2$
Extinction correction	$\chi = 0.0032 (9)$, where $F^* = F[1 + 0.002\chi^2 F^2 / \sin 2\theta]^{-1/4}$
Goodness of fit	1.14
Largest peak in difference map, eÅ ⁻³	0.20
Largest hole in difference map, eÅ ⁻³	-0.17

The $\log K$ values for these interactions (2.47 and 2.07, respectively) were less than those for the interactions of (*S,S*)-**9** with the corresponding ammonium salts (3.41 and 3.05, respectively). Nevertheless, the $\Delta \log K$ values for these interactions were similar (0.40 for chiral amine recognition and 0.36 for chiral ammonium salt recognition).

EXPERIMENTAL

Pyrimidinocrown ethers **1-5** were prepared as reported [19]. The perchlorate salts of all the ammonium cations were prepared as described [27,29]. All ¹H nmr spectra were recorded on Varian Gemini 200 MHz or Varian 500 MHz spectrometers. Mass spectra were measured on a Finnegan 8430 high resolution mass spectrometer using electron impact and chemical ionization methods. Elemental analyses were performed by M.H.W. Laboratories, Phoenix, Arizona.

General Procedure for the Preparation of the Proton-Ionizable Pyrimidinocrown Ethers **6-10** (Scheme 1).

The appropriate methoxy-substituted pyrimidinocrown ether **1-5** was stirred under reflux in a solution of 5 M sodium hydroxide made from a 1:1 alcohol:water mixture for 48 hours (or until completion as shown by tlc). The mixture was cooled in an ice/salt bath and then acidified to a pH of 6 with glacial acetic acid. This cooled mixture was mixed with 100 ml of cold dichloromethane and 20 g of ice and the organic layer was separated. The aqueous layer was extracted two times with 100 ml portions of cold dichloromethane. The solvent was then evaporated and the crude products were purified and characterized as described below for each individual proton-ionizable pyrimidinocrown ether.

15-Methyl-16-oxo-3,6,9,12-tetraoxa-17,18-diazabicyclo[12.3.1]-octadecane-1(18),14-diene (**6**) (Scheme 1).

Proton-ionizable macrocycle **6** was prepared as described above using 0.7 g of pyrimidinocrown ether **1** and 33 ml of 5 M sodium hydroxide solution made from a 1:1 methanol:water mixture. The crude product was first purified by column chromatography on neutral alumina using ethanol/toluene:1/40 as eluant. The solid was then dried over phosphorous pentoxide in a high vacuum oven for 48 hours to give 0.59 g (88%) of **6** as a solid, mp 128-130°; ir (potassium bromide): 2868, 1730, 1578, 1465, 1414, 1367, 1293, 1250, 1190, 1106, 939, 856, 789 cm⁻¹; ¹H nmr (deuteriochloroform): δ : 1.95 (s, 3 H), 3.50-3.85 (m, 12 H), 4.48 (s, 2 H), 4.53 (s, 2 H), 10.7 (bs, 1H, exchangeable with deuterium oxide); ms: (CI), m/z 285 (M⁺ + 1, base peak).

Anal. Calcd. for C₁₃H₂₀N₂O₅: C, 54.92; H, 7.09. Found: C, 55.07; H, 7.15.

18-Methyl-19-oxo-3,6,9,12,15-pentaoxa-20,21-diazabicyclo[15.3.1]heneicosa-1(21),17-diene (**7**) (Scheme 1).

Proton-ionizable macrocycle **7** was prepared as described above using 0.5 g of pyrimidinocrown ether **2** and 33 ml of 5 M sodium hydroxide solution made from a 1:1 methanol:water mixture. The crude product was recrystallized from ethyl acetate and then dried over phosphorus pentoxide in a high vacuum oven for 48 hours to give 0.42 g (88%) of **7** as a white solid, mp 85-86°; ir (potassium bromide): 2907, 2860, 1672, 1528, 1454, 1288, 1119, 1112, cm⁻¹; ¹H nmr (deuteriochloroform and deuterium oxide): δ 2.00 (s, 3 H), 3.56-3.85 (m, 16 H), 4.41 (s, 2 H),

4.43 (s, 2 H), 4.75 (HDO) (peak at δ 11.2 disappeared); ms: (low voltage), m/z 328 (M^+), 153 (base peak).

Anal. Calcd. for $C_{15}H_{24}N_2O_6$: C, 54.87; H, 7.37. Found: C, 54.67; H, 7.33.

21-Methyl-22-oxo-3,6,9,12,15,18-hexaoxa-23,24-diazabicyclo[18.3.1]tetracos-1(24),20-diene (**8**) (Scheme 1).

Proton-ionizable macrocycle **8** was prepared as described above using 0.44 g of pyrimidinocrown ether **3** and 33 ml of 5 M sodium hydroxide solution made from a 1:1 methanol:water mixture. The crude product was first purified by column chromatography on neutral alumina using ethanol/toluene:1/40 as eluant. The solid was then dried over phosphorus pentoxide in a high vacuum oven for 48 hours to give 0.30 g (73%) of **8** as a white solid, mp 53-55°; ir (potassium bromide): 2900, 2860, 1672, 1528, 1119, 1112, cm^{-1} ; 1H nmr (deuteriochloroform and deuterium oxide): δ 2.00 (s, 3 H), 3.56-3.85 (m, 20 H), 4.41 (s, 2 H), 4.43 (s, 2 H), 4.75 (HDO) (peak at δ 11.2 disappeared); ms: (CI), m/z 373 ($M^+ + 1$, base peak).

Anal. Calcd. for $C_{17}H_{28}N_2O_7$: C, 54.83; H, 7.58. Found: C, 54.62; H, 7.75.

(4*S*,14*S*)-19-Oxo-4,14,18-trimethyl-3,6,9,12,15-pentaoxa-20,21-diazabicyclo[15.3.1]heneicos-1(21),17-diene (**9**) (Scheme 1).

Proton-ionizable macrocycle **9** was prepared as described above using 0.10 g of pyrimidinocrown ether **4** and 33 ml of 5 M sodium hydroxide solution made from a 1:1 ethanol:water mixture. The crude product was first purified by column chromatography on neutral alumina using ethanol/toluene:1/40 as eluant and then further purification on a silica gel column using methanol/ethyl acetate:1/3 as eluent. Further purification was done using preparative tlc. silica plates and methanol/ethyl acetate:1/3 and finally ethanol/dichloromethane:1/5 as eluents. The solid was then dried over phosphorous pentoxide in a high vacuum oven for 48 hours to give 80 mg (83%) of **9** as a solid, mp 90-93°; ir (potassium bromide): 2900, 2869, 1675, 1528, 1454, 1112, cm^{-1} ; 1H nmr (deuteriochloroform) 1.27 (m, 6 H) 2.00 (s, 3 H), 3.56-3.85 (bm, 12 H), 4.00 (d, 2 H), 4.56 (m, 4 H), 10-12 (bs, 1H, exchangeable with deuterium oxide); ms: (low voltage), m/z 356 (M^+), 195 (base peak).

Anal. Calcd. for $C_{17}H_{28}N_2O_6$: C, 57.29; H, 7.92. Found: C, 57.10; H, 8.02.

18-Methyl-19-oxo-7 (or 11)-octyl-3,6,9,12,15-pentaoxa-20,21-diazabicyclo[15.3.1]heneicos-1(21),17,19-triene (**10**) (Scheme 1).

Proton-ionizable macrocycle **10** was prepared as described above using 0.50 g of pyrimidinocrown ether **5** and 33 ml of 5 M sodium hydroxide solution made from a 1:1 ethanol:water mixture. The crude product was first purified by column chromatography on neutral alumina using ethanol/toluene:1/40 as eluant. The solid was then dried over phosphorous pentoxide in a high vacuum oven for 48 hours to give 0.40 g (81%) of **10** as a waxy white solid, mp 100-101°; ir (potassium bromide): 2907, 2860, 1670, 1528, 1454, 1119, 1112, cm^{-1} ; 1H nmr (deuteriochloroform): δ 0.88 (t, 3H), 1.27 (bm 14 H), 2.02 (s, 3 H), 3.56-3.85 (bm, 15 H), 4.48 (m, 4 H), 10.5 (bs, 1H, exchangeable with deuterium oxide); ms: (low voltage), m/z 440 (M^+), 69 (base peak).

Anal. Calcd. for $C_{23}H_{40}N_2O_6$: C, 62.72; H, 9.15. Found: C, 62.85; H, 9.02.

X-ray Crystal Structure Analysis.

A single crystal of pyrimidinocrown ether **7** was isolated from ethyl acetate and mounted on a Siemens R3m/V automated diffractometer for the structural study. The lattice parameters and

orientation matrix for the crystal were determined using a least-squares procedure involving 30 carefully centered reflections ($9.17^\circ < 2\theta < 28.11^\circ$). Crystal data and experimental conditions for this study are summarized in Table 6. Single crystal data were collected using a variable-speed 2θ - θ scanning mode to $\sin \theta/\lambda$ limit of 55° . MoK α radiation ($\lambda = 0.71073 \text{ \AA}$) was used in this study. The lattice parameters indicated that the compound crystallized in the triclinic crystal system and intensity statistics indicated that the space group was $P\bar{1}$. This choice of space group was verified by the successful solution of the structure. The intensity data were corrected for extinction effects and a weighting scheme based on counting statistics was applied to the data.

The structure was solved using direct methods. All non-hydrogen atoms were refined anisotropically. The positions for the hydrogen atoms bonded to the methyl carbon, C4, and N7 (see Figure 2) were obtained from a difference map. The positions for the rest of the hydrogen atoms were calculated based on stereochemistry conditions. During the refinement process the hydrogen atoms were allowed to ride on their neighboring heavy atoms, while their thermal parameters were refined isotropically. Atomic scattering factors used for the atoms are those found in The International Tables of X-ray Crystallography [34]. The programs used in the solution, refinement and display of the structure are contained in the SHELXTL-PLUSTM program package [35].

1H nmr Titration Procedure.

The 1H nmr titration experiment for determining log K values involves the titration of a guest solution of known concentration into a host solution of known concentration until no significant changes of chemical shifts are observed in the successive nmr spectral plots. The procedure is fully described [25,30,32]. The log K values are shown in Table 4.

Variable Temperature NMR Procedure.

The values of ΔG_c^\ddagger were obtained as reported [24-26].

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