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PYRIMIDINO- AND PROTON-IONIZABLE PYRIMIDONO-CROWN ETHER LIGANDS: SYNTHESIS AND PRELIMINARY COMPLEXATION STUDIES

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Abstract. Pyrimidino-crown ethers were prepared in 30-50% yields by reacting the ditosylate derivative of the appropriate oligoethylene glycol with 4-methoxy-5-methyl-2,6-pyrimidinedimethanol under basic conditions. A new macrocyclic ligand containing a proton-ionizable pyrimidone subcyclic unit was prepared in 88% yield by treating the appropriate pyrimidino-crown ether with 5 M NaOH in 50% (v/v) aqueous methanol. Preliminary complexation properties of some of these new compounds were studied using various NMR spectral techniques. Good enantiomeric recognition was exhibited by a chiral pyrimidino-crown ether for the enantiomers of 1-(α-naphthyl)ethylammonium perchlorate.

Key words. Crown ether, pyrimidine-containing crown ether, pyrimidone-containing crown ether, benzylammonium complexes.

1. Introduction

Macrocyclic ligands are polydentate species containing their donor atoms either incorporated in or, less commonly, attached to a cyclic backbone. Examples of naturally occurring macrocyclic ligands are the ionophore antibiotics such as nonactin, gramicidin A, and valinomycin, which bind potassium selectively and act as carriers for this ion across cell membranes. Various other naturally occurring macrocycles

capable of binding cations are known [1]. The significance of metal complexes of different macrocyclic ligands in the mechanisms of a variety of biological systems has long been recognized [2]. The possibility of using synthetic macrocycles as models for ligands in biochemical reactions provided the impetus for investigations of the metal ion chemistry of biological systems as well as that of synthetic cyclic ligand systems.

The unique complexing characteristics of cyclic polyethers first reported by Pedersen [3] about a quarter of a century ago led to a large variety and number of macrocyclic compounds. The complexation properties of these host ligands have been reviewed [4-7]. Among the synthetic macrocyclic ligands, crown ethers containing donor atoms (mainly oxygen) incorporated in the cyclic backbone have contributed abundantly to modern coordination chemistry.

Work in our laboratories has been directed toward the systematic determination of parameters that affect complex stability in terms of thermodynamic and kinetic data for complex formation [7,8]. We have made various structural changes to the basic crown ether molecules in attempts to enhance the stability of the complexes and selectivity toward both metal and organic cations. Some of these modifications involve the substitution of sulfur and/or nitrogen for one or more of the several polyether oxygen atoms that create the cavity. Other substitutions have involved the insertion of aromatic and/or heterocyclic systems into the macroring. The many changes to the crown ether ligands done in our laboratory are summarized in an accompanying paper [9]. A short review of the interactions of some of our macrocyclic ligands with metal ions is likewise included in this special issue [10].

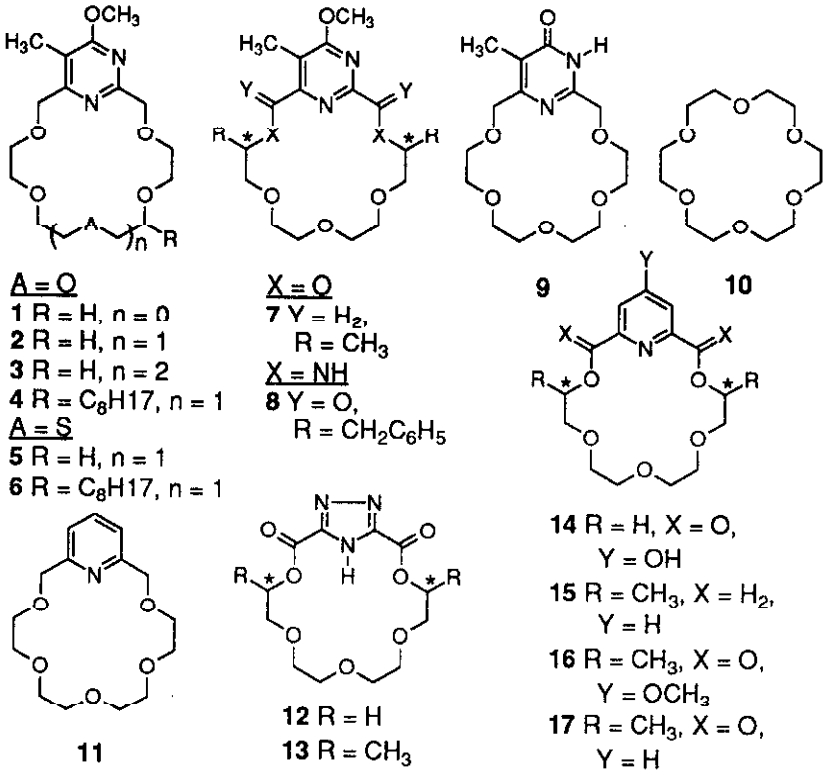
The present paper focuses on the synthesis and complexation properties of a new class of macrocycles containing pyrimidine and pyrimidone subcyclic units. These new ligands are capable of complexing organic ammonium cations and amines. The presence of a pyrimidine nitrogen as one of the ligand donor atoms may favor a three-point hydrogen bond interaction between the primary ammonium cation and the macrocycle as has been observed for crown ethers containing a pyridine unit [11]. In general, a N-H···N hydrogen bond is stronger than a N-H···O bond [12]. Thus, the typical tripod hydrogen bond involving the pyrimidine nitrogen and two alternate oxygen atoms of the macrocycle and the three hydrogen atoms of the ammonium cation should be possible. The pyrimidine ring will also provide a π-π interaction with the aromatic group of the ammonium cation as observed in the pyridino-crown ethers [13].

Enantiomeric recognition of organic amines and ammonium salts by chiral macrocycles is an area of molecular recognition that has received considerable attention [14-17]. Our interest in enantiomeric recognition has focused on the interaction of chiral crown ethers containing pyridine derivatives as a part of the macroring with chiral organic ammonium salts [11,16,18,19]. In certain cases [20], these chiral pyridine-containing crown ethers have demonstrated appreciable

enantiomeric recognition. The pyrimidine- and pyrimidone-containing chiral crown ethers are expected to likewise have good recognition for the enantiomers of chiral primary amines and ammonium salts.

Crown ethers containing proton-ionizable groups are of interest to many researchers [21]. The majority of these ligands have the proton-ionizable moiety as 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 without the need for an anion to accompany the macrocycle-ion complex [22,23]. The transport of these metal cations, in many cases, is pH dependent so that the transport can be turned on or off by adjusting the pH [23,24].

Figure 1. Crown ether ligands



2. Preparation of Pyrimidine- and Pyrimidone-containing Crown Ethers

Pyrimidine-containing crown ethers **1-6** (Figure 1) were prepared by treating the appropriate oligoethylene glycol ditosylate with 4-methoxy-5-methyl-2,6-

pyrimidinedimethanol and base as reported [25]. The pyrimidinedimethanol starting material was prepared from acetamidine and diethyl oxalpropionate by a six-step process [25]. (*S,S*)-**7** was prepared by treating (*S,S*)-1,11-dimethyl-3,6,9-trioxa-1,11-undecanediol [26] with 4-methoxy-5-methyl-2,6-pyrimidinedimethanol ditosylate [25]. (*S,S*)-Diazapyrimidino-crown **8** was synthesized by reacting (*S,S*)-1,11-dibenzyl-3,6,9-dioxa-1,11-undecanediamine [27] with dimethyl 4-methoxy-5-methyl-2,6-pyrimidinedicarboxylate [25].

Proton-ionizable pyrimidono-crown ether **9** was synthesized by refluxing for 48 hours pyrimidino-crown ether **2** in a 5 M NaOH solution in 50% (v/v) aqueous methanol. The proton-ionizable pyrimidono-crown ether was isolated in an **88%** yield as a solid (mp, 85-86 °C) [28].

3. Complexation of Organic Ammonium Perchlorate Salts and Amines by the Pyrimidine- and Pyrimidone-containing Crown Ethers

Table I shows the coalescence temperatures (T_C) and free energy of activation ($\Delta G_C^{\ddagger}$) values for the dissociation of the complexes of various crown ether ligands with benzylammonium perchlorate as determined by a temperature dependent ^1H NMR

Table I. $\Delta G_C^{\ddagger}$ and T_C Values for the Interaction in CD_2Cl_2 of Various Macrocycle Hosts with Benzylammonium Perchlorate and Benzylamine Guests as Determined by a Variable Temperature ^1H NMR Method.

Host	Guest[a]	$\Delta G_C^{\ddagger}$ (kcal/mol)	T_C (°K)	ref
2	Bz-NH_3^+	13.4	258	b
9	Bz-NH_2	10.5	213	b
10	Bz-NH_3^+	8.4	173	31
11	Bz-NH_3^+	11.9	238	32
12	Bz-NH_3^+	10.4	219	33
	Bz-NH_2	14.0	288	33
13	Bz-NH_2	12.7	267	33
14	Bz-NH_3^+	14.1	308	34
	Bz-NH_2	12.3	263	34
15	Bz-NH_3^+	11.7	244	11
16	Bz-NH_3^+	13.4	265	11

[a]Bz-NH_3^+ = benzylammonium perchlorate, Bz-NH_2 = benzylamine.
[b]This work

process [29,30]. It is apparent from these $\Delta G_C^{\ddagger}$ values that the compounds containing a heteroaromatic ring moiety form kinetically more stable complexes with benzylammonium perchlorate than does the polyether 18-crown-6 (**10**). Pyrimidine-containing ligand **2** forms a complex with Bz NH_3^+ which has a similar kinetic stability to that of the complex with methoxypyridino-crown **16**, more stable than the complex with **11** and **15**, and less stable than the complex with **14** as shown in Table I (compare $\Delta G_C^{\ddagger}$ values of 13.4 kcal/mol for the complex of **2** with 11.9, 14.1, 11.7 and 13.4 kcal/mol for **11**, **14**, **15**, and **16**, respectively). Macrocycles **14** and **16** are diester crown ethers, while **11** and **15** do not have ester functions. Thus, the complex of **2** is kinetically more stable than those of **11** and **15** which are structurally similar. Likewise the complex of **2** with benzylammonium perchlorate is kinetically more stable than the complexes of triazole-derived crown ethers **12** and **13**. The $\Delta G_C^{\ddagger}$ value for proton-ionizable pyrimidono-crown **9** with benzylamine was 10.5 kcal/mol, much lower than those for the complexes of **12** (14.0 kcal/mol) and **14** (12.2 kcal/mol) with benzylamine.

Formation of complexes between $BzNH_3^+$ and pyrimidino-crown ligands **2** and **7** and pyrimidono-crown ligand **9** was accompanied by significant ^1H NMR chemical shift changes. For example, the signal at $\delta = 4.56$ attributable to the methylene hydrogens located between the pyrimidone ring and the ether oxygen of **9** shifted upfield to $\delta - 4.29$ upon complexation with benzylamine. In all of the complexes involving ligands **2** and **9**, the signals for substituents attached to the pyrimidine (pyrimidone) ring exhibit upfield shifts (shielding) in the ^1H NMR spectra while those for the methylene hydrogens of the oligoether macroring exhibit downfield shifts (deshielding). This suggests 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 various hydrogens. The magnetic shielding and deshielding of proton signals corresponding to the pyridine protons of pyridine-containing crown ethers have also been observed and discussed [35].

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 (see Table II). Conversion of the pyrimidine methoxy group into the pyrimidone oxo group lowers the log K value of the host-guest complex from 5.72 to 3.74 in the 1:1 mixed methanol and chloroform solvent (compare values for the **2**-Bz-NH_3^+ and **9**-Bz-NH_3^+ interactions).

Table III lists the values of $\Delta\log K$ as determined by a ^1H NMR titration spectroscopic method for various chiral macrocycle-chiral primary ammonium salt interactions at 25 °C. The chiral ligands included in Table 3 have a common methyl group that generates the stereocenters. Thus the stereocenters have the same bulkiness. The $\Delta\log K$ values range from 0.95 for the complexes of (*S*,*S*)-**7** with the

Table II. Log K Values for the Interaction of Pyrimidino- and Pyrimidono Crown Ethers with Two Primary Organic Ammonium Perchlorates and One Amine as Determined by a ^{1}H NMR Method at 25 °C.[a]

Ligand	Cation[b]	Solvent[c]	Log K	Δlog K
2	Bz-NH_3^+	IM/IC	5.72	
		M	4.27	
9	Bz-NH_3^+	IM/IC	3.74	
	Bz-NH_2	IM/IC	3.31	
7	(*R*)-NapEt-NH_3^+	IM/IC	5.18	0.95
	(*S*)-NapEt-NH_3^+	IM/IC	4.23	
	(*R*)-NapEt-NH_3^+	M	3.73	
	(*S*)-NapEt-NH_3^+	M	3.35	0.38

[a]Varian Gemini-200 and 500 MHz spectrometers were used to record the ^{1}H NMR spectra. [b]Bz-NH_3^+ = benzylammonium perchlorate, Bz-NH_2 = benzylamine, NapEt-NH_3^+ = the (*R*)- or (*S*)-form of 1-(α-naphthyl)ethylammonium perchlorate. [c]M = CD_3OD, C = $CDCl_3$.

Table III. Δlog K Values[a] for the Interactions of Various Macrocycles with Enantiomeric Organic Ammonium Perchlorate Salts.

Ligand	Cations[b]	Solvent[c]	ΔLog K	ref
(*S,S*)-**7**	NapEt-NH_3^+	IM/IC	0.95	d
	NapEt-NH_3^+	M	0.38	d
(*S,S*)-**15**	NapEt-NH_3^+	IM/IC	0.54	35
	NapEt-NH_3^+	M	0.40	35
(*S,S*)-**17**	NapEt-NH_3^+	IM/IC	0.60	32
	NapEt-NH_3^+	M	0.41[e]	11
(*R,R*)-**17**	NapEt-NH_3^+	IM/IC	0.60	35
	NapEt-NH_3^+	M	0.42	36
(*S,S*)-**16**	NapEt-NH_3^+	IM/IC	0.80	35
	NapEt-NH_3^+	M	0.45[e]	35

[a]Determined by ^{1}H NMR spectral method at 25 °C using Varian Gemini-200 and 500 MHz spectrometers to record the ^{1}H NMR Spectra. [b]NapEt-NH_3^+ = 1-(α-naphthyl)ethylammonium perchlorate. [c]M = CD_3OD, C = $CDCl_3$. [d]This work. [e]Determined by a calorimetric method.

enantiomeric forms of NapEt-NH_3^+ in a 1:1 deuteriomethanol-deuteriochloroform mixture, to 0.54 for the NapEt-NH_3^+ complexes of (*S,S*)-**15** in the same solvent system. The consistency in the $\Delta\log K$ values in duteriomethanol which range from 0.45 for the NapEt-NH_3^+ complexes of (*S,S*)-**16** to 0.38 for the NapEt-NH_3^+ complexes of (*S,S*)-**7** is interesting. Perhaps the polar nature of the solvent is reducing the effect of the stereocenters of the macrocycle so that similar stereochemical results are obtained in each case. It is evident from Table 3 that enantiomeric recognition by the pyrimidine-derived (*S,S*)-**7** compares favorably to the more studied pyridine-derived crown ethers in both solvent systems.

4. Experimental

The pyrimidino- and pyrimidono-crown ether ligands used in this study were prepared as reported [25,28]. The free energy of activation measurements ($\Delta G_C^{\ddagger}$) were determined as reported for the pyridino-crown systems [11,29,30]. The $\Delta G_C^{\ddagger}$ values are listed in Table I. The log *K* values were determined by a ^1H NMR spectral titration method as reported [36] and are listed in Table II.

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