Ag^+ Selection by Aza-18-crown-6 Ethers *N*-Substituted on Heterocyclic Aromatics†

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Dedicated to Professor Leo A. Paquette on the occasion of his 70th birthday

Substitution on the nitrogen atom, where necessary by high-pressure S_NAr reactions, of aza-18-crown-6 ethers linked to heterocyclic aromatics has extended the number of potential host compounds for Ag^+. The complexation of Ag^+ by the new compounds has been evaluated by liquid membrane ion transport and ion extraction experiments. The nature of the binding sites of these new host compounds for Ag^+ has been assessed, in DMF/D_2O (4/1), by ^{13}C nmr titration experiments with $AgClO_4$.

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Introduction.

Many accounts of host-guest chemistry of crown ethers, ranging from reviews [1-6] to syntheses and evaluations of new compounds, attest to a continued interest in the nature of the selectivity and transport properties of crown ethers. Recent accounts encompass basic crown ethers and azacrown ethers [7-10], more diverse crown ethers that incorporate heteroatoms of sulphur [11-24], or selenium [25], where Ag^+ was the predominantly complexed metal ion. Further evidence of the bacteriostatic properties of Ag^+ was successfully demonstrated by using a chitosan-crown ether macromolecule loaded with Ag^+ [26]. Other accounts of the diversity of the chemistry of crown ethers comprise the evaluation of diaza-18-crown-6 ligand bearing two quinolin-8-methyl side arms [27], and the enantiomeric discrimination afforded by Yb^{3+} chelated by (+)-(18-crown-6)-2,3,11,12-tetracarboxylic acid [28]. The continued development of crown ethers as sensors for ions and also as molecular scaffolds for materials and biological models has recently been reviewed by Gokel *et al*. [29].

Earlier accounts by Matsumoto and his colleagues have recounted high-pressure S_NAr reactions for the preparation of mono- and diazacrown ethers linked directly to aromatic heterocycles and their selective binding and transport properties for Ag^+ [11-14]. In this account we report the derivatization of heterocyclic trichlorotriazines and dichlorodiazines, 1,3-bis-(bromomethyl)benzene and 2,6-dibromomethylpyridine by reaction with 4,7,10,13,16-pentaoxa-1-azacyclooctadecane (henceforth, mono-aza-18-crown-6) to form, as appropriate to the reaction conditions, azacrown ethers as mono-, di- and tri-substituted moieties (**1-12**). The propensity of the various azacrown ethers (**1-12**) for association with Ag^+ has been determined by: (i) measurement of chemical shift changes of ^{13}C atoms, in the neighbourhood of complexed Ag^+, by ^{13}C nmr; (ii) extraction of Ag^+ into dichloromethane in the presence of **1-12**; and (iii) liquid membrane ion transport of Ag^+ by **1-12**.

Results and Discussion.

The results of the liquid membrane ion transport as well as ion extraction experiments are summarized in Tables 1 and 2. As previously found [14], guest salts were hardly transported at all in the absence of a carrier.

A reduction in the electron density on the azacrown nitrogen atom, by the direct substitution of electron-deficient heteroaromatic groups on the azacrown nitrogen atom, was characterized by a poor extraction of alkali metal ions. The compounds in which an aromatic

Scheme 1

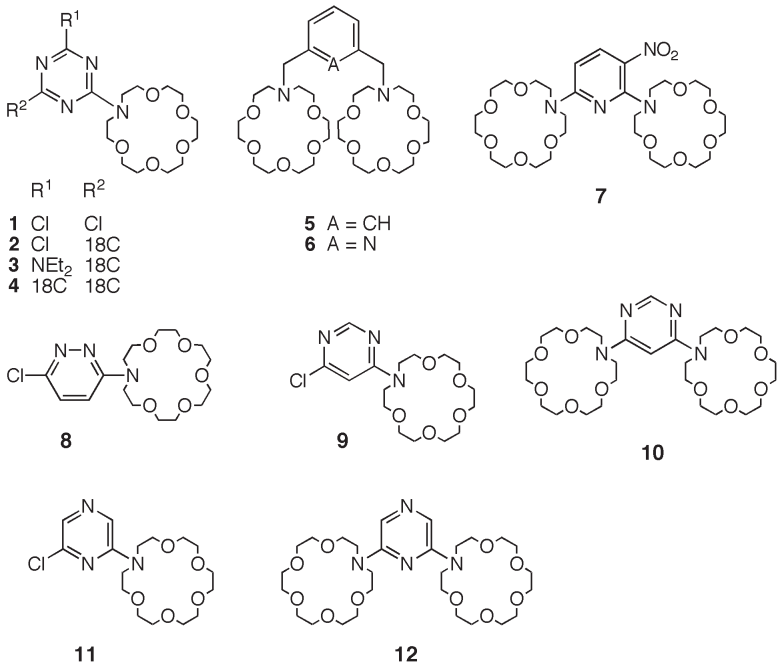

Table 1

Transport Properties of Crown Ethers **1-12** for Li^+, Na^+, K^+, and Ag^+ [a]

Transport rate x 10^6 (mole /h) of cations by azacrown ether carriers

	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Li^+			*	*	*	0.5	*	*	*	*	*	0.1
Na^+	*	*	0.1	*	0.2	2.3	0.1	*	*	0.1	*	0.1
K^+	*	*	0.2	0.2	4.1	3.6	0.3	*	*	0.2	*	0.3
Ag^+	0.4	2.0	2.0	3.5	0.8	1.3	2.4	1.7	2.0	3.5	0.7	2.1

[a] Conditions. Aqueous phase 1: guest perchlorate, 0.10 mol H_2O solution, 5 ml; membrane: carrier, 0.0372 mmol/CH_2Cl_2, 12 ml. Aqueous phase 2: H_2O, 5 ml. Below limit of detection (<0.1).

Table 2

Cation Extraction Properties of Crown Ethers **1-12** for Li^+, Na^+, K^+, and Ag^+ [a]

Extraction ratio (%) of cations by azacrown ether carriers

	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Li^+	*	*	*	*	*	*	*	*	*	*	*	*
Na^+	*	*	*	*	*	5	*	*	*	*	*	7
K^+	*	*	*	*	18	32	*	*	*	*	*	5
Ag^+	*	*	*	*	36	43	*	*	9	9	9	27

[a] Conditions. Aqueous phase: guest perchlorate, 0.01 mol solution in H_2O (2 ml). Organic phase: azacrown ether, 0.02 mmol/CH_2Cl_2 (2ml). Below limit of detection (<5%).

ring is bonded directly to the azacrown nitrogen atom, other than in compounds **5** and **6** where interposing methylene moieties reduced electron withdrawal, exhibited weak interaction with Na^+ and K^+ (Table 2). The electron attracting effect of the electron-deficient heteroaromatic rings leads to a reduced electron density on the azacrown nitrogen atoms and thus reduced the interaction of these compounds with the hard cations Na^+ and K^+. In contrast, compounds **5** and **6** in which an aromatic ring is bonded indirectly to the azacrown nitrogen atom through interposing methylene groups, exhibited relatively high transport and extraction properties for alkali metals however low selectivity arose as a result of their flexible structure. The same pattern of a more effective selectivity of Ag^+ over Na^+ and K^+ by a series of N-substituted monoazacrown ethers has been reported [14].

The mono-, bis-, and tris-azacrown ethers **1-4** selectively transported Ag^+. The transportability of the cation increased with the number of azacrown ring substituents on the symmetrical triazine. Transport and extraction properties for Ag^+ by mono-crown ethers **9** and **11** were slightly different from those of bis-crown ethers **10** and **12**. In addition, significantly different transport and extraction properties were also noted for Hg^{2+} [30].

In addition to evaluating, by ^{13}C nmr titration experiments, the binding of species such as Ag^+, it is also possible to evaluate metal ion binding by macrocycles by electrospray ionization mass spectrometry, a technique recently used by Williams *et al*. [24] to evaluate

the effectiveness of some caged macrocycles for complexation of Ag^+.

As Ag^+ is a soft cation, it can be expected to interact more readily with the relatively soft azacrown nitrogen than nearby oxygen atoms. This study shows that by selective substitution of aromatic moieties on the azacrown nitrogen atom, it is possible to manipulate the electron density on the foregoing nitrogen atom so that the resulting host compounds possess a varying degree of softness on the azacrown nitrogen atom and, thus, a varying degree of receptivity for soft transition metal ions such as Ag^+. X-ray crystal structural analysis of the co-ordination of Ag^+, when complexed by *N*,*N*-dithiazoly-diaza-18-crown-6-ether, demonstrates participation of thiazole, the azacrown nitrogen atom and a counter anion in the complexation of Ag^+ [31].

The ^{13}C nmr titration studies of mono-, bis-, and tris-crown ethers **1-4**, and **7**, which had all exhibited good transportability of Ag^+ in the perchlorate form, have been compared with related host compounds **5** and **6**. From these comparative studies (Figures 1-7), it is clear that the

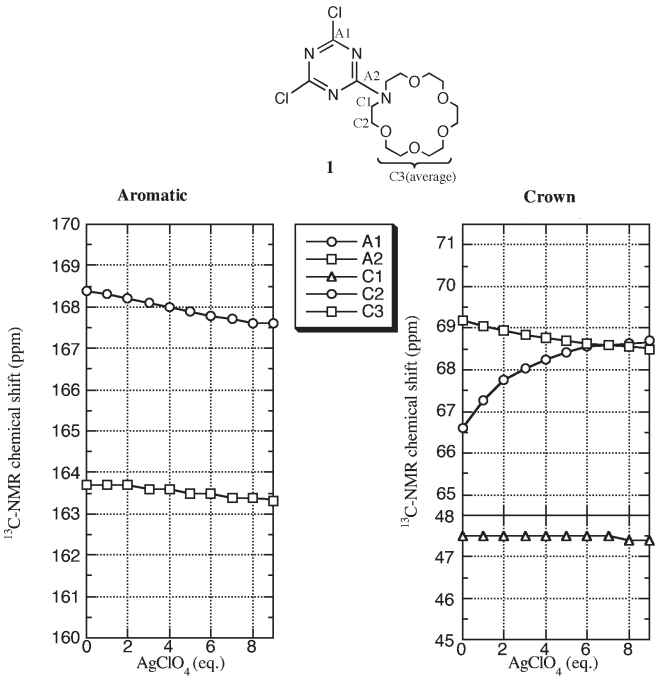

Figure 1. ^{13}C nmr chemical shifts of **1** in DMF/D_2O (4/1) at positions A1 and A2 of the aromatic moiety and at positions C1, C2 and C3 of the crown ether moiety.

aromatic triazine moiety of host compounds **1-4** and the nitrogen atom from the azacrown ring, are not participants in the binding of Ag^+. The decrease in electron density at the cation-binding site is characterized by a ^{13}C chemical

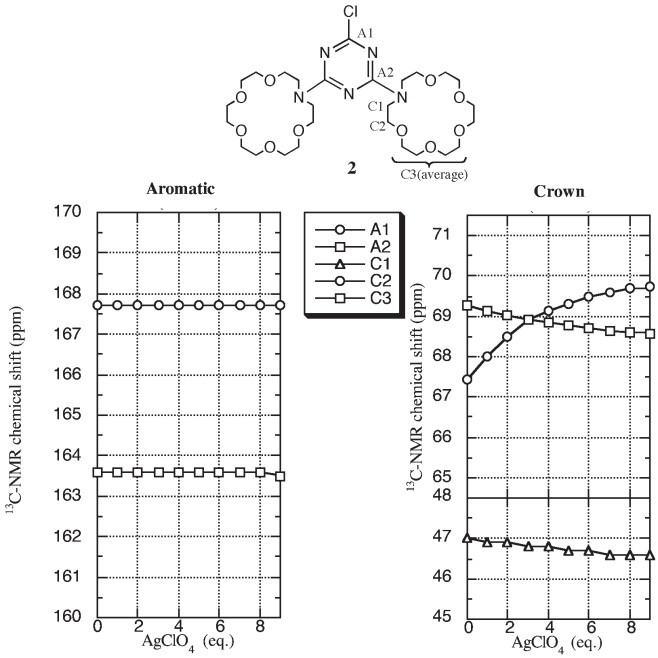

Figure 2. ^{13}C nmr chemical shifts of **2** in DMF/D_2O (4/1) at positions A1 and A2 of the aromatic moiety and at positions C1, C2 and C3 of the crown ether moiety.

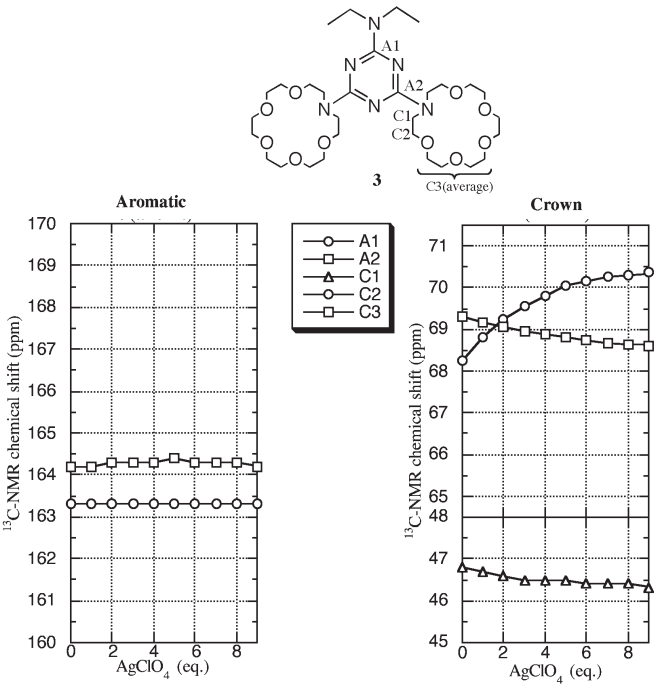

Figure 3. ^{13}C nmr chemical shifts of **3** in DMF/D_2O (4/1) at positions A1 and A2 of the aromatic moiety and at positions C1, C2 and C3 of the crown ether moiety.

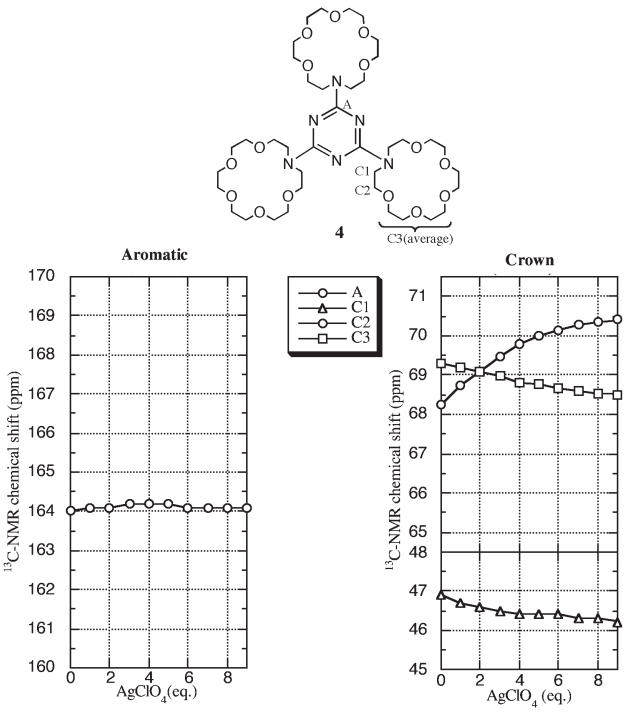

Figure 4. ^{13}C nmr chemical shifts of **4** in DMF/D_2O (4/1) at position A of the aromatic moiety and at positions C1, C2 and C3 of the crown ether moiety.

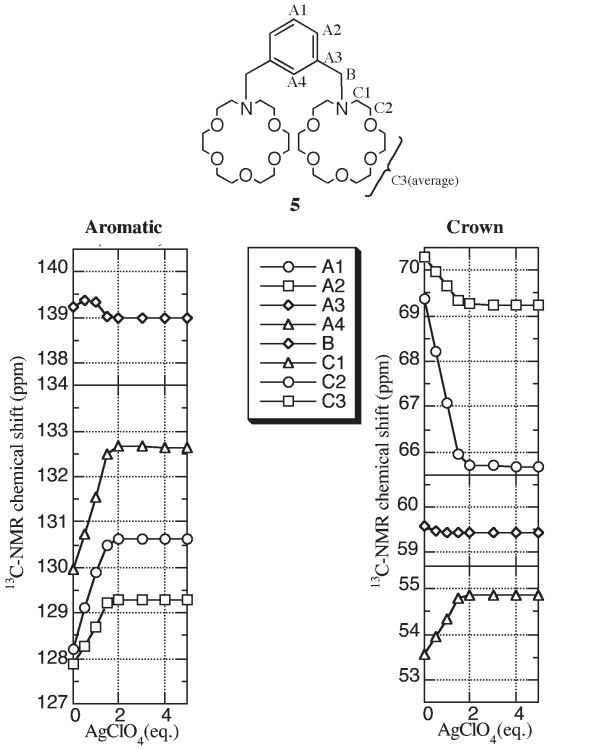

Figure 5. ^{13}C nmr chemical shifts of **5** in DMF/D_2O (4/1) at positions A1, A2, A3 and A4 of the aromatic moiety, at position B of the methylene moiety, and at positions C1, C2 and C3 of the crown ether moiety.

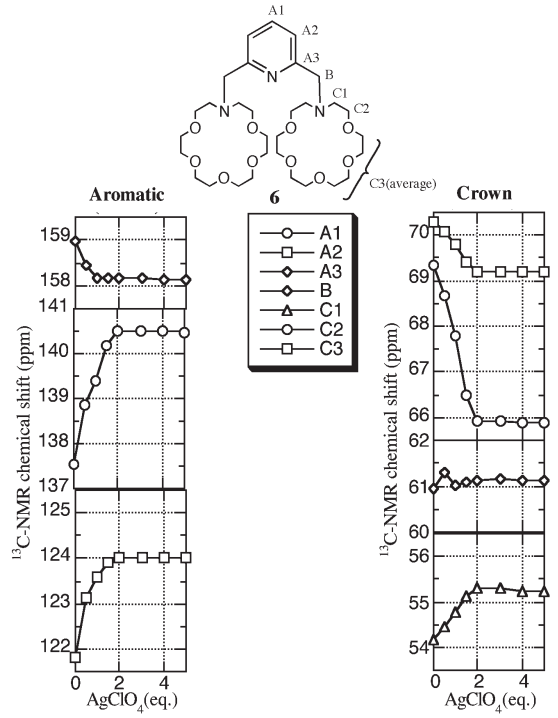

Figure 6. ^{13}C nmr chemical shifts of **6** in DMF/D_2O (4/1) at positions A1, A2 and A3 of the aromatic moiety, at position B of the methylene moiety, and at positions C1, C2 and C3 of the crown ether moiety.

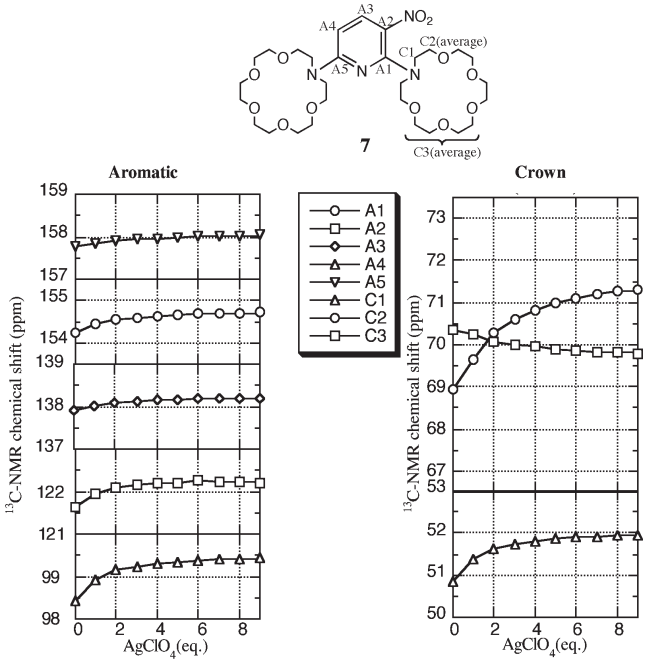

Figure 7. ^{13}C nmr chemical shifts of **7** in DMF/D_2O (4/1) at positions A1, A2, A3, A4 and A5 of the aromatic moiety and at positions C1, C2 and C3 of the crown ether moiety.

shift downfield on the adjacent carbon atom. The occurrence of a carbon atom with an upfield shift suggests the existence of a counter anion in proximity to the carbon atom. The host compounds **5**, **6** and **7** exhibit down field shifts both at C1 (positions 2 and 18) of the azacrown ring and at the aromatic ring, whereas the host compounds **1-4** and **7** show a downfield shift at C2 (positions 3 and 17) of the azacrown ring. Therefore, the binding sites for Ag^+, in **1-4**, are considered to be the oxygen atoms at positions 4 and 16 of the azacrown ring. In compounds **5** and **6** the Ag^+ binding site is on the azacrown nitrogen atom and the aromatic ring. For **7** the Ag^+ binding site is at the monoaza nitrogen atom and 4 and 16 (both O) of the crown ring.

An absence of coordination by the monoaza nitrogen atom is presumably determined by the high π-electron deficiency of the triazine ring, which in turn lowers the electron density of the azacrown nitrogen atom to such a level that it becomes a poor ligand for Ag^+. In compound **7** the azacrown nitrogen atom and the oxygen atoms at positions 4 and 16 participate in the binding of Ag^+. Therefore, the behaviour of compound **7** is intermediate between that of compounds **5** and **6** and compounds **1-4**. These studies with compounds **1-4**, **5**, **6** and **7** demonstrate the nature of the binding site on Ag^+ can be manipulated by the electron density through the linkage between the aromatic moieties and the nitrogen atom of the azacrown rings.

In further studies, with compounds **8-12**, the electron-withdrawing properties of pyridazine, pyrimidine or pyrazine moieties were evaluated in a series of ^{13}C nmr titration experiments (Figures 8-12). The results show, for

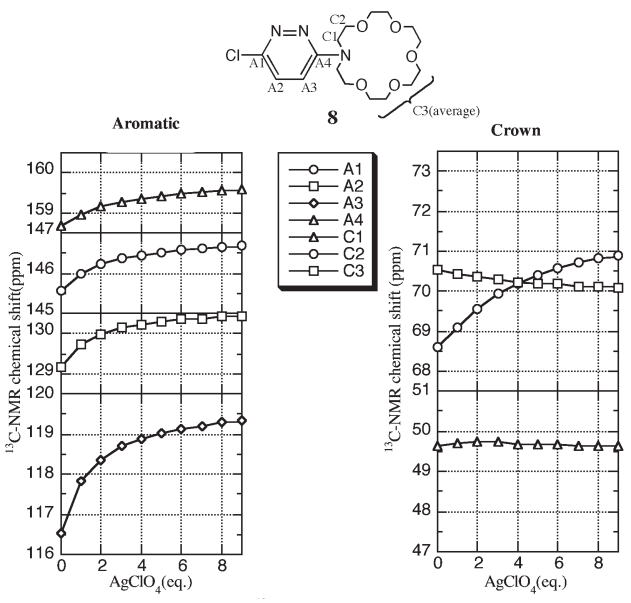

Figure 8. ^{13}C nmr chemical shifts of **8** in DMF/D_2O (4/1) at positions A1, A2, A3 and A4 of the aromatic moiety and at positions C1, C2 and C3 of the crown ether moiety.

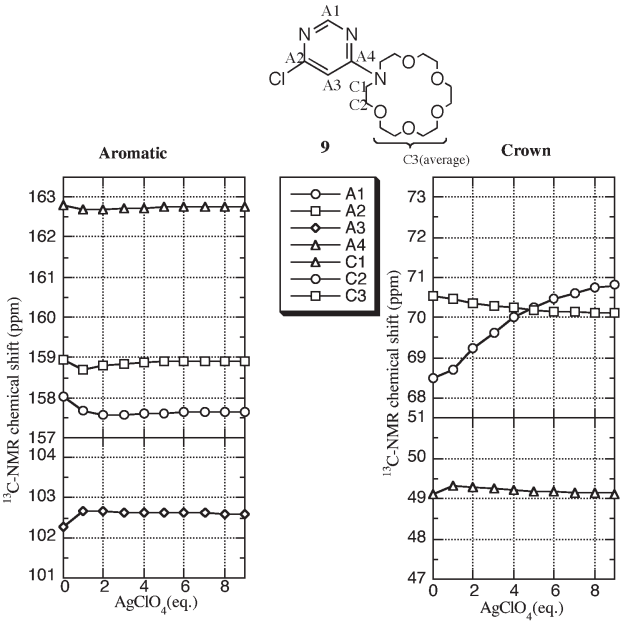

Figure 9. ^{13}C nmr chemical shifts of **9** in DMF/D_2O (4/1) at positions A1, A2, A3 and A4 of the aromatic moiety and at positions C1, C2 and C3 of the crown ether moiety.

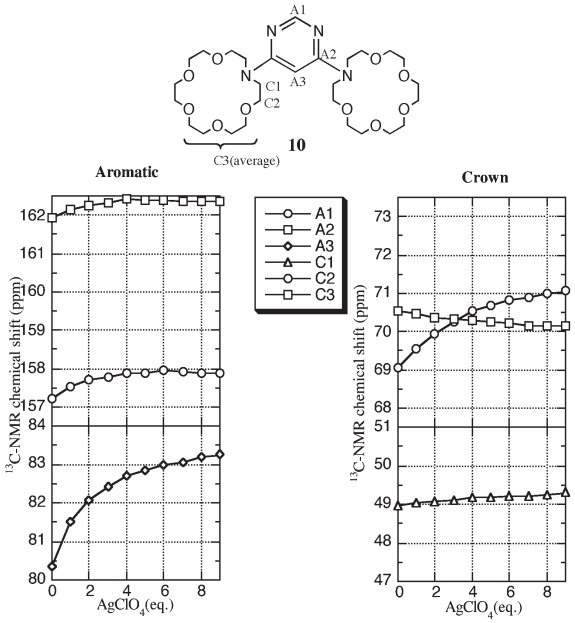

Figure 10. ^{13}C nmr chemical shifts of **10** in DMF/D_2O (4/1) at positions A1, A2 and A3 of the aromatic moiety and at positions C1, C2 and C3 of the crown ether moiety.

compounds **8-12**, other than **9**, downfield shift was observed on the aromatic rings at A3 (or A1) but was only at C2 (positions 3 and 17) on the crown ring. Thus, the electron-withdrawing property of pyridazine, pyrimidine,

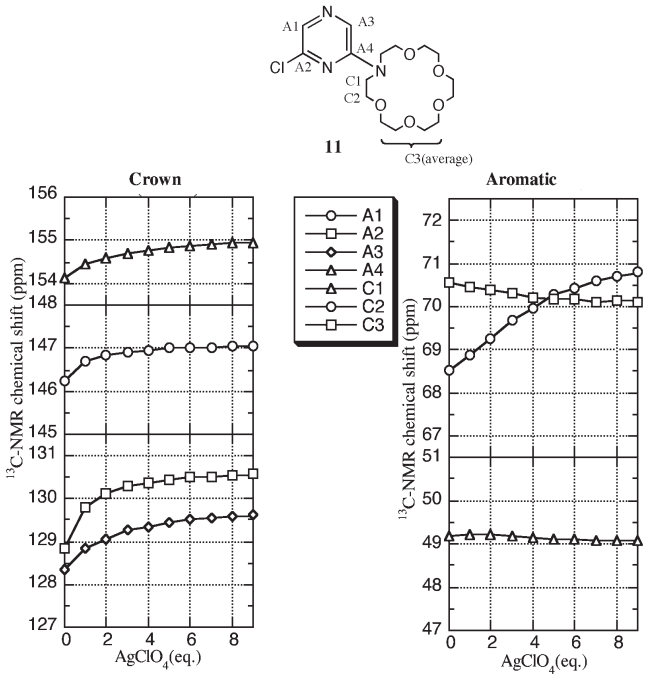

Figure 11. ^{13}C nmr chemical shifts of **11** in DMF/D_2O (4/1) at positions A1, A2, A3 and A4 of the aromatic moiety and at positions C1, C2 and C3 of the crown ether moiety.

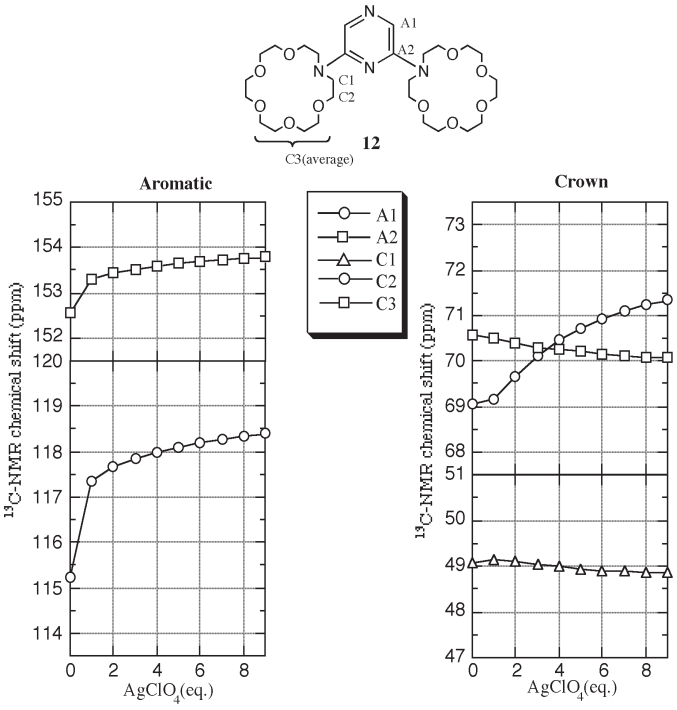

Figure 12. ^{13}C nmr chemical shifts of **12** in DMF/D_2O (4/1) at positions A1 and A2 of the aromatic moiety and at positions C1, C2 and C3 of the crown ether moiety

and pyrazine moieties was so significant that the azacrown nitrogen atom became an ineffective ligand for Ag^+. On the other hand, the downfield shift was observed at the aromatic ring, except for **9**. Therefore, the binding site for Ag^+ is probably located only at oxygen atoms of positions 4 and 16 in compound **9** and at oxygen atoms at positions 4 and 16 of the azacrown ring and aromatic ring for compounds **10-12**. The Ag^+-binding behaviour of compounds **8** and **10-12** is intermediate between that of compounds **1-4** and compound **7**.

As the number of nitrogen atoms in the intervening aromatic moieties increases so the electron attraction is in the direction of the aromatic substituent. These studies reveal, as shown in Figure 13, that the binding site for Ag^+ is determined by the electron deficiency in the aromatic moiety that serves as a spacer between the azacrown ethers.

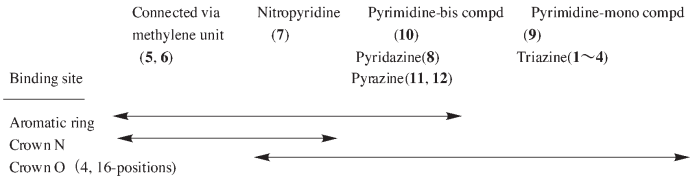

Figure 13. Illustration of the influence of the aromatic moieties on the ligands that contribute to the Ag^+ binding sites of compounds **1-12**.

In the cases of **5** and **6**, where the chemical shift changes remain constant after addition of two equivalents of silver perchlorate, a relatively stable 1:2 complex is formed with Ag^+. However, all attempts to obtain suitable crystals for an X-ray analysis were unsuccessful.

In summary, the results indicate that two mono-aza-18-crown-6 rings cooperatively function as a host for the guest Ag^+. The ability of the hosts to entrap Ag^+ increases by more than mere increment of host site and, therefore, the construction of bis- or tris-crown ethers is a useful strategy for improving the guest-capturing properties of host molecules.

EXPERIMENTAL

General.

Elemental analysis was performed on Yanaco CHN-CORDER MT or MY-3 or MT-5 instruments by the department services at the laboratory for organic elemental microanalysis, Faculty of Pharmaceutical Sciences, Kyoto University. All solvents were distilled before use, and where necessary dried by using Merck silica gel 60 (70-200 mesh) or Wacogel C-200 (100-200 mesh) or Wacogel C-300 (220-300 mesh). Column chromatography was conducted on alumina (Merck acid activity grade 1). When the eluent was a mixture of two solvents they were used in equal volumes.

IR spectra were obtained on a JASCO IR-G spectrometer. The ^{1}H nmr spectra were measured on a JEOL JNM-EX270

(270 MHz) or a JNM-ALPHA500 (500 MHz) instrument. ^{13}C nmr spectra were recorded on a JEOL JNM-EX270 or on a JNM-ALPHA500 pulsed Fourier-transform spectrometer operating at 67.80 MHz and 125.65 MHz, respectively. Chemical shifts are expressed in parts per million downfield from tetramethylsilane, the internal standard. Either partial proton decoupling or DEPT (distortionless enhancement by polarization transfer) was used to distinguish between individual carbon atoms.

Transport and Extraction Experiments.

Evaluation of liquid membrane ion transport and dichloromethane liquid membrane ion extraction by the azacrown ethers was performed by exactly the same procedure as described previously [13,14]. Perchlorate was measured in the extraction and transport investigations by using a perchlorate ion-selective electrode and an Orion EA940 Autochemical System Ion meter. The cations Li^+, K^+, Na^+ and Ag^+ were determined with a Shimadzu EA-940 Atomic Absorption /Flame Emission Spectrophotometer.

^{13}C nmr and Assignment of Binding Sites of Crown Ethers for Ag^+.

By using ^{13}C nmr to measure changes in the chemical shifts of ^{13}C in azacrown ether rings it is possible to identify those components of the host compounds which contribute to the binding of Ag^+. The resulting decreases in the electron density at the cation binding sites leads to changes in the chemical shift of adjacent ^{13}C atoms. The presence of a ^{13}C atom with a high field implies the existence of a counter ion close to the ^{13}C atom. The procedure has already been described [13,14]. To solutions (0.5 ml) of 0.050 mmol of the azacrown ether in DMF/D_2O (4/1), contained in three nmr tubes, was added 0.5 equivalent, 1 equivalent, and 2 equivalents of silver percholorate to provide the range indicated in Figures 1-12. To solutions (0.5 ml) of 0.050 mmol of the azacrown ether in DMF/D_2O (4/1), contained in three nmr tubes, was added 0.5 equivalent, 1 equivalent, and 2 equivalents of silver percholorate to provide the range indicated in Figures 1-12. Immediately after addition of perchlorate the ^{13}C nmr spectrum was measured. A control experiment for each of the azacrown ethers **1-12** was also performed in the absence of silver perchlorate to facilitate deduction of ^{13}C nmr chemical shifts induced by complexation of Ag^+.

1,3-Dichloro-5-(4,7,10,13,16-pentaoxa-1-azacyclooctadecyl)-2,4,6-triazine (**1**) and 1-Chloro-3,5-bis(4,7,10,13,16-pentaoxa-1-azacyclooctadecyl)-2,4,6-triazine (**2**).

A mixture of mono-aza-18-crown-6 (2.9 g, 11 mmoles), 1,3,5-trichloro-2,4,6-triazine (0.973 g, 5 mmoles) and triethylamine (2.23 ml, 16 mmoles) in dichloromethane (50 ml) was refluxed for 25 hours. The solvent was evaporated *in vacuo* and the residue purified by column chromatography on alumina. Successive elution with hexane-ethyl acetate gave colourless compound **1** (0.25 g), as an oil, in 12% yield and then elution with ethyl acetate and ethyl acetate - ethanol gave **2** (2.63 g) as an oil in 82% yield.

1: ^1H nmr (270 MHz, $CDCl_3$): δ 3.66 (s,8H), 3.68 (s, 8H), 3.73 (t, 4H,J=5.8 Hz, 3.94 (t,4H,J=5.8 Hz); ^{13}C nmr (67.80 MHz, $CDCl_3$): δ 48.82, 68.36, 70.46, 70.53, 70.59, 70.82, 164.73, 169.86.

Anal. Calcd for $C_{15}H_{24}N_4Cl_2$: C, 43.81; H, 5.88; N, 13.62. Found: C, 43.95; H, 5.91; N, 13.56.

2: ^1H nmr (270 MHz, $CDCl_3$): δ 3.66 (8H, s), 3.61-3.72 (40H, m), 3.82 (8H, t) ; ^{13}C nmr (67.8 MHz, $CDCl_3$) : δ 47.7, 48.0, 69.1, 70.0, 70.1, 70.2, 70.4, 70.4, 164.2, 168.2; IR ν_{max} (neat): 1561, 1489, 1114 cm^{-1}.

Anal. Calcd for $C_{27}H_{48}O_{10}N_5Cl$: C, 50.82; H, 7.58; N, 10.97. Found: C, 51.10; H, 7.84; N, 10.97.

1,3-Bis(4,7,10,13,16-pentaoxa-1-azacyclooctadecyl)-5-diethylamino-2,4,6-triazine (**3**).

Monoaza-18-crown-6 (0.79 g, 3 mmoles), THF (20 ml), triethylamine (0.42 ml, 4 mmoles) and 1,3-dichloro-5-diethylamino-2,4,6-triazine [15] (0.26 g, 0.96 mmole) were heated at reflux for 16 hours and the solvent evaporated *in vacuo*. The residue was purified by column chromatography on alumina. Successive elution with hexane-ethyl acetate, ethyl acetate, ethyl acetate-ethanol gave compound **3** (0.56 g, 0.88 mmole) as a yellow oil in 92% yield; ^1H nmr (270.0 MHz, CDCl3): δ 1.12 (t, 6H, J=7.2Hz), 3.50 (q, 4H, J= 7.0 Hz), 3.60-3.80 (m, 48 H); ^{13}C-nmr (67.80 MHz, $CDCl_3$): δ 13.6, 41.1, 48.1, 69.8, 69.9, 70.5, 70.7, 70.9, 164.7, 165.1. IR ν_{max} (neat): 1528, 1489, 1113 cm^{-1}.

Anal. Calcd for $C_{31}H_{58}O_{10}N_6$: C, 55.18; H, 8.66; N, 12.45. Found: C, 54.97; H, 8.84; N, 12.73.

1,3,5-Tris-(4,7,10,13,16-pentaoxa-1-azacyclooctadecyl)-2,4,6-triazine (**4**).

A mixture of mono-aza-18-crown-6 (0.30 g, 1 mmole), **2** (1.43 g, 2.2 mmoles) and triethylamine (0.56 ml, 4 mmoles) in tetrahydofuran (THF, 4 ml) was reacted under pressure (0.8 GPa) in a Teflon vessel at 100°C for 7 days. The solvent was evaporated *in vacuo* and the residue purified by chromatography on alumina. Successive elution with hexane-ethyl acetate, ethyl acetate and ethyl acetate-ethanol gave **4** as a colorless oil 0.350 g in 22% yield; **4** : ^1H nmr (270 MHz, $CDCl_3$): δ 3.60-3.80 (72H, m); ^{13}C nmr (67.8 MHz, $CDCl_3$) : 47.9, 69.5, 70.2, 70.4, 70.4, 70.6, 164.6; IR ν_{max} (neat): 1527, 1487, 1109 cm^{-1}.

Anal. Calcd for $C_{39}H_{72}O_{15}N_6$: C, 54.15; H, 8.39; N, 9.72. Found: C, 54.24; H, 8.39; N, 9.55.

1,3-Bis-(4,7,10,13,16-pentaoxa-1-azacyclooctadecyl)-methylbenzene (**5**).

Compound **5** was prepared accoding to the procedure reported by Johnson *et al*. [32].

1,3-Bis-(4,7,10,13,16-pentaoxa-1-azacyclooctadecyl)-methylpyridine (**6**).

A solution of monoaza-18-crown-6 (1.45 g (5.5 mmoles), THF (60 ml), 2,6-bis(iodomethyl)-pyridine (0.97 g, 2.7 mmoles) and triethylamine (1.39 ml, 10 mmoles) was refluxed for 6 hours. After removal of precipitated material, the solvent was evaporated *in vacuo* and the residue dissolved in diethyl ether. The product, **6**, was purified by column chromatography on alumina. Successive elution with hexane-ethyl acetate, ethyl acetate and ethanol gave **6** (1.13 g, 69% yield) as a yellow oil; ^1H nmr (270 MHz, $CDCl_3$): δ 2.85 (t, J=4.6 Hz, 8H), 3.61-3.69 (m, 40H); ^{13}C nmr (67.8 MHz, $CDCl_3$) : δ 53.7, 69.2, 69.8, 70.2, 70.3, 120.5, 136.3, 158.6.

Anal. Calcd for $C_{31}H_{55}O_{10}N_3$: C, 59.12; H, 8.80; N, 6.67. Found: C, 58.76; H, 8.74; N, 6.52.

2,6-Bis(4,7,10,13,16-pentaoxa-1-azacyclooctadecyl)-3-nitropyridine (**7**).

A mixture of monoaza-18-crown-6 (1.05 g, 4 mmoles), 2,6-dichloro-3-nitropyridine (0.39 g, 2 mmoles), triethylamine (1.12 ml, 8 mmoles) and THF (4 ml) was reacted under about 0.8 GPa in a Teflon vessel at 100°C for 4 days. The solvent was evaporated *in vacuo* and the residue purified by column chromatography on alumina. Successive elution with hexane-ethyl acetate, ethyl acetate and ethyl acetate-ethanol gave **7** (1.03 g, 80% yield) as a yellow oil; ^{1}H nmr (270 MHz, $CDCl_3$): δ 3.88-3.67 (m, 48H), 6.09 (d J = 9.4 Hz, 1H), 8.16 (d, J = 9.6 1H); ^{13}C nmr (67.8 MHz, $CDCl_3$): δ 51.1, 69.5, 70.4, 70.56, 70.64, 70.68, 70.71, 97.4, 121.9, 138.1, 154.1, 157.4.

Anal. Calcd. for $C_{29}H_{50}N_4Cl_{12}H_2O$: C, 52.40; H, 7.88; N, 8.43. Found: C, 52.52; H, 7.74; N, 8.53.

3-(4,7,10,13,16-pentaoxa-1-azacyclooctadecyl)-6-chloropyridazine (**8**).

The synthesis of this compound has been already reported by Matsumoto *et al*. [14].

4-(4,7,10,13,16-Pentaoxa-1-azacyclooctadecyl)-6-chloropyrimidine (**9**) and 4,6-Bis(4,7,10,13,16-pentaoxa-1-azacyclooctadecyl)-pyrimidine (**10**).

A mixture of monoaza-18-crown-6 (1.20 g, 4 mmoles), 4,6-dichloropyrimidine (0.461 g, 3 mmoles) and triethylamine (1.67 ml, 12 mmoles) was reacted in THF (4 ml) under 0.8 GPa in a Teflon vessel at 100°C for 4 days. The solvent was evaporated *in vacuo* and the residue purified by column chromatography on alumina. Successive elution with hexane-ethyl acetate, ethyl acetate and ethyl acetate-ethanol gave **9** (0.35 g) as a yellow oil compound, in 31% yield, and **10** (0.60 g) as a yellow oil in 33% yield.

9: ^{1}H nmr (270 MHz, $CDCl_3$): δ 3.60-3.79 (m, 24H), 6.59(s, 1H), 8.33 (s, 1H); ^{13}C nmr (67.80 MHz, $CDCl_3$): δ 49.22, 68.70, 69.85, 70.68, 70.78, 101.73, 157.83, 159.42, 162.46.

Anal. Calcd for $C_{16}H_{26}N_3O_5Cl$: C, 51.13; H, 6.97; N, 11.18. Found: C, 50.98; H, 6.88; N, 10.96.

10: ^{1}H nmr (270 MHz, $CDCl_3$): δ 3.59-3.77 (m, 48H), 5.57 (s, 1H), 8.15 (s, 1H); ^{13}C nmr (67.80 MHz, $CDCl_3$): δ 48.93, 69.27, 70.53, 70.64, 70.68, 70.75, 80.09, 157.03, 161.81.

Anal. Calcd for $C_{28}H_{50}N_4O_{10}$: C, 55.80; H, 8.36; N, 9.30. Found: C, 55.61; H, 8.33; N, 9.23.

3-(4,7,10,13,16-pentaoxa-1-azacyclooctadecyl)-5-chloropyrazine (**11**).

A mixture of monoaza-18-crown-6 (1.58 g, 6 mmoles), 3,5-dichloropyrazine (0.745 g, 5 mmoles), triethylamine (1.67 ml, 12 mmoles) and THF (30 ml) was refluxed with stirring for 14 days. The solvent was evaporated *in vacuo* and the residue purified by column chromatography on alumina. Successive elution with hexane-ethyl acetate and ethyl acetate gave **11** (1.453 g, in 77% yield) as a yellow oil; ^{1}H nmr (270 MHz, $CDCl_3$): δ 3.65-3.84 (m, 20H), 7.74 (s, 1H), 7.98(s, 1H); ^{13}C nmr (67.80 MHz, $CDCl_3$) : δ 49.36, 68.77, 70.68, 70.77, 127.69, 129.27, 146.38, 153.50.

Anal. Calcd for $C_{16}H_{26}ClN_3O_5$: C, 51.13; H, 6.97; Cl, 9.43; N, 11.18. Found: C, 50.98; H, 6.88;Cl, 9.38, N, 10.96.

3,5-Bis-(4,7,10,13,16-pentaoxa-1-azacyclooctadecyl)-pyrazine (**12**).

A mixture of monoaza-18-crown-6 (1.05 g, 4 mmol), **11** (0.752 g, 2 mmoles) and triethylamine (1.12 ml, 8 mmoles) in THF (4 ml) was reacted at 0.8 GPa in a Teflon vessel at 100°C for 9 days. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography on alumina. Successive elution with ethyl acetate gave **12** (0.775 g), in 62% yield, as an orange oil; ^{1}H nmr (270 MHz, $CDCl_3$): δ 3.61-3.75 (m, 48H, 7.29 (s, 2H); ^{13}C nmr (67.80 MHz, $CDCl_3$) : δ 49.11, 69.15, 70.57, 70.66, 70.78, 115.74, 151.93.

Anal. Calcd for $C_{28}H_{50}N_4O_{10}$: C, 55.80; H, 8.36; N, 9.30. Found: C, 55.52; H, 8.40; N, 9.13.

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