Synthetic Molecular Receptors for Urea. Macrocyclic Ligands with Intraannular Acidic Groups and the Complexes with Urea[1]

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Abstract: Measurements of the acidities of macrocycles containing intraannular acidic groups provide a method to evaluate the complexation of these crown ethers with neutral molecules in polar media. Six types of crown ethers (**1–6**) possessing intraannular pyridinium, phenolic, and/or carboxylic groups were synthesized. The complexation with urea was assessed by accurate potentiometric titrations, liquid–liquid or solid–liquid extraction experiments, and X-ray crystallography. In solid–liquid extraction experiments efficiencies of complexation of urea by the macrocycles as high as 0.54 were found. In liquid–liquid extraction experiments competition with water caused lower extraction efficiencies. The crystal structures of 2-carboxyl-1,3-xylyl-24-crown-7·H_2O (**3d**·H_2O), 2-carboxyl-1,3-xylyl-30-crown-9·urea (**3f**·urea), and **6b**·urea are reported. All these structures show the encapsulation of the guest and prove that the acidic groups are involved in hydrogen bonding to the guest.

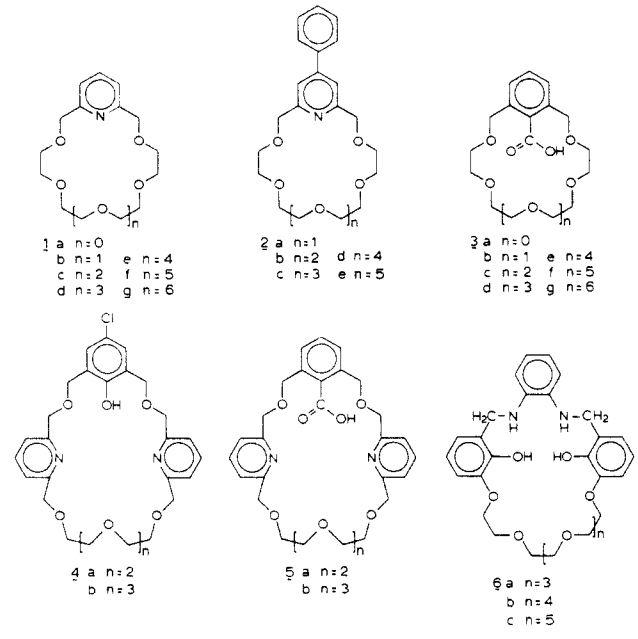
One of the major aims in supramolecular chemistry is the design of host molecules for specific guests. Hitherto the complexation of small centrosymmetric cations by host molecules with ring sizes of 12–21 ring atoms has received most of the attention.[2] However, there is an increasing interest in the complexation of neutral guest species.[3] For the efficient complexation of uncharged guests of either biochemical or industrial significance, e.g., urea, formaldehyde, or methanol via encapsulation, larger macrocycles are needed.[4]

In one of the first papers on crown ether chemistry, Pedersen showed that urea interacts with simple crown ethers such as benzo-18-crown-6.[5] However, the nature of the interaction between host and guest was not further studied. The design and synthesis of receptor molecules for neutral polyfunctional polar molecules such as urea is one of our major targets.[6] Previously we have reported the X-ray crystal structures of the 1:5 complexes of 18-crown-6 and aza-18-crown-6 with urea.[7] In these complexes urea is bound in a perching fashion, and the association constants of these complexes are very low (urea-18-crown-6, log $K_s < 0.1$, H_2O, 25 °C).[8]

We are currently studying the possibilities of inducing a charge separation in complexes with neutral guests by means of a (partial) proton transfer reaction from host to guest, thus increasing their mutual binding. Previously we have reported that protonated 2,6-pyrido crown ethers can form complexes with water[9] and with guanidine.[10] Owing to the pK_a difference between host and guest, in the former complexes the proton is not transferred, whereas in the latter complexes complete proton transfer was observed. X-ray structure determinations showed that in both cases the guest molecules are encapsulated by the macrocycle. Liquid–liquid extraction experiments in which guanidinium or uronium salts were extracted into a chloroform solution containing the crown ether showed that the selectivities for the guest molecules depend very strongly on the ring size of the ligand.[10,11] For good efficiencies of extraction ring sizes of ≥27 are required. Uronium perchlorate extractions with efficiencies up to 70% were achieved.[11] Recent complexation experiments with macrocycles that have a carboxylic acid group in a pendant arm have shown that an acidic group located close to the cavity increases the extraction urea from neutral solution when compared with macrocycles without such an acidic group.[12]

The ultimate objective of our work was to design receptor molecules for urea that are able (i) to solubilize urea in apolar solvents and (ii) to assist in the selective transport of urea through liquid immobilized membranes.

Chart I



In this paper we report a systematic study of the effect of intraannular acidic groups present in macrocyclic cavities on the

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(1) Part of this work appeared in preliminary form: Aarts, V. M. L. J.; van Staveren, C. J.; Grootenhuis, P. D. J.; van Eerden, J.; Kruise, L.; Harkema, S.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1986**, *108*, 5035–5036.

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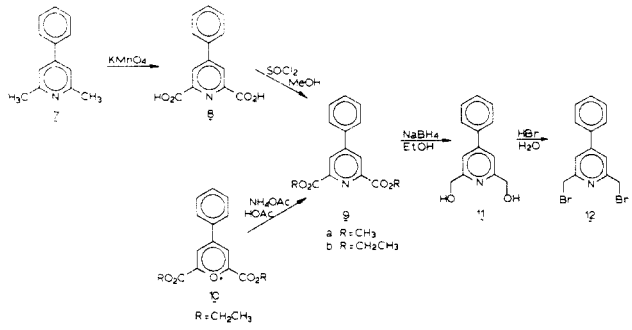
Scheme I



complexation of urea. Quantitative information about the complexation in solution was obtained by accurate pK_a measurements of the ligands in the presence and absence of urea. Furthermore, complexation was studied by solid–liquid and liquid–liquid extraction experiments. The structures of three crystalline complexes obtained in these studies were investigated by X-ray crystallography.

Synthesis of the Macrocyclic Hosts. All macrocycles used in this study (Chart I) possess one or two intraannular proton-donating groups, which can be used to protonate a neutral guest molecule or to form a strong hydrogen bond with the guest species. The 2,6-pyrido crown ethers (**1**) were synthesized as reported previously.[10] Earlier results showed that these macrocycles can undergo self-complexation, a process in which the polyether encapsulates the pyridine moiety, when the ring size is 24 ring atoms or larger.[9] This self-complexation of the 2,6-pyrido crown ethers was shown both in the crystalline phase, with X-ray structure determinations, and in solution, by means of ^{13}C NMR T_1 relaxation time measurements. The self-complexation was observed in the crystalline state, both in the protonated and in the nonprotonated ligands. These macrocycles are readily soluble in aqueous solution and this would be a disadvantage in liquid–liquid extraction experiments or membrane transport.

Therefore we synthesized the 4-phenyl-2,6-pyrido crown ethers **2**. Firstly, we expected that self-complexation would not be possible for these macrocycles. Secondly, the presence of the lipophilic phenyl group would decrease their solubility in water. The synthesis of 4-phenyl-2,6-pyrido crown ethers (**2**) was carried out via two routes. The first route comprises a classical Hantzsch[13] synthesis and the second route employs a synthesis of pyridines from the corresponding pyrylium salts.[14] Condensation of benzaldehyde, ethyl acetoacetate, and ethyl 2-aminocrotonate in EtOH followed by oxidation, hydrolysis of the ester groups, and decarboxylation yielded 2,6-dimethyl-4-phenylpyridine (**7**).[15] Oxidation with $KMnO_4$ in water gave the corresponding dicarboxylic acid (**8**) in poor yield.[16] 4-Phenyl-2,6-bis(bromomethyl)pyridine (**12**) was obtained by esterification, reduction, and bromination (Scheme I).[17]

Alternatively 4-phenyl-2,6-dicarbethoxypyrylium tetrafluoroborate[18] (**10**) was heated with ammonium acetate in acetic acid to give the corresponding 4-phenylpyridine diester **9b**[19] which was reduced with sodium borohydride in EtOH to give **11**. Subsequent bromination with HBr yielded 4-phenyl-2,6-bis(bromomethyl)-pyridine (**12**) (Scheme I).

Although the pyrylium salt formed in poor yield, the easily accessible starting materials render the latter route more attractive than the former where the cumbersome oxidation with $KMnO_4$ is a serious disadvantage.

The 4-phenyl-2,6-pyrido crown ethers **2a–e** were synthesized by reaction of 4-phenyl-2,6-bis(bromomethyl)pyridine with the appropriate polyethylene glycol in THF with NaH as a base. All reactions were carried out under high dilution conditions, and the crown ethers were obtained in 40–60% yield. All 4-phenyl-2,6-pyrido crown ethers showed 80 MHz ^1H NMR as well as ^{13}C NMR spectra in agreement with their structures. The ^{13}C NMR T_1 relaxation time measurements (vide infra) showed that for these 4-substituted pyrido crown ethers the self-complexation in solution does not take place.

The 2-carboxyl-1,3-xylyl-crown ethers (**3**) were synthesized by a modification of the reaction described by Cram and co-workers[20] from methyl 2,6-bis(bromomethyl)benzoate and the disodium salt of the appropriate polyethylene glycol in THF. Purification of these macrocycles was accomplished by chromatography, and the crown ethers were obtained in 36–85% yield. The crown ether esters were hydrolyzed in quantitative yield to give the acids **3**. An alternative route for the synthesis of these macrocycles comprises the reaction of 2-bromo-1,3-xylyl crown ethers with *n*-BuLi, followed by reaction with CO_2.[21] The IR and ^1H NMR spectral data of **3a–c** and **3f** were in agreement with the literature data, and those of **3d,e** and **3g** were in agreement with the proposed structures. In the mass spectra the signal with the highest m/e corresponds to the crown ether after loss of one molecule of water.

Two types of macrocycles (**4** and **5**) that contain both acidic and basic functionalities were synthesized. Both have pyrido groups as the basic functionality, but they differ in the nature of the acidic group, which is either a carboxylic acid or a phenolic hydroxyl group.

6-(Bromomethyl)-2-pyridinemethanol[17] reacts under basic conditions to form polymeric products, and consequently the hydroxyl group was protected as the tetrahydropyranyl ether. The protected alcohol **13** was used without purification in the reactions with the polyethylene glycols to give the protected diols **14**. The protecting tetrahydropyranyl ether moiety hydrolyzed during the acidic workup procedure and the diols **15** were purified by chromatography to give colorless oils in 24 and 26% yield (Scheme II).

In the ^1H NMR spectrum of **15a** two singlets at δ 4.72 and 4.67 ppm were observed for the benzylic protons. In **15b** these benzylic protons are present as a broad singlet at δ 4.7 ppm. In the ^{13}C NMR spectra of **15a** and **15b** all five aromatic carbons are observed as separate signals.

The diols **15** were cyclized with two different dibromides in tetrahydrofuran with NaH as a base and template ion. A phenolic hydroxyl group was introduced with the protected phenol equivalent 1,3-bis(bromomethyl)-5-chloro-2-(2-propenoxy)-benzene (**16**) as the dibromide,[22] and cyclization gave the protected phenols **17** in 45–65% yield. The protecting group was removed with 5% Pd/C in refluxing methanol/water (80/20) with a trace of acid to give the macrocycles **4** in 80–85% yield as white crystalline compounds (Scheme II).

Macrocycles incorporating an intraannular carboxylic acid group were synthesized by cyclization of **15** with methyl 2,6-bis(bromomethyl)benzoate[20] (**18**) in tetrahydrofuran with NaH

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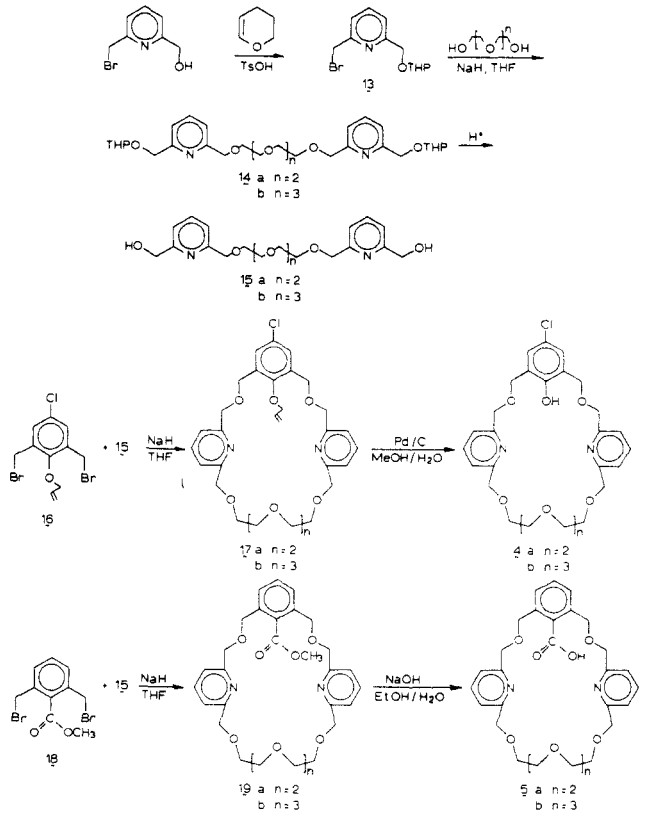
Scheme II



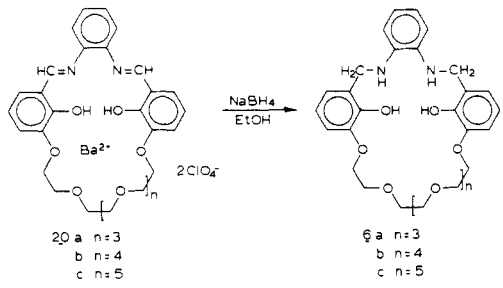
as a base and template ion to give the crown ether esters **19** in 42–52% yield. Subsequently, these were hydrolyzed to the corresponding acids **5** with NaOH in ethanol/water in 85–88% yield (Scheme II).

In the ^1H NMR ($CDCl_3$) spectra of the macrocycles **4**, **5**, **17**, and **19** the $ArCH_2$ and $Ar'CH_2$ protons were observed as singlets. For the *O*-allyl protected phenolic macrocycles **17** only one singlet was observed, whereas for the other macrocycles the three different types of benzylic protons were observed as three singlets. It is likely that in these macrocycles inversion of the macroring is fast, because no AB quartets were observed for the $ArCH_2$ protons in contrast with the small (15- and 18-membered) 2-carboxyl-1,3-xylyl crown ethers.[20]

A comparison of the ^{13}C NMR spectra in $CDCl_3$ of the macrocycles **4** and **5** with the spectra of 2,6-pyrido crown ethers,[10] their protonated analogues,[9,10] and their complexes with guanidinium perchlorate[10] shows that in the macrocycles **4** and **5** the proton of the acidic group is not transferred to the pyridine nitrogen. The ^{13}C NMR spectra of the nonprotonated pyridine macrocycles show resonances for C-2,6, C-3,5, and C-4 at approximately δ 158, 121, and 137 ppm, whereas in the protonated form these resonances are observed at approximately δ 153, 125, and 145 ppm, respectively.[9,10] In the macrocycles **4** and **5** we found the resonances for the pyridine carbon atoms at approximately δ 158, 120, and 137 ppm. This indicates that the proton is not transferred to the pyridine nitrogen which is in agreement with the results reported by Cram et al. for the 18-membered macrocycle incorporating both a carboxyl group and a 2,6-pyrido moiety.[23]

During our work on the cocomplexation of neutral molecules and soft metal cations, we have synthesized "Saleno" macrocycles that contain two phenolic hydroxyl groups.[24] These macrocycles were obtained as the corresponding $Ba(ClO_4)_2$ complexes **20** in a template reaction of 1,2-diaminobenzene and an appropriate dialdehyde. The uncomplexed macrocycles are not stable and

Scheme III



slowly hydrolyze to form the dialdehyde and the diamine.

Because these macrocycles contain two intraannular acidic groups they might be of interest for the complexation of urea. In order to prevent hydrolysis of the reactive imine linkages these were reduced to the corresponding diamines with $NaBH_4$ in EtOH (Scheme III). The reduced macrocycles **6** were obtained as white crystalline products in 63–71% yield.

These macrocycles gave ^1H and ^{13}C NMR spectra in agreement with the indicated structures. In the ^1H NMR spectra a singlet at 4.39 ppm (**6a**) or 4.30 ppm (**6b** and **6c**) showed that an $ArCH_2$ was present. In the ^{13}C NMR spectra the signal for $ArCH_2$ was observed at 47.5 ppm (**6a**), 45.7 ppm (**6b**), and 45.3 ppm (**6c**), respectively. In the mass spectra the molecular ion peak was observed. Elemental analysis showed that the larger macrocycles crystallized with one or two molecules of water. The water molecules are possibly encapsulated in the macrocyclic cavity as is the case for the protonated 2,6-pyrido crown ethers.[9]

Relaxation Time Measurements. In order to investigate whether the self-complexation of the pyrido crown ethers is an important factor that might reduce the complexation of urea, the 4-phenyl-2,6-pyrido crown ethers were synthesized. The introduction of a large substituent at the 4-position of the pyridine moiety should effectively prevent self-complexation of the macrocycle. Previously, we have calculated for **1d** in the gas phase only a small difference in energy between the "in" and the "out" conformation, the conformation in which the macrocycle encapsulates the pyridine moiety being the most favorable.[25] By imposing a steric barrier, the "out" conformation may become energetically more favorable. Consequently the complexation may be enhanced because the conformation of the macrocycle is already preorganized for complexation of a guest molecule.

^{13}C NMR T_1 relaxation time values of the 4-phenyl-2,6-pyrido crown ethers **2**, measured by the inversion recovery method,[25] are depicted as a function of the ring size and compared with the unsubstituted 2,6-pyrido crown ethers in Figure 1. The NOE factors of all "protonated" carbons were between 1.7 and 2, indicating that the dipole–dipole (DD) relaxation mechanism is dominating.

For the 2,6-pyrido crown ethers **1** an abrupt decrease of the T_1 values is observed between 21 and 24 ring atoms. We have interpreted this change in terms of self-complexation of the aromatic moiety by the crown ether. The loss of degrees of freedom in such an intramolecular complex, probably combined with a change in solvation, is expressed in the decreased mobilities of both the aromatic and polyether chain ^{13}C nuclei. A minimum ring size of 24 atoms is needed to allow the encapsulation of the aromatic moiety by the polyether chain.[25]

The 4-phenyl-2,6-pyrido crown ethers do not show such a discontinuity in the T_1 values. Apparently self-complexation is not important in these macrocycles. The T_1 values of the 4-phenyl-2,6-pyrido ligands gradually increase with the ring size, after which they decrease. It is known from an X-ray study of 2,6-pyrido-18-crown-6 that the distance between the pyridine nitrogen and a C–H of the polyether chain is relatively short although no hydrogen bond is present in the solid state.[9] In solution this interaction might freeze the conformation of the

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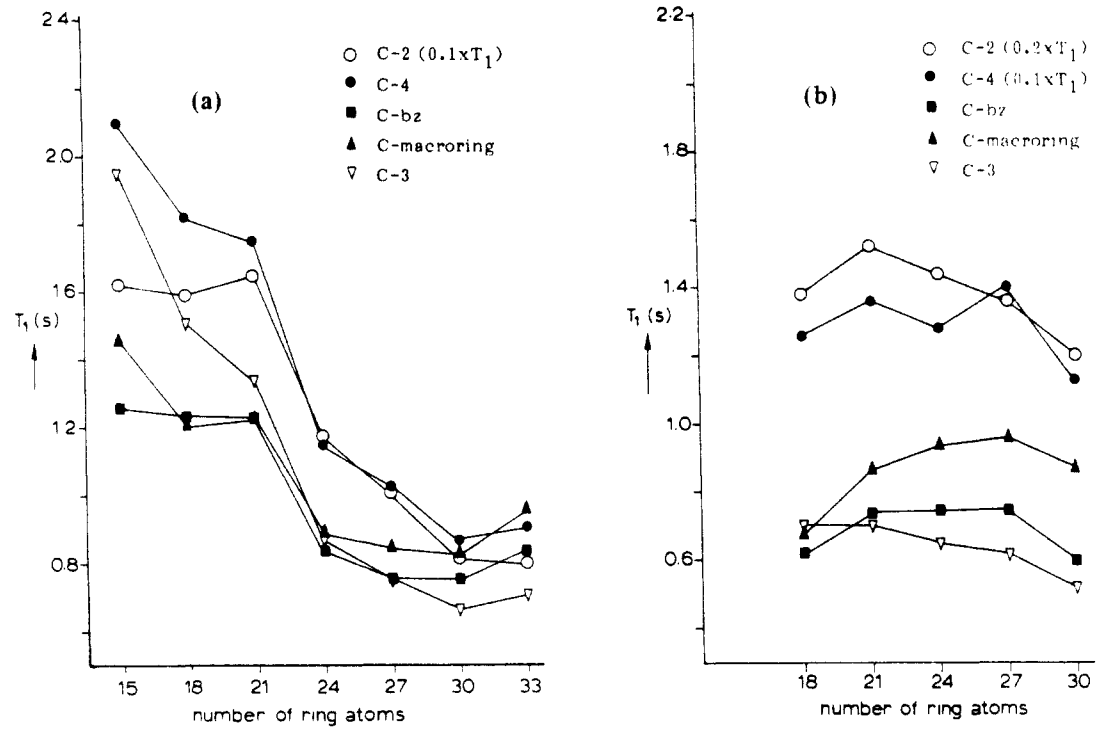

Figure 1. ^{13}C NMR T_1 values of (a) 2,6-pyrido crown ethers (**1**) and (b) 4-phenyl-2,6-pyrido crown ethers (**2**).

18-membered macrocycle. For the 21-membered macrocycle this interaction will be weaker, and a small increase in the mobilities is observed. For 4-phenyl-2,6-pyrido crown ethers which are somewhat more basic than the unsubstituted pyrido crown ethers this effect might be more pronounced.

pK_a Measurements and Complexation of Urea. Although in the literature systematic studies of the acidities of crown ethers with intraannular acidic groups are lacking, there are some indications that the pK_a values of acidic groups in molecular cavities may show large deviations in comparison to representative linear compounds. An example is the enzyme acetoacetate decarboxylase in which the pK_a of the lysine ammonium group at the active site is 6.0, in contrast with a pK_a of 10.7 for lysine in H_2O.[26,27] It should be emphasized that the cavities of synthetic macrocycles are much more accessible to solvent molecules, but a few examples of perturbations of acid–base equilibria as a result of preferential complexation have been reported. Masci found an increased apparent basicity of 4-nitroaniline and 4-toluidine in methanol, due to the complexation of the corresponding anilinium ions with macrocyclic polyethers.[28] Lehn and co-workers reported an apparent pK_a value of a complexed ammonium ion of 15.3 (uncomplexed ammonium ions in H_2O, pK_a = 9.3) due to the ideal fit of this cation in the cavity of a macrotricyclic receptor.[29] The increased pH of a mixture of an alkylamine and an alkylammonium salt upon addition of 18-crown-6 has been used to determine the association constants of complexes with alkylammonium ions.[30]

The pK_a values of crown ethers with an intraannular functional group may serve as a sensitive probe for the systematic study of (weak) host–guest interactions in polar media. Previously we have shown that relatively large pK_a differences of the 2,6-pyridinium crown ethers can be attributed to the complexation of water.[9] We have estimated roughly the stability constants (K_s) of these H_2O complexes from the apparent experimental pK_a value of a cyclic compound and the pK_a of a suitable noncyclic reference compound (log K_s = p$K_{a(exptl)}$ − p$K_{a(ref)}$). The K_s values determined by this potentiometric method varied between 39 L·mol^{-1} (2,6-pyridinium-18-crown-6) to 2 L·mol^{-1} (2,6-pyridinium-27-crown-9).[9]

Table I. pK_a Values of **1**–**3**[a]

ring size	pK_a (**1**)	pK_a (**2**)	pK_a (**3**)
15 (a)	4.88		5.31
18 (b)	4.95	5.12	5.71
21 (c)	4.16	4.25	4.38
24 (d)	3.95	3.97	4.06
27 (e)	3.70	3.74	3.80
30 (f)	3.53	3.70	3.94
33 (g)	3.36		3.93

[a] In H_2O at 25.0 °C;[9] estimated uncertainty in the pK_a values ±0.02.

In analogy with this potentiometric method we can estimate approximate association constants of 4-phenyl-2,6-pyridinium and 2-carboxyl-1,3-xylyl crown ethers (**1**–**3**) with urea in aqueous solution. The potentiometric titration technique that we have used has been described previously for the determination of association constants of complexes of *cations* and cryptands or simple crown ethers in direct or competition experiments.[31] Association constants as low as 100 L·mol^{-1} can be accurately determined in this way. We assumed that the technique can also be used *for the complexation of neutral guest molecules like urea.* The assumption is based on the fact that (i) the addition of even a large excess of the neutral guest does not affect the activities of the charged species, (ii) simple polarity effects on the apparent pK_a would be the same for all crown ethers, *irrespective the ring size*, and (iii) pK_a values can be measured with sufficient accuracy (pK_a ± 0.02). These conditions are met in our experiments.

For these experiments, the pK of the acidic group of the crown ethers **1**–**3** was determined. Subsequently the titrations were repeated in the presence of an excess of the neutral guest urea. We observed differences in pK_a that varied from 0.03 (for the 15–21-membered rings) to 0.15 (for the 27–33 membered rings). With the computer program SUPERQUAD[32,33] it is possible to it-

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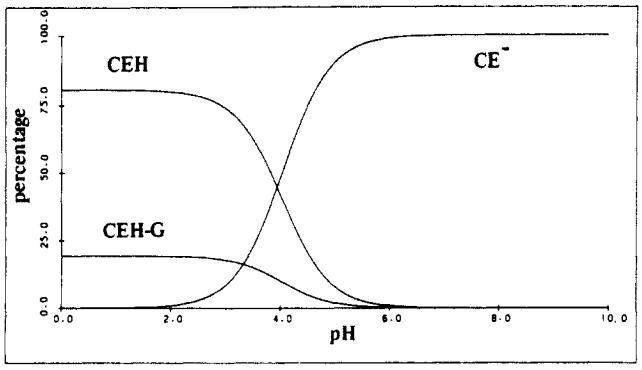

Figure 2. Calculated distributions of the species in a mixture of 2-carboxyl-1,3-xylyl-30-crown-9 (**3f**, C_o = 0.00262 M) and excess of urea (C_o = 0.2571 M) in H_2O as a function of pH. CEH = **3f**, CE^- = anion of **3f**, and CEH-G = **3f**·urea complex.

Table II. Hydrogen-Bonding Parameters[a] in the Crystal Structures

compd	D	A	d(D···A), Å	∠(D–H···A), deg
3d·H_2O	O_{water}	O_{ether}	2.81–2.92	164–168
	$O_{carboxyl}$	O_{water}	2.58	155
3f·urea	N_{urea}	O_{ether}	3.02–3.22	153–173
	$O_{carboxyl}$	O_{urea}	2.54	167
6b·urea	N_{urea}	O_{ether}	2.85–3.18	155–172
	$O_{phenolic}$	O_{urea}	2.58	*b*

[a] D = hydrogen bond donor, A = hydrogen bond acceptor, d(D···A) = distance between donor and acceptor, and ∠(D–H···A) = angle subtended at the hydrogen atom. [b] H atom not located.

eratively calculate the relevant association constants combining the pH data of several titration experiments. In addition, SUPERQUAD[32,33] offers statistical tests for the evaluation of the statistical significance of the various equilibria involved in the complexation.

Because of the relatively weak interactions of crown ethers with neutral guest molecules in polar media a considerable excess of guest must be added in order to generate detectable amounts of complexed guest. In order to study the species distributions as a function of the pH we have used the computer program HALTAFALL.[34] A representative result is given in Figure 2.

The pK_a values of the crown ethers **1**, **2**, and **3** (Table I) exhibit some remarkable features.

The pK_a values of the 4-phenyl-2,6-pyridinium crown ethers show similar variations with the ring size as we reported previously[9] for the 2,6-pyridinium crown ethers. In these macrocycles the protonated 18-membered macrocycle can be stabilized by the formation of a highly structured water complex, which may account for the relatively low acidity of the 18-membered ring. A similar phenomenon is observed for the 2-carboxyl-1,3-xylyl crown ethers **3**. The high pK_a values for the compounds **3a** and **3b** can be explained by the formation of an intraannular hydrogen bond across the macrocyclic ring. The presence of such an intraannular hydrogen bond was shown by Cram and co-workers[20] in the crystal structure of **3b**. The relatively high pK_a values of **3c** and **3d**, when compared with **3e–g**, may be the result of specific complexation of water within the macrocycle, thus stabilizing the protonated form of the ligand as we have observed previously for the 2,6-pyridinium crown ethers.[9]

This assumption was supported by the isolation of a water complex of 2-carboxyl-1,3-xylyl-24-crown-7 (**3d**) from a water/methanol solution. The elemental analysis of this complex (mp 65–67 °C) corresponded to a 1:1 stoichiometry.

The crystal structure of **3d**·H_2O was determined by X-ray crystallography. The ORTEP[35] view of the structure (Figure 3)

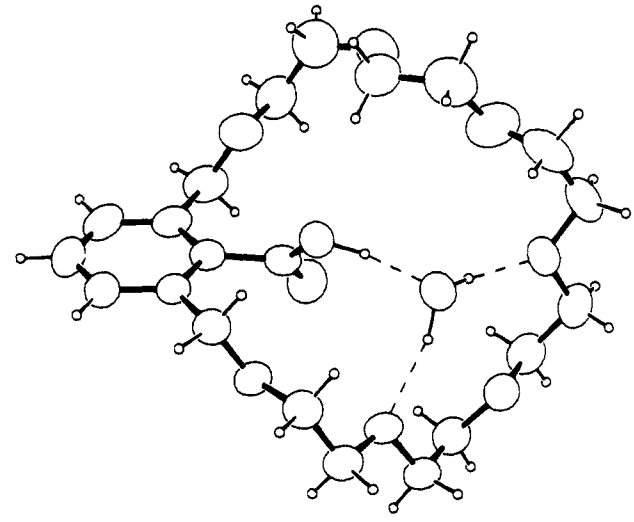

Figure 3. X-ray crystal structure of 2-carboxyl-1,3-xylyl-24-crown-7-(**3d**)·H_2O.

reveals the encapsulation of the water molecule by the macrocycle. The water is bound via three hydrogen bonds. Two are donated to ether oxygens of the crown ether, and one is accepted from the carboxylic OH group (see Table II). No proton transfer from carboxyl to water oxygen is observed. ($O_{carboxyl}$–H 1.01 (4) Å versus H···O_{water} 1.63 (4) Å). The water molecule is displaced from the plane, defined by the three oxygens involved in the hydrogen bonding with water, by 0.83 Å, which indicates a pyramidal coordination of the water oxygen.

The hydrogen-bonding geometry found in this water complex is similar to that in other crown ether–water complexes, where a protonated nitrogen atom[9,36,37] or a phenolic group of a third constituent of a ternary complex acts as a hydrogen bond donor.[38–40] The donor–acceptor distance between the water and the carboxylic oxygen (2.58 Å) is short, compared to the distances of water to other neutral hydrogen-bonding groups.[9,38,39,41] In the ternary complex of 18-crown-6, cyanoacetic acid, and water[41] a similar value (2.60 Å) was observed. The structure of **3d**·H_2O resembles the 3,3′-(1,1′-bi-2-naphthol)-21-crown-5·H_2O complex[42] with respect to the hydrogen bonding and the conformational disorder in part of the macrocycle not involved in the hydrogen bonding. For two ring atoms (in the upper part of Figure 3) two partly occupied positions were found. The conformation associated with the minority positions (not shown in Figure 3, see Supplementary Material) has approximately D_{2d} symmetry, when neglecting the substituent. This conformation was also found in the crystal structure of 2,6-pyrido-24-crown-8·H_2O·$HClO_4$ (1:2:1)[9] and of bis(2-carboxyl-1,3-xylyl)-24-crown-6.[43] It was predicted to be of relatively low steric energy,[25,44] but because the water is too small to fill the cavity completely the conformation with an inwardly oriented methylene group, as shown in Figure 3, is preferred.

(33) For a critical evaluation of the most frequently used computer programs for the evaluation of potentiometric data see: (a) Casassas, E.; Tauler, R.; Filella, M. *Anal. Chim. Acta* **1986**, *191*, 399–411. (b) Casassas, E.; Filella, M.; Tauler, R. *Anal. Chim. Acta* **1986**, *191*, 413–423.

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Table III. Association Constants (K) of the Complexes of **1–3** with Urea[a]

ligand	K (L·mol^{-1})	solvent	ligand	K (L·mol^{-1})	solvent
1b	0.40	*b*	**2e**	1.25	*b*
1f	1.42	*b*	**2f**	1.15	*b*
2b	<0.1	*b*	**3b**	0.41	*c*
2c	0.76	*b*	**3f**	0.79	*c*
2d	0.55	*b*	**3g**	0.68	*c*

[a] Determined in the presence of a 100-fold excess of urea; estimated uncertainty in the K values ±0.10. [b] In H_2O–0.1 M tetraethylammonium chloride. [c] In H_2O.

Table IV. Crystal Data and Data Collection Parameters

compd	**3d**·H_2O	**3f**·urea	**6b**·urea
formula	$C_{21}H_{34}O_{10}$	$C_{26}H_{44}N_2O_{12}$	$C_{33}H_{46}N_4O_{10}$
fw	446.50	576.65	658.76
lattice type	monoclinic	monoclinic	tetragonal
space group	$P2_1/c$	$P2_1/n$	$I4_1/a$
T, K	292	159	179
cell dimensions			
a, Å	12.980 (3)	19.990 (2)	20.016 (8)
b, Å	8.132 (3)	8.943 (1)	
c, Å	22.398 (9)	16.660 (1)	34.307 (10)
β, deg	103.17 (3)	94.54 (1)	
V, Å^3	2302 (3)	2969 (1)	13745 (15)
Z	4	4	16
D_c, g cm^{-3}	1.29	1.29	1.29
F(000)	960	1240	5632
μ, mm^{-1}	0.10	0.10	0.09
θ-range, deg	3–25	3–22.5	3–20
no. of unique refl			
measd	4048	3887	3191
obsd	2077	1988	1865[a]
no. of variables	312	382	422
R, %	4.0	3.6	11.4
R_w, %	5.8	3.8	8.3
weighting factor p	0.06	0.04	0.05
extinction g ($\times 10^{-7}$)	1.9 (7)	1.6 (3)	0.5 (3)

[a] $F_o^2 > \sigma(F_o^2)$.

When the macrocycles **1–3** were titrated in the presence of a 100-fold excess of urea, we found small but significant enhancements of the pK_a values when the presence of urea was neglected in the calculation of the dissociation constant. These pK_a shifts can be explained by assuming the formation of complexes in which urea solvates the acidic moiety of the crown ether. When the formation of (1:1) complexes with urea is included in the calculation it is possible to obtain formation constants of the complexes (vide supra). Indications for other stoichiometries were absent.

The association constants of the crown ethers with urea, calculated from the titrations carried out in the presence of urea, are collected in Table III. The association constants seem low, compared with the constants for the complexes of 18-crown-6 with Na^+, K^+, and NH_4^+ (6, 109, and 17 L·mol^{-1}, respectively),[2] but it should be emphasized that the association constants relate to the complexation of a neutral guest. The largest association constants are observed for the complexes of the 27- and 30-membered pyridinium crown ethers with urea. Since the pyridinium moiety is positively charged in the complex, it is capable of forming a strong hydrogen bond to the complexed species.

The order of magnitude of the association constants in Table III is in agreement with data derived polarographically by Zollinger et al., who found that the association constants of the complexes of simple crown ethers with 27 and 30 ring atoms and urea in polar media are larger than for the corresponding complexes with 18-membered macrocycles.[45] Solid–liquid and liquid–liquid extraction experiments and X-ray structure determinations confirm the encapsulation of urea by 27-, 30-, and 33-membered macrocycles (vide infra).

(45) Zollinger, D. Ph.D. Thesis, University of Twente, Enschede, The Netherlands, 1986.

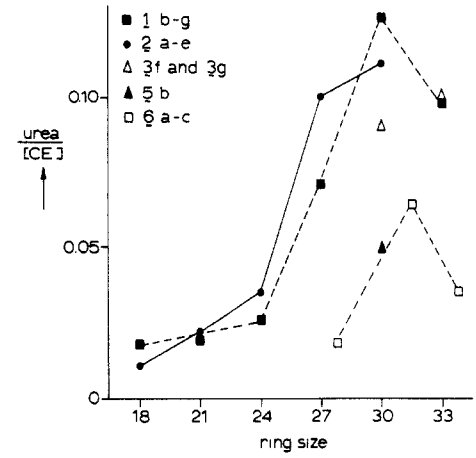

Figure 4. L-L phase transfer of urea by macrocycles (**1–3, 5, 6**). Conditions for **1** and **2** (H_2O phase 2 M urea and 2.8 M $HClO_4$, $CDCl_3$ phase 0.2 M crown ether). Conditions for **3**, **5**, and **6** (H_2O phase 2 M urea and 0.2 M $HClO_4$, $CDCl_3$ phase 0.1 M (**3**) or 0.2 M crown ether (**5**) and (**6**)).

Extraction Experiments. In addition to the determination of association constants of the complexes of crown ethers and urea in H_2O, using the pK_a method, the complexation of the macrocycles with urea was studied by both solid–liquid and liquid–liquid extraction methods. In all experiments the amount of urea or uronium salt transferred to the organic phase was determined by enzymatic degradation of urea by urease in combination with coulometric detection of the NH_3 formed in the reaction.[11] Details of the extraction procedures and of the urea determination are given in the Experimental Section.

2,6-Pyrido Crown Ethers (1 and 2). In the first type of experiment solid urea was stirred with a 0.1–0.2 M solution of a 2,6-pyrido crown ether (**1**) in $CDCl_3$. The amounts of urea present in the organic phase after equilibration show a very low efficiency of extraction (2–4%), and the differences in extraction efficiency between the crown ethers are only small. It was only possible to obtain a solid 1:5 complex of 2,6-pyrido-18-crown-6 and urea when both components were dissolved in MeOH and the solvent was partly evaporated (mp 115 °C, dec).

These results indicated that efficient complexation of urea cannot be achieved with nonprotonated 2,6-pyrido crown ethers. However, protonation of the crown ether might increase the interaction of the crown ether with urea, because the protonated pyridine moiety should be able to form a strong hydrogen bond with the urea carbonyl group. Therefore two-phase liquid–liquid extraction experiments were carried out with an aqueous phase that contained 2 M urea and 2.8 M $HClO_4$ and a 0.2 M solution of a 2,6-pyrido crown ether in $CDCl_3$ containing 1,2,4,5-tetramethylbenzene as an internal NMR standard. Under these conditions more than 99% of the macrocycles are protonated.[34] These experiments showed that more than 98% of the crown ether was transferred to the aqueous phase, and thus no conclusions concerning the complexation could be obtained.

The amount of $HClO_4$ was subsequently decreased to exactly 1 equiv of acid per crown ether. Under these conditions 89–99% of the macrocycles are protonated, depending on ring size, whereas only approximately 0.01 mol/L of protonated urea is present.[34]

The amounts of crown ethers retained in the organic phase varied from 50–71%, depending on ring size. The results of these extraction experiments are summarized in Figure 4.

Although the amount of urea transferred to the organic phase is rather small, there is clearly an optimum in the complexation with the larger (27-, 30- and 33-membered) rings, analogous to the complexation of guanidinium perchlorate for which the association constant has an optimum for the 30-membered ring.[46]

(46) Stolwijk, T. B.; Grootenhuis, P. D. J.; van der Wal, P. D.; Sudhölter, E. J. R.; Reinhoudt, D. N.; Harkema, S.; Uiterwijk, J. W. H. M.; Kruise, L. *J. Org. Chem.* **1986**, *51*, 4891–4898.

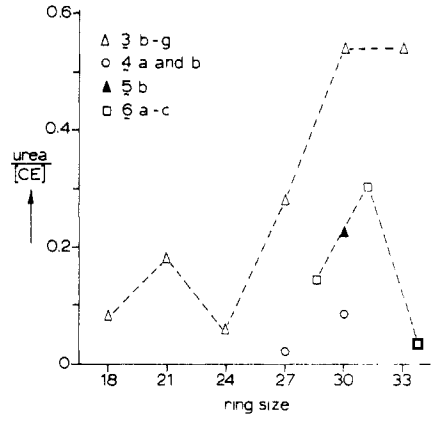

Figure 5. S-L phase transfer of urea by **3–6**. Conditions, 0.1 M (**3**) or 0.2 M (**4–6**) crown ether and excess solid urea suspended in $CDCl_3$.

Consequently the observed optimal extraction of urea by the 30-membered macrocycle is in line with the complexation of guanidinium salts.

The complexation of the 4-phenyl-2,6-pyridinium crown ethers (**2**) with urea was tested only under the conditions that were found to be optimal for the complexation of the 2,6-pyrido crown ethers (**1**). Since the 4-phenyl-2,6-pyrido crown ethers are much less water soluble than the unsubstituted 2,6-pyrido crown ethers, 85–100% of the macrocycles, depending on the ring size, are retained in the organic phase. The results of the extraction experiments are given in Figure 4.

The complexation of urea by the protonated 4-phenyl-2,6-pyrido crown ethers is not very efficient, although there is a pronounced ring size selectivity. The protonated 27- and 30-membered macrocycles are the most effective ligands for urea, whereas the smaller macrocycles hardly extract any urea into the organic phase. From the ^1H NMR spectra it is obvious that all 2,6-pyrido macrocycles (**1** and **2**) extract considerable amounts of water into the organic phase. Although there is no self-complexation possible in **2** as can be concluded from the T_1 measurements, the cavities of both **1** and **2** are obviously occupied by water. This explains why the phenyl group in **2** has hardly any effect.

2-Carboxyl-1,3-xylyl Crown Ethers. The participation of the more acidic and neutral intraannular carboxyl group in the complexation of urea was studied with solid–liquid and liquid–liquid extraction experiments, with a 0.1 M solution of the crown ethers **3** in $CDCl_3$. The results, summarized in Figures 4 and 5 clearly show the participation of the carboxylic group, reflected in enhanced extraction observed relative to the nonprotonated 2,6-pyrido macrocycles and also relative to lariat macrocycles containing an acidic group in a pendant arm.[12] Furthermore a pronounced ring effect is observed with good extraction efficiencies for the larger macrocycles. The complex of 2-carboxyl-1,3-xylyl-30-crown-9 and urea could be isolated, and the X-ray crystal structure revealed the complete encapsulation of urea in the macrocyclic cavity (Figure 6).

There are four hydrogen bonds between the urea NH_2 groups and ether oxygens, and the urea oxygen is hydrogen bonded by the carboxylic OH group (see Table II). This latter hydrogen bond is very strong, judging from the very short donor–acceptor distance (2.54 Å). But, as with the 2-carboxyl-1,3-xylyl-24-crown-7·H_2O complex, no proton transfer from the carboxylic to the urea oxygen is observed ($O_{carboxyl}$–H 0.97 (4) Å versus H···O_{urea} 1.58 (4) Å).

The urea is displaced by 0.2 Å from the mean plane of the five host oxygens involved in hydrogen bonding. The macrocyclic cavity seems slightly too large for urea, but there is no evidence for conformational disorder or large thermal motion, as was observed in the 2-carboxyl-1,3-xylyl-24-crown-7·H_2O complex for the part of the macrocycle not involved in host–guest interaction.

The ^1H NMR spectrum of a $CDCl_3$ solution containing 0.05 mol/L of the complex is temperature dependent. Upon cooling, line broadening and finally two signals were observed for the urea

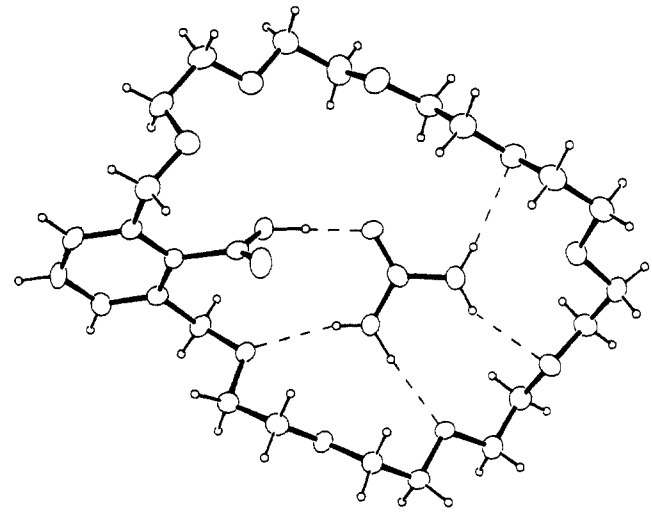

Figure 6. X-ray crystal structure of 2-carboxyl-1,3-xylyl-30-crown-9-(**3f**)·urea.

NH_2 groups, at 5.9 and 6.2 ppm, respectively. This can be ascribed to the two different environments of the urea NH_2 groups in the complex. At the coalescence temperature (245 K) a free energy of activation of 12 kcal/mol for an exchange process can be calculated.[47]

In liquid–liquid extraction experiments (0.1 M crown ether in $CDCl_3$, 2 M urea in H_2O), the extraction efficiency of the carboxyl crown ethers is approximately equal to the efficiency of the 2,6-pyridinium crown ethers. The 2-carboxyl-1,3-xylyl crown ethers are retained in the organic phase for more than 99%.

Crown Ethers with Acidic and Basic Functionalities. The complexation of the macrocycles **6** with urea was studied with solid–liquid and liquid–liquid extraction experiments. In these experiments a 0.1 M solution of the crown ether was used. The results are summarized in Figures 4 and 5.

The extraction efficiency (S-L) of the macrocycles **6a** and especially **6b** is quite appreciable. However, the extraction ability of these ligands in a liquid–liquid system is disappointingly low.

When the crown ether **6b** was dissolved in MeOH/$CHCl_3$ (5/1) and a solution of urea in MeOH was added, a crystalline product was obtained (mp 135–136 °C). Elemental analysis showed this to be the 1:1 complex of **6b** and urea. Analogous experiments with the smaller and larger macrocycles **6a** and **6c** did not yield crystalline complexes.

Recrystallization of **6b**·urea from MeOH/diisopropyl ether gave crystals suitable for X-ray analysis. The structure of the complex **6b**·urea was determined by X-ray crystallography. The ORTEP[35] view of the structure is given in Figure 7. The urea is completely encapsulated in the macrocyclic cavity and it is hydrogen bonded to three ether oxygens and to one of the phenolic oxygens via the NH_2 groups (Table II). The urea carbonyl oxygen is bound to the other phenolic oxygen at a short distance (2.58 Å), which indicates a strong hydrogen bond. Unfortunately the hydrogen atom involved could not be located, but difficulties with locating a hydrogen atom in a strong hydrogen bond have been observed before.[40] An alternative hydrogen-bonding geometry, with the urea carbonyl oxygen bound to both phenolic groups and with four hydrogen bonds donated by the NH_2 groups to ether oxygens is not observed, although the two phenolic oxygens are far enough apart (3.95 Å) to allow participation of both hydrogen atoms in hydrogen bonding to the urea oxygen. The conformation of the macrocyclic host is not as regular as in 2-carboxyl-1,3-xylyl-30-crown-9·urea, which is reflected in the conformational disorder and large thermal motion in the polyether chain. The maximum deviation of the five host oxygens, involved in hydrogen bonding to urea, from their mean plane is 0.67 Å (0.35 Å in 2-

(47) $k_{coalescence} = \pi\Delta\nu/\sqrt{2}$ where $\Delta\nu$ is the maximum chemical shift difference between the NH_2 resonances of complexed urea. $\Delta G^{\ddagger} = 4.57T_c(9.97 + \log(T_c/\Delta\nu))$ cal/mol.

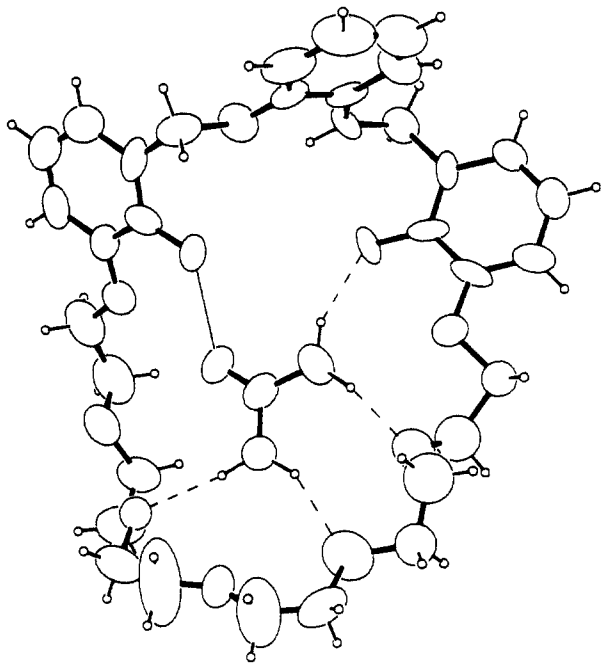

Figure 7. X-ray crystal structure of **6b**·urea.

carboxyl-1,3-xylyl-30-crown-9·urea). The angle between this plane and the molecular plane of urea is 10° (3° in 2-carboxyl-1,3-xylyl-30-crown-9·urea). The angles between adjacent aromatic rings are 60 and 86°, respectively.

The complexation of macrocyclic ligands that possess both acidic OH or COOH and basic pyrido functionalities was studied in order to establish whether more basic binding sites in the macrocycle improve the binding of neutral guest species. Such crown ethers that contain both acidic and basic functionalities have been reported in only a few papers in the literature.[23,48-51] Cram et al.[23] have described an 18-membered crown ether in which a carboxylic acid group and a 2,6-pyrido moiety are combined. The X-ray crystal structure of the macrocycle shows that a strong hydrogen bond (OH···N 1.8 Å) is formed between the acidic and the basic group. From the X-ray structure it can be concluded that the proton is not transferred from the acidic to the basic group. Many crown ethers that contain acidic groups in side arms of (poly)aza crown ethers have been described.[48-51] In all cases the acidic group was used as an additional binding site in the complexation of cations. Crown ethers of this type have been used in the solubilization of $BaSO_4$ in oil wells.[48] Hitherto such crown ethers have not been used in the complexation of neutral molecules.

The extraction experiments were carried out only with the crown ethers **4a**, **4b**, and **5b**, because our earlier experiments with the 2-carboxyl-1,3-xylyl crown ethers had shown that when an intraannular carboxyl group is present, a ring size of 30 ring atoms is required for effective complexation of urea. Because all the macrocycles contain an intraannular proton-donating group no additional external acid was added to the urea solution. The results of the extraction experiments are summarized in Figures 4 and 5. More than 95% of the macrocycles are retained in the organic phase. In these experiments we observed some remarkable features in the ^1H NMR spectra. In the case of the 27-membered macrocycle the spectra before and after the liquid–liquid extraction experiments are identical, whereas in the case of the 30-membered ligands **4b** and **5b** a broad singlet was observed in addition to the signals of the macrocycle. In the spectrum of **4b** the singlet was observed at δ 1.63 ppm, whereas for the carboxyl crown ether **5b** the signal appeared at δ 4.94 ppm. In both spectra the intensity of the signals corresponded to approximately five hydrogen atoms. However, the amount of urea determined from the enzymatic degradation is not in agreement with the intensity for these signals. These new signals are attributed to the inclusion of water by the macrocycles, as was also observed for 2,6-pyridinium-24-crown-8.[9] This would correspond to the inclusion of approximately 2.5 molecules of water for each of the macrocycles **4b** and **5b**.

The complexation of macrocycles containing carboxylic acid groups or phenolic hydroxyl groups is efficient when urea is extracted from the solid phase. In these macrocycles the acidic group can form a strong hydrogen bond with the urea oxygen atom (Figure 6).

The complexation of the macrocycles that contain both acidic and basic groups shows no enhanced selectivity for urea. The same trend as for the macrocycles which contain only an acidic group is observed; i.e., in solid–liquid extraction urea is extracted rather well, whereas in liquid–liquid extraction experiments the complexation of water predominates.

Conclusions

Intraannular proton-donating groups in macrocyclic ligands can assist in the complexation of urea. Accurate potentiometric titrations indicate that the acidic group is involved in the hydrogen bonding with the guest molecule and moreover provide a means to assess the complexation constant of the complexes of the ligand and urea in aqueous solution. The association constants of the macrocycles with urea in water are small (less than 1.5 L·mol^{-1}), and a significant dependence on the ring size of the macrocycle is observed. The association constants of the complexes of the 2,6-pyridinium crown ethers and urea in H_2O were the largest. However, the extraction efficiencies of these crown ethers in liquid–liquid extraction experiments are low. When the self-complexation, observed for these macrocycles in solution, is prevented by a phenyl group in the 4-position, the extraction of urea does not improve. Macrocycles containing carboxyl and hydroxyl groups show good efficiencies in solid–liquid extraction but low extraction efficiencies in liquid–liquid phase transfer. The X-ray crystal structure of 2-carboxyl-1,3-xylyl-30-crown-9·urea shows the involvement of the acidic group in hydrogen bonding. A strong hydrogen bond is also present in the complex of **6b** and urea. The presence of both acidic and basic groups, as in the macrocycles **4** and **5**, does not improve the complexation with urea.

Experimental Section

Caution. Although during these experiments no accidents have occurred, extreme care should be taken when perchlorates are handled, because they may explode spontaneously and may be sensitive to shock. The perchlorates should only be prepared in small quantities.

Melting points were determined with a Reichert melting point apparatus and are uncorrected. The ^1H NMR spectra were recorded with Bruker WP-80 and/or WM-500 spectrometers in $CDCl_3$ or DMSO-d_6, and the ^{13}C NMR spectra were recorded with a Nicolet NT-200 WB spectrometer, with Me_4Si as an internal standard. Mass spectra were obtained with a Varian Mat 311A. Elemental analyses were carried out by the laboratory of Chemical Analysis.

Materials. THF was freshly distilled from sodium/benzophenone prior to use. The 2,6-pyrido crown ethers[10] and 2-carboxyl-1,3-xylyl crown ethers[1] were prepared as described earlier. 2-(Bromomethyl)-6-(hydroxymethyl)pyridine,[7] 2,6-dimethyl-4-phenylpyridine,[15] 1,3-bis-(bromomethyl)-4-chloro-2-(2-propenoxy)benzene, and methyl 1,3-bis-(bromomethyl)benzoate[11] were prepared according to literature procedures. All other chemicals were reagent grade and were used without further purification.

Solid–Liquid Extraction Experiments (Urea). A solution of 0.1–0.2 mmol of crown ether in 1 mL of $CDCl_3$ was equilibrated with 0.2 g (3.3 mmol) of urea. The resulting suspension was filtered, and the filter was thoroughly washed with $CDCl_3$. The solvent of the filtrate was evaporated, and the resulting residue was dissolved in MeOH. This solution was used in the urea determination. In the absence of a crown ether the solubility of urea in chloroform is 4.8×10^{-4} mol·L^{-1}.[52]

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(49) Kaden, T. A. *Top. Curr. Chem.* **1984**, *121*, 157–179.
(50) Stetter, H.; Frank, W. *Angew. Chem.* **1976**, *101*, 760.
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(52) Professor T. W. Bell has kindly informed us that he has used a solubility of urea in chloroform of approximately 5×10^{-4} mol·L^{-1} for the calculation of K_a values of urea complexes in chloroform. When this value is used, the experiment with **3f** and **3g** would give K_a values of 2×10^3 L·mol^{-1} (25 °C, chloroform).
(53) Germain, G.; Main, P.; Woolfson, M. M. *Acta Crystallogr., Sect. A* **1971**, *27*, 368–376.

Liquid–Liquid Extraction Experiments (Urea). A $CDCl_3$ solution (1 mL) containing 0.1–0.2 mmol of crown ether and 0.04 mmol of 1,2,4,5-tetramethylbenzene was equilibrated with an aqueous solution (1 mL) containing 2 mmol of urea and either 0.2 or 2.8 mmol of $HClO_4$. A sample of 0.5 mL of the organic phase was taken, and the solvent was evaporated. The residue was dissolved in MeOH, and the urea content of this sample was determined. The amount of crown ether transferred to the aqueous phase was determined from the ratio of the absorptions of the crown ether and 1,2,4,5-tetramethylbenzene in the ^1H NMR spectrum.

Procedure for Urea Determination. The coulometric titrations were carried out with a coulometric titrator from Tacussel, type TT700, a glass electrode EA109 Metrohm, a reference electrode R112 Electrofact, a pH meter type 742 Knick, and a cation exchange membrane from Ionics. The titration vessel was filled with 40 mL of 0.5 M Na_2SO_4 and 1 mL of urease solution (10 mg/mL of H_2O), and the pH was adjusted to 7.50. After the introduction of the sample containing $0.1–7.0 \times 10^{-6}$ mol urea, also adjusted to pH 7.50, the coulometric titration was started. When the pH value of 7.50 was reestablished, the amount of acid generated was read from the coulometric titrator.

2,6-Pyrido-18-crown-6·Urea (1:5). To a solution of 0.297 gram (1.00 mmol) of 2,6-pyrido-18-crown-6 (**1b**) in 50 mL of methanol was added 0.300 g (5.00 mmol) of urea. The mixture was heated to reflux for 5 min, and the solvent was allowed to evaporate partly at room temperature. The crystals were filtered off: yield 65%; mp 115 °C dec; ^1H NMR (DMSO-d_6) δ 7.9–7.2 (m, 3 H, ArH), 5.4 (br s, 20 H, NH_2), 4.58 (s, 4 H, $ArCH_2$), 3.7–3.5 (m, 8 H, OCH_2), 3.5–3.3 (m, 8 H, OCH_2); ^{13}C NMR (DMSO-d_6) δ 159.5 (C=O), 157.3 (Ar C-2, C-6), 136.7 (Ar C-4), 120.8 (Ar C-3, C-5), 72.9 ($ArCH_2$), 69.9, 69.6, 69.5, 69.0 (OCH_2). Anal. Calcd for $C_{20}H_{43}N_{11}O_{10}$: C, 40.20; H, 7.25; N, 25.78. Found: C, 40.20; H, 7.36; N, 25.66.

4-Phenyl-2,6-pyridinedicarboxylic Acid (8). 2,6-Dimethyl-4-phenylpyridine (9.15 gram, 0.05 mol) and $KMnO_4$ (31.60 gram, 0.20 mol) were refluxed in 250 mL of H_2O for 18 h. The reaction mixture was filtered while hot to remove MnO_2, and subsequently 125 mL of 4 M aqueous HCl was added carefully. The resulting suspension was heated until all solid material dissolved, and the product was crystallized on standing at room temperature: yield 40%; mp 218–220 °C dec; ^1H NMR (DMSO-d_6) δ 8.42 (s, 2 H, ArH), 7.9–7.7 (m, 2 H, Ar'H), 7.7–7.3 (m, 3 H, Ar'H); ^{13}C NMR (DMSO-d_6) δ 165.3 (COOH), 149.8 (Ar C-2, C-6), 148.6 (Ar C-4), 135.4 (Ar' C-1), 129.8, 129.1, 126.8, 124.2 (Ar C-3, C-5, Ar' C-2, C-3, C-4, C-5, C-6); mass spectrum, *m/e* 243.052 (M^+; calcd 243.053). Anal. Calcd for $C_{13}H_9NO_4 \cdot 2.5H_2O$: C, 54.17; H, 4.90; N, 4.86. Found: C, 53.86; H, 4.42; N, 4.83.

4-Phenyl-2,6-pyridinedicarboxylic Acid Dimethyl Ester (9a). To a solution of 4-phenyl-2,6-pyridinedicarboxylic acid (2.00 gram, 0.008 mol) in 100 mL of methanol was added $SOCl_2$ (4.80 gram, 40 mmol) dropwise. The mixture was refluxed for 2 h, and the solvent was evaporated: yield 93%; mp 149–150 °C; ^1H NMR ($CDCl_3$) δ 8.54 (s, 2 H, ArH), 7.9–7.4 (m, 5 H, Ar'H), 4.06 (s, 6 H, CO_2CH_3); ^{13}C NMR ($CDCl_3$) δ 165.2 (COOR), 151.1 (Ar C-2, C-6), 148.8 (Ar C-4), 136.1 (Ar' C-1), 130.1, 129.4, 127.1, 125.6 (Ar C-3, C-5, Ar' C-2, C-3, C-4, C-5, C-6), 53.3 (CH_3); mass spectrum, *m/e* 271.082 (M^+; calcd 271.085). Anal. Calcd for $C_{15}H_{13}NO_4$: C, 66.41; H, 4.83; N, 5.16. Found: C, 66.14; H, 4.81; N, 5.09.

2,6-Dicarbethoxy-4-phenylpyrylium Tetrafluoroborate (10). To a mixture of 11.6 g (0.1 mol) of ethyl pyruvate and 5.3 g (0.05 mol) of benzaldehyde was added 65 mL of BF_3 etherate. The exothermic reaction warmed the mixture to 60 °C, and after stirring at 100 °C for 30 min the product was poured into 1000 mL of diethyl ether. The pyrylium salt precipitated and was filtered off to yield (12%) a yellow powder: mp 167–170 °C; ^1H NMR (acetone-d_6) δ 9.46 (s, 2 H, ArH), 8.8–8.5 (m, 2 H, Ar'H), 8.0–7.8 (m, 3 H, Ar'H), 4.65 (q, J = 7 Hz, 4 H, CH_2), 1.48 (t, J = 7 Hz, 6 H, CH_3); ^{13}C NMR (acetone-d_6) δ 173.1 (Ar C-2 or C-4), 160.8 (C=O), 157.4 (Ar' C-1), 139.0 (Ar' C-4), 132.4 (Ar' C-2, C-6), 131.5 (Ar' C-3, C-5), 124.4 (Ar C-3, C-5), 65.5 (CH_2), 14.1 (CH_3). One signal, Ar C-2 or Ar C-4, was not observed. Mass spectrum, *m/e* 301.107 ($C_{17}H_{17}O_5^+$; calcd 301.108). Anal. Calcd for $C_{17}H_{17}O_5BF_4 \cdot 0.5H_2O$: C, 51.41; H, 4.57. Found: C, 51.06; H, 4.36.

4-Phenyl-2,6-pyridinedicarboxylic Acid Diethyl Ester (9b). To a solution of 2.8 g (36 mmol) of ammonium acetate in 20 mL of acetic acid was added 1.0 g (2.6 mmol) of 2,6-dicarbethoxy-4-phenylpyrylium tetrafluoroborate in 10 mL of acetic acid. The mixture was heated at 120 °C for 3 h, and after cooling to room temperature the mixture was neutralized with 4 N NaOH and extracted with 3 × 150 mL of $CHCl_3$. The organic phase was dried over $MgSO_4$, and the solvent was evaporated. The product was purified by trituration with methanol: yield 60%; mp 118–120 °C; ^1H NMR ($CDCl_3$) δ 8.50 (s, 2 H, ArH), 7.3–7.8 (m, 5 H, Ar'H), 4.42 (q, J = 7 Hz, 4 H, CH_2), 1.48 (t, J = 7 Hz, 6 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 164.8 (COOR), 150.9 (Ar C-4), 149.3 (Ar C-2, C-6), 136.4 (Ar' C-1), 130.0, 129.4, 127.1, 125.5 (Ar C-3, C-5, Ar' C-2, C-3, C-4, C-5, C-6), 62.4 (CH_2), 14.3 (CH_3); mass spectrum, *m/e* 299.117 (M^+; calcd 299.166). Anal. Calcd for $C_{17}H_{17}NO_4$: C, 68.22; H, 5.72; N, 4.68. Found: C, 67.90; H, 5.58; N, 4.62.

4-Phenyl-2,6-pyridinedimethanol (11). A suspension of 0.015 mol of 4-phenyl-2,6-pyridinedicarboxylic acid dimethyl ester (**9a**) or 4-phenyl-2,6-pyridinedicarboxylic acid diethyl ester (**9b**) in 100 mL of EtOH was cooled to 0 °C, and 2.5 g (0.066 mol) of $NaBH_4$ was added carefully. The mixture was heated to reflux, and heating was continued until the pink solution became colorless (approximately 1 h). Concentrated aqueous K_2CO_3 was added, and most of the solvent was evaporated. The product was isolated by continuous extraction with $CHCl_3$: yield 100%; mp 105–108 °C; ^1H NMR ($CDCl_3$) δ 7.8–7.3 (m, 7 H, ArH, Ar'H), 4.80 (s, 4 H, $ArCH_2$), 3.9 (br s, 2 H, OH); ^{13}C NMR ($CDCl_3$) δ 159.4 (Ar C-2, C-6), 149.9 (Ar C-4), 137.9 (Ar' C-1), 129.1, 129.0, 127.0 (Ar' C-2, C-3, C-4, C-5, C-6), 117.2 (Ar' C-3, C-5), 64.5 (CH_2); mass spectrum, *m/e* 215.094 (M^+; calcd 215.095). Anal. Calcd for $C_{13}H_{13}NO_2 \cdot 0.5H_2O$: C, 69.64; H, 6.29; N, 6.25. Found: C, 69.51; H, 6.09; N, 5.98.

4-Phenyl-2,6-bis(bromomethyl)pyridine (12). A solution of 4-phenyl-2,6-pyridinedimethanol (**11**, 1.08 g, 0.005 mol) in 50 mL of 48% aqueous HBr was refluxed for 16 h. The mixture was cooled to 0 °C and neutralized with 4 M aqueous NaOH. The aqueous phase was extracted with $CHCl_3$, the organic layers were dried over $MgSO_4$, and the solvent was evaporated. A white solid was obtained: yield 60%; mp 167–169 °C; ^1H NMR ($CDCl_3$) δ 7.7–7.3 (m, 7 H, ArH, Ar'H), 4.59 (s, 4 H, $ArCH_2$); ^{13}C NMR ($CDCl_3$) δ 157.2 (Ar C-2, C-6), 150.8 (Ar C-4), 137.3 (Ar' C-1), 129.4, 129.1, 127.0 (Ar' C-2, C-3, C-4, C-5, C-6), 120.8 (Ar C-3, C-5), 33.5 (CH_2); mass spectrum, *m/e* 338.923 (M^+; calcd 338.926). Anal. Calcd for $C_{13}H_{11}Br_2N$: C, 45.78; H, 3.25; N, 4.11. Found: C, 45.63; H, 3.17; N, 4.02.

General Procedure for the Synthesis of 4-Phenyl-2,6-pyrido Crown Ethers (2a–e). To a refluxing, stirred mixture of 0.04 mol of NaH (80% in oil) and 200 mL of dry THF were added over a period of 3 h separate solutions of 0.01 mol of 4-phenyl-2,6-bis(bromomethyl)pyridine in 100 mL of dry THF and 0.01 mol of the appropriate polyethylene glycol in 100 mL of dry THF. The mixture was allowed to cool to 25 °C, and 25 mL of water was added carefully to decompose residual NaH. The solvent was evaporated, and the residue was mixed with 100 mL of $CHCl_3$ and extracted with 3 × 100 mL of 1 M aqueous HCl. After addition of aqueous 10% NaOH to pH 10, the combined aqueous layers were extracted with 3 × 100 mL of $CHCl_3$. The $CHCl_3$ layers were dried over $MgSO_4$, and the solvent was evaporated in vacuo. The crown ethers were then purified by chromatography.

4-Phenyl-2,6-pyrido-18-crown-6 (2a). 4-Phenyl-2,6-pyrido-18-crown-6 was prepared by using tetraethylene glycol, according to the general procedure. Purification of the product was accomplished by chromatography (neutral Al_2O_3, activity I-II, $CHCl_3$) to yield (41%) an oil: ^1H NMR ($CDCl_3$) δ 7.8–7.3 (m, 7 H, ArH, Ar'H), 4.81 (s, 4 H, $ArCH_2$), 3.9–3.3 (m, 16 H, OCH_2); ^{13}C NMR ($CDCl_3$) δ 158.6 (Ar C-2, C-6), 149.4 (Ar C-4), 138.4 (Ar' C-1), 129.0, 128.9, 127.0 (Ar' C-2, C-3, C-4, C-5, C-6), 118.7 (Ar C-3, C-5), 73.8 ($ArCH_2$), 71.0-69.6 (OCH_2); mass spectrum, *m/e* 373.190 (M^+; calcd 373.189).

4-Phenyl-2,6-pyrido-21-crown-7 (2b). 4-Phenyl-2,6-pyrido-21-crown-7 was prepared by using pentaethylene glycol, according to the general procedure. Purification of the product was accomplished by chromatography (neutral Al_2O_3, activity II-III, $CHCl_3$): ^1H NMR ($CDCl_3$) δ 7.8–7.3 (m, 7 H, ArH, Ar'H), 4.78 (s, 4 H, $ArCH_2$), 3.9–3.4 (m, 20 H, OCH_2); ^{13}C NMR ($CDCl_3$) δ 158.2 (Ar C-2, C-6), 149.6 (Ar C-4), 138.1 (Ar' C-1), 129.0, 128.9, 127.0 (Ar' C-2, C-3, C-4, C-5, C-6), 118.9 (Ar C-3, C-5), 74.0 ($ArCH_2$), 70.8–68.7 (OCH_2); mass spectrum, *m/e* 417.214 (M^+; calcd 417.215).

4-Phenyl-2,6-pyrido-24-crown-8 (2c). 4-Phenyl-2,6-pyrido-24-crown-8 was prepared by using hexaethylene glycol, according to the general procedure. Purification of the product was accomplished by chromatography (neutral Al_2O_3, activity II-III, $CHCl_3$) to yield (60%) an oil: ^1H NMR ($CDCl_3$) δ 7.7–7.3 (m, 7 H, ArH, Ar'H), 4.73 (s, 4 H, $ArCH_2$), 3.8–3.4 (m, 24 H, OCH_2); ^{13}C NMR ($CDCl_3$) δ 158.5 (Ar C-2, C-6), 149.4 (Ar C-4), 138.3 (Ar' C-1), 128.9, 128.9, 127.1 (Ar' C-2, C-3, C-4, C-5, C-6), 118.4 (Ar C-3, C-5), 74.1 ($ArCH_2$), 70.7–70.0 (OCH_2); mass spectrum, *m/e* 461.241 (M^+; calcd 461.241).

4-Phenyl-2,6-pyrido-27-crown-9 (2d). 4-Phenyl-2,6-pyrido-27-crown-9 was prepared by using heptaethylene glycol, according to the general procedure. Purification of the product was accomplished by chromatography (neutral Al_2O_3, activity II-III, $CHCl_3$) to yield (52%) an oil: ^1H NMR ($CDCl_3$) δ 7.8–7.3 (m, 7 H, ArH, Ar'H), 4.74 (s, 4 H, $ArCH_2$), 3.8–3.3 (m, 28 H, OCH_2); ^{13}C NMR ($CDCl_3$) δ 158.2 (Ar C-2, C-6), 149.4 (Ar C-4), 138.4 (Ar' C-1), 129.0, 129.0, 127.1 (Ar' C-2, C-3,

(54) Structure determination package, B. A. Frenz and Associates Inc., College Station, TX, and Enraf Nonius, Delft, 1983.

C-4, C-5, C-6), 118.1 (Ar C-3, C-5), 73.9 ($ArCH_2$), 70.7–70.0 (OCH_2); mass spectrum, *m/e* 505.267 (M^+; calcd 505.268).

4-Phenyl-2,6-pyrido-30-crown-10 (2e). 4-Phenyl-2,6-pyrido-30-crown-10 was prepared by using octaethylene glycol, according to the general procedure. Purification of the product was accomplished by chromatography (neutral Al_2O_3, activity II-III, $CHCl_3$) to yield (56%) an oil: ^1H NMR ($CDCl_3$) δ 7.7–7.3 (m, 7 H, ArH, Ar'H), 4.73 (s, 4 H, $ArCH_2$), 3.9–3.4 (m, 32 H, OCH_2); ^{13}C NMR ($CDCl_3$) δ 158.5 (Ar C-2, C-6), 149.5 (Ar C-4), 138.3 (Ar' C-1), 128.9, 128.9, 127.1 (Ar' C-2, C-3, C-4, C-5, C-6), 118.0 (Ar C-3, C-5), 73.9 ($ArCH_2$), 70.8–68.7 (OCH_2); mass spectrum, *m/e* 549.295 (M^+; calcd 549.294).

4-Phenyl-2,6-pyrido-27-crown-9-Guanidinium Perchlorate. A solution of 4-phenyl-2,6-pyrido-27-crown-9 (**2d**, 1 mmol) in 2 mL of $CDCl_3$ was equilibrated with a solution of guanidinium sulfate (2 mmol) and lithium perchlorate (2 mmol) in 2 mL of water. The organic phase was separated off, and after drying over $MgSO_4$ the solvent was evaporated to yield an oil. This product was dissolved in a minimal amount of EtOH, and petroleum ether 60–80 was allowed to diffuse into the solution. Crystals were formed, and these were filtered off: mp 130–132 °C; ^1H NMR ($CDCl_3$) δ 7.8–7.3 (m, 7 H, ArH, Ar'H), 7.0 (br s, 6 H, NH_2), 4.72 (s, 4 H, $ArCH_2$), 3.8–3.5 (m, 28 H, OCH_2); ^{13}C NMR ($CDCl_3$) δ 157.6 (C-NH_2), 156.9 (Ar C-2, C-6), 150.9 (Ar C-4), 137.1 (Ar' C-1), 129.6, 129.2, 127.1 (Ar' C-2, C-3, C-4, C-5, C-6), 121.2 (Ar C-3, C-5), 74.0 ($ArCH_2$), 70.5–70.3 (OCH_2). Anal. Calcd for $C_{28}H_{45}ClN_4O_{12}$: C, 50.56; H, 6.82; N, 8.42. Found: C, 50.31; H, 6.67; N, 8.17.

6,6'-(2,5,8,11-Tetraoxadodecane-1,12-diyl)bis(2-pyridinemethanol) (15a). 2-(Bromomethyl)-6-(hydroxymethyl)pyridine (10.05 g, 0.05 mol) and 2.10 g (0.01 mol) of *p*-toluenesulphonic acid were dissolved in 25 mL of dichloromethane. At room temperature, 16.80 g (0.20 mol) of dihydropyran was added. The mixture was stirred at room temperature for 3 days, after which it was washed with 0.1 M aqueous NaOH to remove the acid and filtered over neutral Al_2O_3. The crude product could not be purified by distillation and was used as such in the next step.

To a refluxing mixture of 2.10 g (0.07 mol) of NaH (80% in oil) and 200 mL of dry THF were added the crude 2-(bromomethyl)-6-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)pyridine (**13**) (0.05 mol) and 3.60 g (0.024 mol) of triethylene glycol, dissolved in 150 mL of dry THF over a period of 1 h. The mixture was refluxed for an additional hour and cooled to room temperature, and residual NaH was decomposed by careful addition of 25 mL of water. The solvent was evaporated, 100 mL of chloroform was added, and the solution was extracted with 200 mL of 1 M aqueous hydrochloric acid in two portions. The combined water phases were made alkaline with NaOH and extracted with chloroform. The organic layers were dried over $MgSO_4$ and concentrated. The product was purified by chromatography (silica gel, $CHCl_3$/EtOH, 96/4) and was obtained as a light yellow oil: yield 24%; ^1H NMR ($CDCl_3$) δ 7.8–7.0 (m, 6 H, ArH), 4.72 (s, 4 H, $ArCH_2$), 4.67 (s, 4 H, $ArCH_2$), 3.8–3.7 (m, 12 H, OCH_2); ^{13}C NMR ($CDCl_3$) δ 158.6, 157.4 (Ar C-2, C-6), 137.3 (Ar C-4), 119.9, 119.1 (Ar C-3, C-5), 73.8 ($ArCH_2$), 70.6–70.1 (OCH_2); mass spectrum, *m/e* 392.191 (M^+; calcd 392.195).

6,6'-(2,5,8,11,14-Pentaoxapentadecane-1,15-diyl)bis(2-pyridinemethanol) (15b). The diol **15b** was prepared by a procedure analogous to the preparation of **15a**, with tetraethylene glycol, and the product was obtained as a light yellow oil: yield 26%; ^1H NMR ($CDCl_3$) δ 7.8–7.0 (m, 6 H, ArH), 4.7 (br s, 8 H, $ArCH_2$), 3.8–3.6 (m, 16 H, OCH_2); ^{13}C NMR ($CDCl_3$) δ 158.5, 157.5 (Ar C-2, C-6), 137.3 (Ar C-4), 119.8, 119.1 (Ar C-3, C-5), 73.8 ($ArCH_2$), 70.6–70.1 (OCH_2), 64.1 ($ArCH_2$); mass spectrum, *m/e* 436.215 (M^+; calcd 436.221).

7-Chloro-36-(2-propenyloxy)-3,11,19,22,25,28-hexaoxa-34,35-diazatetracyclo(28.3.1.1^{5,9}.1^{13,17})hexatriaconta-1(34),5,7,9(36),13,15,17(35),30,32-nonaene (17a). To a refluxing mixture of 1.20 g (0.04 mol) of NaH (80% in oil) in 300 mL of dry THF was added dropwise over a period of 5 h a mixture of 3.92 g (0.01 mol) of 6,6'-(2,5,8,11-tetraoxadodecane-1,12-diyl)bis(2-pyridinemethanol) (**15a**) and 3.52 g (0.01 mol) of 1,3-bis(bromomethyl)-2-(2-propenyloxy)-5-chlorobenzene (**16**) in 200 mL of dry THF. The reaction mixture was cooled to room temperature, and 25 mL of water was carefully added to decompose residual NaH. The solvent was evaporated, and the reaction mixture was acidified with 1 M HCl and washed with chloroform. Aqueous 4 M NaOH solution was added to pH 10, and the mixture was extracted with chloroform. The organic phase was dried over $MgSO_4$, the solvent was evaporated, and the product was purified by chromatography (silica gel, $CHCl_3$/EtOH, 98/2), to give the product as a colorless oil which solidified to a white solid on standing: mp 63–65 °C; yield 45%; ^1H NMR ($CDCl_3$) δ 7.8–7.1 (m, 8 H, Ar'H, ArH), 6.0–5.5 (m, 1 H, CH), 5.3–5.0 (m, 2 H, CH_2), 4.59 (br s, 12 H, $ArCH_2$, $Ar'CH_2$), 4.3–4.1 (m, 2 H, CH_2), 3.7–3.6 (m, 12 H, OCH_2); ^{13}C NMR ($CDCl_3$) δ 157.8, 157.2 (Ar C-2, Ar C-6), 154.4 (Ar' C-1), 137.0 (Ar C-4), 133.1 (CH), 133.1 (Ar' C-2, Ar' C-6), 129.8 (Ar' C-3, Ar' C-5), 129.1 (Ar' C-4), 120.4, 120.6 (Ar C-3, Ar C-5), 117.2 (CH_2), 75.8, 74.0, 72.9, 70.6, 70.5, 70.0, 66.9 (OCH_2); mass spectrum, *m/e* 584.228 (M^+; calcd 584.229). Anal. Calcd for $C_{31}H_{37}ClN_2O_7$: C, 63.64; H, 6.37; N, 4.78. Found: C, 63.71; H, 6.54; N, 4.78.

7-Chloro-39-(2-propenyloxy)-3,11,19,22,25,28,31-heptaoxa-37,38-diazatetracyclo(31.3.1.1^{5,9}.1^{13,17})nonatriaconta-1(37),5,7,9-(39),13,15,17(38),33,35-nonaene (17b). A similar procedure as given for **17a** yielded **17b** by reaction of 6,6'-(2,5,8,11,14-pentaoxapentadecane-1,15-diyl)bis(2-pyridinemethanol) (**15b**) and 1,3-bis(bromomethyl)-2-(2-propenyloxy)-5-chlorobenzene as an oil (65%): ^1H NMR ($CDCl_3$) δ 7.8–7.2 (m, 8 H, Ar'H, ArH), 6.1–5.5 (m, 1 H, CH), 5.4–4.9 (m, 2 H, CH_2), 4.60 (s, 12 H, $ArCH_2$, $ArCH_2$, $Ar'CH_2$), 4.3–4.1 (m, 2 H, OCH_2), 3.7–3.5 (m, 16 H, OCH_2); ^{13}C NMR ($CDCl_3$) δ 157.9, 157.1 (Ar C-2, C-6), 154.4 (Ar' C-1), 137.1 (Ar C-4), 133.3 (CH), 133.1 (Ar' C-2, Ar' C-6), 129.8 (Ar' C-3, Ar' C-5), 129.1 (Ar' C-4), 120.5, 120.3 (Ar C-3, Ar C-5), 117.2 (CH_2), 75.9, 73.8, 72.8, 66.9 ($ArCH_2$), 70.5-70.0 (OCH_2); mass spectrum, *m/e* 628.253 (M^+; calcd 628.255).

7-Chloro-3,11,19,22,25,28-hexaoxa-34,35-diazatetracyclo(28.3.1.1^{5,9}.1^{13,17})hexatriaconta-1(34),5,7,9(36),13,15,17(35),30,32-nonaen-36-ol (4a). The allyloxy crown ether **17a** (1.17 g, 2 mmol) was dissolved in 80 mL of MeOH, and the solution was added to a suspension of 0.2 g of 5% Pd/C in 20 mL of H_2O. After addition of 0.1 mL of 70% aqueous $HClO_4$, the mixture was refluxed for 54 h. The solvent was evaporated, and the residue was taken up in $CHCl_3$ and washed with H_2O. The organic phase was dried over $MgSO_4$, and the solvent was evaporated to give a white solid: mp 133 °C; yield 80%; ^1H NMR ($CDCl_3$) δ 7.8–7.2 (m, 8 H, ArH, Ar'H), 4.81, 4.73, 4.62 (s, 12 H, $ArCH_2$), 3.7–3.6 (m, 12 H, OCH_2); ^{13}C NMR ($CDCl_3$) δ 158.4, 157.5 (Ar C-2, C-6), 154.0 (Ar' C-1), 137.5 (Ar C-4), 129.3 (Ar' C-3, Ar' C-5), 126.0 (Ar' C-2, C-6), 123.2 (Ar' C-4), 120.2, 119.7 (Ar C-3, C-5), 73.4, 72.1, 70.7, 70.3, 68.9 ($ArCH_2$, OCH_2); mass spectrum, *m/e* 544.204 (M^+; calcd 544.199). Anal. Calcd for $C_{28}H_{33}ClN_2O_7$: C, 61.70; H, 6.10; N, 5.14. Found: C, 61.85; H, 6.10; N, 5.04.

7-Chloro-3,11,19,22,25,28,31-heptaoxa-37,38-diazatetracyclo(31.3.1.1^{5,9}.1^{13,17})nonatriaconta-1(37),5,7,9(39),13,15,17(38),33,35-nonaen-39-ol (4b). The allyloxy crown ether **17b** was converted in **4b** via the procedure given for the synthesis of **4a**: yield 86%; mp 125–127 °C; ^1H NMR ($CDCl_3$) δ 10.6 (br s, 1 H, OH), 7.8–7.2 (m, 8 H, ArH, Ar'H), 4.80, 4.73, 4.63 (s, 12 H, $ArCH_2$, $ArCH_2$, $Ar'CH_2$), 3.8–3.6 (m, 16 H, OCH_2); ^{13}C NMR ($CDCl_3$) δ 158.4, 157.2 (Ar C-2, C-6), 154.0 (Ar' C-1), 137.7 (Ar C-4), 129.4 (Ar' C-3, Ar' C-5), 125.7 (Ar' C-2, Ar' C-6), 123.2 (Ar' C-4), 120.2, 119.6 (Ar C-3, C-5), 73.3, 72.0, 68.9, ($ArCH_2$, $ArCH_2$, $Ar'CH_2$), 70.8, 70.7, 70.5, 70.3 (OCH_2); mass spectrum, *m/e* 588.227 (M^+; calcd 588.224). Anal. Calcd for $C_{30}H_{37}ClN_2O_8$: C, 61.17; H, 6.33; N, 4.76. Found: C, 60.87; H, 6.28; N, 4.59.

Methyl 3,11,19,22,25,28-Hexaoxa-34,35-diazatetracyclo(28.3.1.1^{5,9}.1^{13,17})hexatriaconta-1(34),5,7,9(36),13,15,17(35),30,32-nonaene-36-carboxylate (19a). To a refluxing mixture of 1.0 g (34 mmol) of NaH (80% in oil) in 200 mL of dry THF was added slowly over a period of 5 h a mixture of 1.96 g (5.0 mmol) of the diol 6,6'-(2,5,8,11-tetraoxadodecane-1,12-diyl)bis(2-pyridinemethanol) (**15a**) and 1.61 g (5.0 mmol) of methyl 1,3-bis-(bromomethyl)benzoate in 200 mL of dry THF. The reaction mixture was cooled to room temperature, and 25 mL of water was added to decompose residual NaH. The reaction mixture was filtered, and the solvent was evaporated. The residue was diluted with 100 mL of water and extracted with 600 mL of chloroform in three portions. The organic layers were combined and dried over $MgSO_4$. After evaporation of the solvent, the crude product was purified by chromatography (silica gel, $CHCl_3$/EtOH 95/5) to yield a colorless oil: yield 42%; ^1H NMR ($CDCl_3$) δ 7.7–7.2 (m, 9 H, Ar'H, ArH), 4.68, 4.61, 4.55 (s, 6 H, $ArCH_2$, $ArCH_2$, $Ar'CH_2$), 3.7–3.5 (m, 12 H, OCH_2), 3.42 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 168.7 (C=O), 157.5, 157.3 (Ar C-2, C-6), 136.9 (Ar C-4), 136.1 (Ar' C-2, Ar' C-6), 132.4 (Ar' C-1), 129.2, 128.5 (Ar' C-3, Ar' C-4, Ar' C-5), 120.5, 120.4 (Ar C-3, Ar C-5), 74.0, 72.9, 69.9, ($ArCH_2$, $ArCH_2$, $Ar'CH_2$), 70.6–70.4 (OCH_2), 51.6 (OCH_3); mass spectrum, *m/e* 552.240 (M^+; calcd 552.247).

Methyl 3,11,19,22,25,28,31-Heptaoxa-37,38-diazatetracyclo(31.3.1.1^{5,9}.1^{13,17})nonatriaconta-1(37),5,7,9(39),13,15,17(38),33,35-nonaene-39-carboxylate (19b). The same procedure as described for the synthesis of **19a** was used for the reaction of the diol 6,6'-(2,5,8,11-pentaoxapentadecane-1,15-diyl)bis(2-pyridinemethanol) (**15b**) and methyl 1,3-bis-(bromomethyl)benzoate to yield **19b** as a colorless oil: yield 52%; ^1H NMR ($CDCl_3$) δ 7.8–7.2 (m, 9 H, Ar'H, ArH), 4.68, 4.62, 4.57 (s, 6 H, $Ar'CH_2$, $ArCH_2$, $ArCH_2$), 3.8–3.5 (m, 16 H, OCH_2), 3.49 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 168.4 (C=O), 157.6, 157.2 (Ar C-2, Ar C-6), 136.6 (Ar C-4), 136.0 (Ar' C-2, Ar' C-6), 132.1 (Ar' C-1), 129.2, 128.1 (Ar' C-3, Ar' C-4, Ar' C-5), 120.1, 119.9 (Ar C-3, Ar C-5), 73.8, 72.9, 69.9 ($ArCH_2$, $ArCH_2$, $Ar'CH_2$), 70.4–70.3 (OCH_2), 51.4 (OCH_3); mass spectrum, *m/e* 596.274 (M^+; calcd 596.273).

3,11,19,22,25,28-Hexaoxa-34,35-diazatetracyclo(28.3.1.1^{5,9}.1^{13,17})-hexatriaconta-1(34),5,7,9(36),13,15,17(35),30,32-nonaene-36-carboxylic

Acid (5a). A mixture of 10 mL of 4 M NaOH in water, 90 mL of EtOH, and 0.7 g (1.2 mmol) of the ester **19a** was refluxed for 18 h. The reaction mixture was allowed to cool to room temperature, and it was neutralized with 4 M HCl solution to pH 7. The aqueous phase was extracted with 3 × 200 mL of $CHCl_3$, the combined organic layers were dried over $MgSO_4$, and the solvent was evaporated to yield (85%) an oil: ^1H NMR ($CDCl_3$) δ 10.3 (br s, 1 H, COOH), 7.8–7.2 (m, 9 H, ArH, Ar'H), 4.73, 4.67, 4.46 (s, 12 H, $ArCH_2$, $ArCH_2$, $Ar'CH_2$), 3.8–3.6 (m, 12 H, OCH_2).

3,11,19,22,25,28,31-Heptaoxa-37,38-diazatetracyclo-(31.3.1.1^{5,9}.1^{13,17})nonatriaconta-1(37),5,7,9(39),13,15,17(38),33,35-nonaene-39-carboxylic Acid (5b). A mixture of 10 mL of 4 M NaOH in water, 90 mL of EtOH, and 0.7 g (1.2 mmol) of the ester **19b** was refluxed for 18 h. The reaction mixture was allowed to cool to room temperature, and it was neutralized with 4 M HCl solution to pH 7. The aqueous phase was extracted with 3 × 200 mL of $CHCl_3$, the combined organic layers were dried over $MgSO_4$, and the solvent was evaporated to yield an oil: yield 88%; ^1H NMR ($CDCl_3$) δ 10.8 (br s, 1 H, COOH), 7.8–7.0 (m, 9 H, ArH, Ar'H), 4.75, 4.66, 4.58 (s, 6 H, $ArCH_2$, $ArCH_2$, $Ar'CH_2$), 3.7–3.3 (m, 16 H, OCH_2); ^{13}C NMR ($CDCl_3$) δ 171.9 (C=O), 157.6, 157.2 (Ar C-2, Ar C-6), 137.4 (Ar C-4), 138.2 (Ar' C-1), 134.6 (Ar' C-2, Ar' C-6), 128.3, 128.0 (Ar' C-3, Ar' C-4, Ar' C-5), 120.6, 120.3 (Ar C-3, Ar C-5), 73.2, 72.8, 71.5 ($ArCH_2$), 70.6, 70.5, 70.4, 70.0 (OCH_2); mass spectrum, *m/e* 582.257 (M^+; calcd 582.258).

1,2,9,10,12,13,15,16,18,19,21,22,29,30-Tetradecahydro-3,7:24,28-dimetheno-8,11,14,17,20,23,1,30-benzohexaoxadiazacyclodotriacontine-35,36-diol (6a). To a suspension of 0.89 g (1.0 mmol) of the $Ba(ClO_4)_2$ complex **20a** in 25 mL of EtOH was added 0.19 g (5.0 mmol) of $NaBH_4$ in small portions at room temperature. The mixture was stirred at room temperature for 1 h, and subsequently the mixture was refluxed until the orange color had disappeared (15 min). After having been cooled to room temperature, water was added, and the solution was neutralized with 4 M HCl to pH 7. The aqueous solution was extracted with $CHCl_3$, and the organic phase was dried over $MgSO_4$. Evaporation of the solvent gave an oil, which was crystallized by trituration with diisopropyl ether: yield 70%; mp 125–126 °C; ^1H NMR ($CDCl_3$) δ 7.2–6.5 (m, 10 H, ArH, Ar'H), 5.2 (br s, 4 H, NH, OH), 4.39 (s, 4 H, $ArCH_2$), 4.2–3.9 (m, 4 H, OCH_2), 3.9–3.7 (m, 4 H, OCH_2), 3.7–3.6 (m, 12 H, OCH_2); ^{13}C NMR ($CDCl_3$) δ 146.8, 146.2 (Ar C-2, C-3), 137.8 (Ar' C-1, C-2), 125.8 (Ar C-1), 124.0 (Ar C-5), 119.5, 119.2, 115.8, 112.8 (Ar C-4, C-6, Ar' C-3, C-4, C-5, C-6), 70.8, 70.7, 70.6, 70.5, 69.4 (OCH_2), 47.5 ($ArCH_2$); mass spectrum, *m/e* 554.258 (M^+; calcd 554.263). Anal. Calcd for $C_{30}H_{38}N_2O_8$: C, 64.97; H, 6.91; N, 5.05. Found: C, 65.00; H, 6.87; N, 5.00.

1,2,9,10,12,13,15,16,18,19,21,22,24,25,32,33-Hexadecahydro-3,7:27,31-dimetheno-8,11,14,17,20,23,26,1,33-benzoheptaoxadiazacyclopentatriacontine-38,39-diol (6b). To a suspension of 0.93 g (1.0 mmol) of the $Ba(ClO_4)_2$ complex **20b** in 25 mL of EtOH was added 0.19 g (5.0 mmol) of $NaBH_4$ in small portions at room temperature. The mixture was stirred at room temperature for 1 h, and subsequently the mixture was refluxed until the orange color had disappeared (15 min). After having been cooled to room temperature, water was added, and the solution was neutralized with 4 M HCl to pH 7. The aqueous solution was extracted with $CHCl_3$, and the organic phase was dried over $MgSO_4$. Evaporation of the solvent gave an oil, which was crystallized by trituration with diisopropyl ether: yield 63%; mp 90–92 °C; ^1H NMR ($CDCl_3$) δ 7.9 (br s, 2 H, OH), 7.0–6.7 (m, 10 H, ArH, Ar'H), 4.30 (s, 4 H, $ArCH_2$), 4.3–4.0 (m, 4 H, OCH_2), 3.9–3.6 (m, 4 H, OCH_2), 3.7–3.5 (m, 16 H, OCH_2) 2.6 (br s, 2 H, NH); ^{13}C NMR ($CDCl_3$) δ 146.6, 146.2 (Ar C-2, C-3), 137.8 (Ar' C-1, C-2), 126.0 (Ar C-1), 123.6 (Ar C-5), 119.3, 119.0 (Ar' C-4, C-5, Ar C-6), 114.6, 112.7 (Ar' C-3, C-6, Ar C-4), 70.6–69.2 (OCH_2), 45.7 (Ar CH_2); mass spectrum, *m/e* 598.285 (M^+; calcd 598.289). Anal. Calcd for $C_{32}H_{42}N_2O_9 \cdot H_2O$: C, 62.32; H, 7.19; N, 4.54. Found: C, 62.11; H, 7.13; N, 4.47.

1,2,9,10,12,13,15,16,18,19,21,22,24,25,27,28,35,36-Octadecahydro-3,7:30,34-dimetheno-8,11,14,17,20,23,26,29,1,36-benzooctaoxadiazacyclooctatriacontine-41,42-diol (6c). To a suspension of 0.97 g (1.0 mmol) of the $Ba(ClO_4)_2$ complex **20c** in 25 mL of EtOH was added 0.19 g (5.0 mmol) of $NaBH_4$ in small portions at room temperature. The mixture was stirred at room temperature for 1 h, and subsequently the mixture was refluxed until the orange color had disappeared (15 min). After having been cooled to room temperature, water was added, and the solution was neutralized with 4 M HCl to pH 7. The aqueous solution was extracted with $CHCl_3$, and the organic phase was dried over $MgSO_4$. Evaporation of the solvent gave an oil, which was crystallized by trituration with diisopropyl ether: yield 71%; mp 63–65 °C; ^1H NMR ($CDCl_3$) δ 8.0 (br s, 2 H, OH), 7.0–6.6 (m, 10 H, ArH, Ar'H), 4.31 (s, 4 H, $ArCH_2$), 4.3–4.0 (m, 4 H, OCH_2), 3.9–3.7 (m, 4 H, OCH_2), 3.7–3.5 (m, 20 H, OCH_2), 2.2 (br s, 2 H, NH); ^{13}C NMR ($CDCl_3$) δ 146.4, 146.3 (Ar C-2, C-3), 137.7 (Ar' C-1), 126.3 (Ar C-1), 123.4 (Ar C-5), 119.2, 118.9 (Ar' C-4, C-5, Ar C-6), 114.2, 112.6 (Ar' C-3, C-6, Ar C-4), 70.5–69.4 (OCH_2), 45.3 ($ArCH_2$); mass spectrum, *m/e* 642.314 (M^+; calcd 642.315). Anal. Calcd for $C_{34}H_{46}N_2O_{10} \cdot 2H_2O$: C, 60.16; H, 7.42; N, 4.12. Found: C, 60.01; H, 7.46; N, 4.01.

1,2,9,10,12,13,15,16,18,19,21,22,24,25,32,33-Hexadecahydro-3,7:27,31-dimetheno-8,11,14,17,20,23,26,1,33-benzoheptaoxadiazacyclopentatriacontine-38,39-diol·Urea (6b·Urea). A solution of 0.26 g (0.43 mmol) of the macrocycle **6b** was dissolved in a mixture of 25 mL of MeOH and 5 mL of $CHCl_3$. A solution of 0.026 g (0.43 mmol) of urea in 3 mL of MeOH was added, and the product was crystallized upon addition of ethanol and filtered off: mp 135–136 °C; ^1H NMR (DMSO-d_6) δ 8.44 (s, 2 H, OH), 7.0–7.5 (m, 10 H, ArH, Ar'H), 5.3 (br s, 4 H, NH_2 urea), 4.56 (br t, J = 5 Hz, 2 H, NH), 4.20 (d, J = 5 Hz, 4 H, $ArCH_2$), 4.2–4.0 (m, 4 H, OCH_2), 3.8–3.6 (m, 4 H, OCH_2), 3.6–3.4 (m, 16 H, OCH_2). Anal. Calcd for $C_{33}H_{46}N_4O_{10}$: C, 60.17; H, 7.04; N, 8.51. Found: C, 60.14; H, 7.42; N, 8.25. Urea determination using urease and coulometric tritration showed 9.4% urea (calcd 9.1%).

Determination of Dissociation and Complexation Constants. Determinations of the pK_a values and complexation constants were carried out in nitrogen-flushed doubly distilled water in a thermostated titration vessel at 25 °C by means of a computerized potentiometric titration device.[9] At least 15 relevant datapoints within 1 pH unit from the pK_a were used in the calculations. Between every (fixed) titrant addition there was a waiting time of at least 60 s in which the pH did not vary more than 0.02 units. The concentrations of the titrants were kept low (<0.005 mol·dm^{-3}) in order to prevent homoconjugation of the carboxylic acids. Titrants were 0.03–0.10 M solutions of tetrabutylammonium and tetramethylammonium hydroxide. For the titrations of the pyrido crown ethers a 0.05 M hydrochloric acid solution in 0.10 M tetraethylammonium chloride was used. The combined glass/silver–silver chloride electrode (Metrohm, 6.0203.000) was calibrated daily in commercially available buffer solutions (Merck). All measurements were carried out at least in duple and showed excellent agreement. All calculations were performed with the SUPERQUAD program on a PDP11 computer. The program allows the input of many models for the dissociation and complexation equilibria. Statistical tests were used to exclude erroneous models. The pH data of several titrations may be included for the final calculations.

X-ray Crystallography. X-ray diffraction measurements were performed on a Philips PW1100 or an Enraf-Nonius CAD4 diffractometer, both with graphite monochromated Mo Kα radiation. Crystal data and data collection parameters are in Table IV. Lattice parameters were determined by least squares from 20–25 centered reflections. Intensities were measured in the $\omega/2\theta$ scan mode and corrected for the decay of three control reflections, measured every hour, and for Lorentz polarization.

The structures were solved by direct methods.[53] Reflections with $F_o^2 > 3\sigma(F_o^2)$ were considered observed and included in the refinement (on F) by full-matrix least squares; weights were calculated as $w = 4F_o^2/\sigma^2(F_o^2)$, $\sigma^2(F_o^2) = \sigma^2(I) + (pF_o^2)^2$, $\sigma(I)$ based on counting statistics, and p an instability factor obtained from plots of F_o versus weighted error. Hydrogen positions were obtained from difference Fourier maps; due to disorder in the structures of **3d**·H_2O and **6b**·urea, not all H atoms were located. Macrocyclic (C–)H atoms were put in calculated positions and treated as riding on their parent atoms, just as the urea H atoms of **6b**·urea, due to its poor data quality. Details concerning the treatment of the H atoms are in the Supplementary Material.

Parameters refined were the overall scale factor, an isotropic extinction parameter g ($F_o = F_c/(1 + gI_c)$), positional and anisotropic thermal parameters for non-H atoms, positional and isotropic thermal parameters for H atoms; the disordered C atoms in **6b**·urea were refined isotropically. Refinement converged with shift/error ratios less than unity. Final difference Fourier maps showed features less than 0.2 eÅ^{-3}, for **3d**·H_2O and **3f**·urea and less than 0.4 eÅ^{-3} in the disordered region of **6b**·urea. All calculations were done using SDP.[54]

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Supplementary Material Available: Tables of positional and thermal parameters of all atoms, bond distances and angles, and torsion angles in the macrocycle for the crystal structures of **3d**·H_2O, **3f**·urea, and **6b**·urea (22 pages). Ordering information is given on any current masthead page.