Tetrahedron Vol 43, No 3, pp. 617 to 624, 1987
Printed in Great Britain.

0040-4020/87 $3.00 + .00
Pergamon Journals Ltd.

LIQUID-LIQUID PHASE TRANSFER OF URONIUM SALTS VIA COMPLEXATION BY (DI)BENZO CROWN ETHERS; X-RAY STRUCTURE OF THE BENZO-27-CROWN-9 URONIUM PERCHLORATE (1:1) COMPLEX

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(*Received in UK* 10 *December* 1986)

Abstract - The complexation of uronium perchlorate with crown ethers of different ringsizes (18-33 ring atoms) has been studied by using two-phase extraction experiments. Crown ethers with 27 or more ring atoms are the best hosts to transfer uronium salts from an aqueous phase to an organic phase. The amount of uronium perchlorate transferred was measured by coulometric titration of the stoichiometric amount of ammonia produced by enzymatic degradation of urea. The crystal and molecular structure of the 1:1 complex of uronium perchlorate with benzo-27-crown-9 has been determined by X-ray crystallography. The uronium cation is encapsulated in the crown ether cavity with all its hydrogen atoms bonded to the macrocyclic host. A 1:1 complex of uronium picrate with benzo-21-crown-7 was isolated and is assumed to be a perching complex.

Introduction

In relation to our work on the synthesis of macrocyclic receptor molecules for the selective complexation of urea we have recently reported the synthesis and X-ray structures of the complexes of urea with 18-crown-6 and with aza-18-crown-6, both with a 5:1 stoichiometry.[1,2] We have also shown that complexes of crown ethers with *neutral* molecules, such as nitromethane, acetonitrile, and malononitrile, are rather weak compared with complexes with charged molecules.[3] This is also the case for complexes of simple crown ethers with urea.[4]

In order to increase the stability of complexes of macrocyclic polyethers with urea we have investigated the effect of protonation of this neutral guest. Since urea is a very weak base and the amount of protonated urea (UrH^+) in a neutral aqueous solution will be low (pK_a(urea, H_2O, 25 °C) = 0.10),[5] we have studied previously the complexation of protonated guanidine (GuH^+) (pK_a(guanidine, H_2O, 25 °C) = 13.6).[5] This cation was regarded as a good model for protonated urea because these compounds are isoelectronic and have a comparable size and shape.

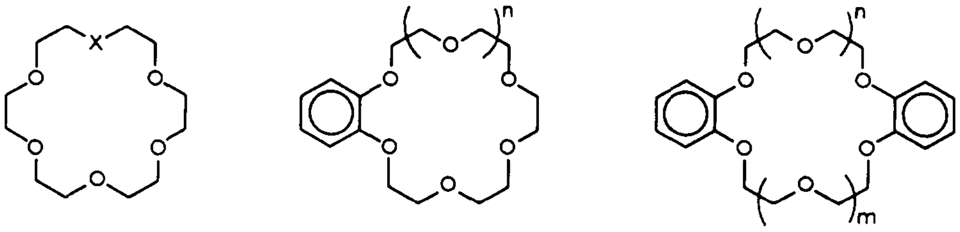
We found that in the solid state crown ethers with at least 27 ring atoms form *encapsulated* complexes with guanidinium salts.[6,7,8] 18-Membered crown ethers also form well defined stoichiometric complexes with guanidinium salts,[6] but we assumed that these are *perching* complexes with the same hydrogen bonding pattern as found by Truter and coworkers[9] for the 18-crown-6.$GuHNO_3$ (1:2) complex.

A convenient method to study the complexation of crown ethers and organic salts in solution is the equilibration of an aqueous solution of the salt and a solution of the crown ether in an apolar organic solvent.[10] Previously we have reported such extraction experiments of $GuHClO_4$ by crown ethers.[6] The ratio of crown ether to guanidinium perchlorate in the organic phase was determined from the intensities of appropriate absorptions in the ^1H NMR spectra.

Recently we have also reported the first results of the complexation of 18-crown-6 with uronium salts.[2] X-ray structures of 18-crown-6 complexes with uronium nitrate (1:1), uronium picrate (1:1), and uronium p-toluenesulphonate (1:2) revealed a perching complexation.

In this paper we describe the results of liquid-liquid phase transfer of urea, in the presence of acid, with macrocyclic polyethers having ring sizes of 18 to 33 atoms.

Chart I



1 X=O
2 X=NH

3 n=1 **6** n=4
4 n=2 **7** n=5
5 n=3

8 m=2, n=2
9 m=1, n=5
10 m=2, n=5

Results and Discussion

The crown ethers used in this study (Chart I), except dibenzo-24-crown-8 (Merck), were prepared according to reported methods.[6,11-14]

The ^{1}H NMR technique for measuring the amount of salt transferred to the organic phase, as used for the guanidinium perchlorate extraction experiments, turned out to be very inaccurate in the case of uronium perchlorate extraction experiments. The intensity of the absorption of the urea protons did not correspond to the amount of urea transferred to the organic phase. Therefore we had to develop another method for measuring the amount of urea in the organic phase.

For the determination of urea several methods are known.[15] We have used a method based on the enzymatic degradation of urea in combination with a coulometric detection method.

Methodology for the Determination of Urea. The urea determination was based on coulometric titration of the amount of ammonia produced by the stoichiometric conversion of urea by the enzyme urease. Prior to the determination the pH values of the sample, the urease solution, and the supporting electrolyte were adjusted to 7.50. The automatic coulometric titration system generates the amount of acid needed to restore this pH-value after the complete conversion of the sample. More details of the determination are given in the experimental part.

The influence of the presence of a crown ether and perchloric acid on the determination was studied in a concentration range of 0.003-0.04 M for two crown ethers, 18-crown-6 (**1**) and dibenzo-30-crown-10 (**9**), a concentration range of 0.03-0.29 M for the perchloric acid, and a urea concentration range of 0.06-0.142 M. The presence of perchloric acid in the sample did not interfere with the urea determination if the samples were carefully adjusted to pH = 7.50 prior to the analysis. If the sample contains a crown ether.urea complex the method still gives the total amount of urea present, since such a complex dissociates on removal of the urea from the solution by its enzymatic conversion. This was confirmed by the analysis of 3.3 mg (0.029 mmol) of an aza-18-crown-6(**2**).urea (1:5) complex.[16] We found an amount of urea of 0.028 mmol, a deviation of only 3%. The addition of some methanol or chloroform to a sample, solvents often required to dissolve the crown ether, had no influence on the urea determination.

From the above mentioned measurements can be concluded that the inaccuracy of this method for the urea determination is less than 5%.

Liquid-Liquid Phase Transfer of Uronium Perchlorate. The complex formation of benzo and dibenzo crown ethers with uronium perchlorate has been studied by means of two-phase liquid-liquid extraction experiments. An aqueous solution of urea and perchloric acid was equilibrated with a solution of a (di)benzo crown ether in $CDCl_3$. The amount of the uronium salt transferred to the organic phase was determined by the method described above, after separation of the two liquid layers, with an overall accuracy of 10%.

The amount of uronium salt transferred to the organic phase depends strongly on the amount of uronium perchlorate in the aqueous phase, as can be seen in Table I. The concentration of protonated urea was calculated from the amount of urea and perchloric acid, in the aqueous phase. The amount of urea transferred to the organic phase is expressed as the extraction efficiency, which is the ratio of the uronium ion concentration and the crown ether concentration in the organic phase. Obviously the urea is extracted as the corresponding uronium perchlorate complex. With an uronium perchlorate concentration of 1.7 M, present in an aqueous solution of 2.0 M urea in 28% perchloric acid, a reasonable extraction efficiency was obtained, and was chosen as the standard aqueous phase used in the two phase extraction experiments. The crown ether concentration in the organic phase has less influence on the extraction efficiency, and a crown ether concentration of 0.2 M in chloroform was chosen for the experiments. The urea determinations were carried out after 17 h of equilibration, since after this period the equilibrium is reached.

The results of the extraction experiments with benzo and dibenzo crown ethers with 18- to 33-membered rings are summarized in Table II. They show a striking analogy with the results of extraction experiments with benzo[6] and pyrido[7] crown ethers and guanidinium salts. The amount of uronium perchlorate extracted into the organic phase is considerably larger with crown ethers that have 27 or more ring atoms than with the smaller crown ethers. These larger crown ethers are able to encapsulate the polar guest and this gives a complex with an apolar exterior and a polar interior. Such complexes will preferably be transferred to the organic phase.

Table I. Extraction Efficiency[a] of (Di)benzo Crown Ethers as a Function of the Uronium Perchlorate Concentration in the Aqueous Phase, the Crown Ether Concentration in the Organic Phase, and the Equilibration Time.

Uronium perchlorate concentration (M)		0.3	0.7	1.7		
Equilibration time (h)		17	17	2	17	72
Crown ether	Concentration (M)					
6	0.05	-	-	-	0.51	-
6	0.1	0.06	0.32	0.34	0.47	0.51
6	0.2	0.08	0.43	0.42	0.57	-
9	0.2	-	-	-	0.57	0.56
10	0.05	-	-	-	0.52	-
10	0.1	0.10	0.44	0.59	0.67	0.70
10	0.2	-	-	-	0.68	0.69

[a] The ratio of the uronium ion concentration and the crown ether concentration in the organic phase.

Table II. Extraction Efficiency[a] of (Di)benzo Crown Ethers.

crown ether	ring size	mmol crown transferred to the aq. phase	mmol urea transferred to the org. phase	extraction efficiency
3	18	0.04	0.04	0.23
4	21	0.05	0.05	0.36
5	24	0.02	0.01	0.06
8	24	0.01	0.02	0.08
6	27	0.05	0.09	0.57
7	30	0.02	0.09	0.52
9	30	0.03	0.10	0.57
10	33	0.01	0.13	0.68

[a] The ratio of the uronium ion concentration and the crown ether concentration in the organic phase.

In the case of benzo-27-crown-9 (**6**) a crystalline benzo-27-crown-9.$UrHClO_4$ (1:1) complex could be isolated from the organic phase. The crystal structure of this complex has been determined by X-ray diffraction.[17] Details of the structure determination are given in the Experimental Section. A stereoscopic ORTEP-view[18] of the complex, including atom numbering, is presented in Figure 1, using 50% probability ellipsoids for all non-hydrogen atoms. The radii of the hydrogens have been chosen arbitrarily. Torsion angles in the macrocycle are given in Table III. Hydrogen bond parameters are presented in Table IV.

The X-ray analysis reveals that the cation is completely encapsulated by the macrocycle, with its molecular framework almost coinciding with the best plane defined by the crown ether oxygens. The anion, on the contrary, is not involved in hydrogen bonding, neither to the polyether nor to the cation. The macroring has the conformation ag^-g^- ag^+a ag^-a ag^-g^- ag^+a ag^-a ag^-g^- g^-g^-a asa ,[19] forming an almost flat ring around the cation. All oxygen atoms of the macroring are directed to the guest molecule. The aromatic ring is directed away from the cavity, almost parallel to the crown ether plane.

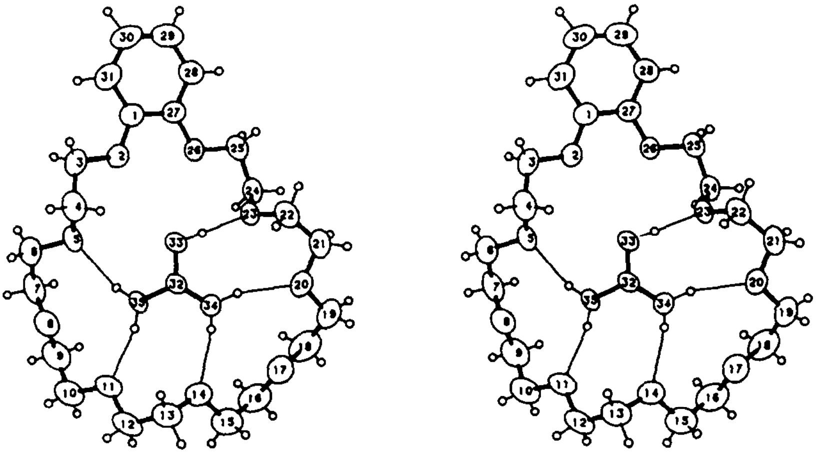


Figure 1. Stereoscopic view of the benzo-27-crown-9.$UrHClO_4$ (1:1) complex, showing atom numbering. The perchlorate ion (numbered Cl36, O37-O40) is omitted.

Table III. Torsion Angles[a] (deg) in the Macrocycle of the Benzo-27-crown-9.$UrHClO_4$ (1:1) Complex.

C1 - O2 - C3 - C4	-158.8(4)
O2 - C3 - C4 - O5	-74.2(5)
C3 - C4 - O5 - C6	-92.3(7)
C4 - O5 - C6 - C7	-168.7(5)
O5 - C6 - C7 - O8	68.5(5)
C6 - C7 - O8 - C9	-170.1(7)
C7 - O8 - C9 - C10	-178.5(7)
O8 - C9 - C10 - O11	-65.4(7)
C9 - C10 - O11 - C12	-170.1(7)
C10 - O11 - C12 - C13	-171.2(6)
O11 - C12 - C13 - O14	-64.3(5)
C12 - C13 - O14 - C15	-91.6(7)
C13 - O14 - C15 - C16	176.0(6)
O14 - C15 - C16 - O17	61.7(6)
C15 - C16 - O17 - C18	-177.7(7)
C16 - O17 - C18 - C19	175.3(6)
O17 - C18 - C19 - O20	-64.1(6)
C18 - C19 - O20 - C21	-160.2(6)
C19 - O20 - C21 - C22	-178.9(5)
O20 - C21 - C22 - O23	-54.2(5)
C21 - C22 - O23 - C24	-78.4(6)
C22 - O23 - C24 - C25	-91.7(5)
O23 - C24 - C25 - O26	-63.9(5)
C24 - C25 - O26 - C27	177.8(4)
C25 - O26 - C27 - C1	-168.8(4)
O26 - C27 - C1 - O2	1.5(4)
C27 - C1 - O2 - C3	173.4(4)

[a] Estimated standard deviations given in parentheses in units of the least significant digit.

All five uronium hydrogen atoms are involved in relatively short hydrogen bonds with crown ether oxygens (O-H...O: 2.54 Å, N-H...O ranging from 2.84-2.93 Å, see Table IV). The short distances between the atoms involved (O8...N35: 3.05 Å and O17...N34: 3.08 Å) suggest considerable electrostatic interaction between these oxygen atoms and the guest. The oxygen atoms adjacent to the benzo-substituent have considerably longer distances to the nearest hetero atom of the cation (O2...O33 : 3.29 Å and O26...O33 : 3.26 Å).

An interesting feature appears when one examines the orientation of the uronium ion within the cavity. There are nine possible ways in which the uronium ion may be oriented, in order to get a complementary relationship between the uronium hydrogens and the crown ether oxygens. These different orientations can be obtained by rotations of the guest by 40 degrees about a central axis perpendicular to the cation. Of the nine possibilities only one orientation leaves out the catecholic oxygen atoms for hydrogen bonding, and this is the one found in the present structure. The same trend of using a minimum number of catecholic oxygen atoms was also found in the 1:1 complexes of guanidinium perchlorate with benzo-27-crown-9, dibenzo-27-crown-9, and dibenzo-30-crown-10.[6,8]

Table IV. Hydrogen-Bond Parameters[a] for the Benzo-27-crown-9.$UrHClO_4$ (1:1) Complex.

donor atom: D	acceptor atom: A	distance D...A (Å)	distance H...A (Å)	angle D-H...A (Å)
O33	O23	2.535(6)	1.67(9)	172(9)
N34	O14	2.842(7)	2.09(6)	166(8)
N34	O20	2.927(8)	2.04(8)	162(6)
N35	O5	2.849(8)	2.05(6)	164(7)
N35	O11	2.849(8)	2.01(5)	163(6)

[a] Estimated standard deviations given in parentheses in units of the least significant digit.

The extraction efficiencies of the benzo- and dibenzo-30-crown-10 are of the same magnitude, suggesting that the catechol group has no noticeable effect on the complexation of uronium perchlorate. This is in contrast with the complexation of guanidinium perchlorate by crown ethers, where a decreasing extraction capability can be seen with an increasing amount of catechol moieties for a 27-membered ring.[6] These findings can be ascribed to the larger ringsize, but can also be explained in terms of hydrogen bonding. Guanidinium ions require six oxygen atoms, whereas uronium ions need only five oxygen atoms to achieve a complementary hydrogen bonding scheme, so the hydrogen bonding scheme for uronium ions is favoured above the hydrogen bonding scheme for guanidinium ions in using as less as catecholic oxygen atoms as possible.

The smaller crown ethers show a lower extraction efficiency. The 24-membered ring hardly extracts uronium perchlorate into the organic phase, a minimum for the extraction that was also observed for guanidinium salt extractions.[6,7] With the 18-membered ring only a small amount of uronium salt can be transferred to the organic phase. The 18-membered ring is capable to form perching complexes with uronium ions,[1,2,6] and although not proven it is assumed that this is also the case for the 21-membered ring. Surprisingly the 21-membered macrocycle shows a relatively high extraction efficiency, which was not observed for the guanidinium salt extractions.[6,7,20] This observation suggests a relatively strong association of the benzo-21-crown-7 (**4**) and the uronium salt. Therefore we have carried out complexation experiments with this crown ether and various uronium salts in a homogenous phase. From a methanol solution of benzo-21-crown-7 and an equimolar amount of uronium picrate, a crystalline complex precipitated after the addition of diethyl ether, with a mp of 120-121°C. The elemental analysis corresponded to a 1:1 stoichiometry.

Conclusions

From the above results can be concluded that the urea determination by enzymatic hydrolysis followed by a coulometric titration is a method with a satisfactory accuracy, and can be used to determine the amount of uronium transferred from an aqueous phase to an organic phase by crown ethers.

As expected from model extraction experiments with guanidinium ions, a reasonable extraction efficiency is found for macrocycles with 27 or more ring atoms.

A stable encapsulated complex is formed between benzo-27-crown-9 and uronium perchlorate, with a complementary H-bonding scheme in which no catecholic oxygen is used for hydrogen bonding. A stable complex was also formed between benzo-21-crown-7 and uronium picrate, which is assumed to be a perching complex.

In the case of 30-membered benzo crown ethers a negative influence of a catechol group on the complexation of $UrHClO_4$ was not observed.

Experimental

Melting points were determined with a Reichert melting point apparatus and are uncorrected. ^1H NMR spectra were recorded with a Bruker WP-80 spectrometer in $CDCl_3$, with Me_4Si as an internal standard.

Materials. Benzo-18-crown-6 (**3**),[11] benzo-21-crown-7 (**4**),[12] benzo-24-crown-8 (**5**),[13] benzo-27-crown-9 (**6**),[14] benzo-30-crown-10 (**7**),[12] dibenzo-30-crown-10 (**9**),[6] and dibenzo-33-crown-11 (**10**)[6] were prepared according to known methods. Dibenzo-24-crown-8 (**8**) (Merck) was used without further purification. Urea (Merck) was recrystallized from methanol. Urease (Sigma) had an activity of 20,000-50,000 units per gram. Uronium picrate was prepared according to a previous described method.[2]

Procedure for the Urea Determination. The coulometric titration equipment consisted of 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 0.5 M Na_2SO_4 and 1 mL urease solution (100 mg/ 10 mL H_2O) and adjusted to pH = 7.50. After the introduction of the sample or a standard solution, previously also adjusted to pH = 7.50, containing 0.1 - 7.0 μmol of urea, 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.

Extraction Experiments. A $CDCl_3$ solution (1 mL) containing 0.2 mmol crown ether, and about 0.2 mmol of 1,2,4,5-tetramethylbenzene, was agitated for 17 h with 1 mL of a H_2O solution, containing 2.0 mmol urea in 28% $HClO_4$. Subsequently 0.5 mL of both layers were separated with a syringe for analysis. The water solution could immediately be used for the urea determination, the chloroform layer had to be concentrated and the residue redissolved in water or methanol/water prior to use it for the urea determination. The other 0.5 mL of the chloroform layer was used to determine by ^1H NMR spectroscopy the amount of crown ether transferred to the water phase during the equilibration, by comparing the ratios of crown ether to 1,2,4,5-tetramethylbenzene of the chloroform solution before and after the period of equilibration.

Synthesis of the Uronium Perchlorate Complexes.

Benzo-27-crown-9.Uronium Perchlorate (1:1). A solution of 300 mg (0.67 mmol) benzo-27-crown-9 in 2 mL chloroform was equilibrated for 30 min., with a solution of 300 mg (5.0 mmol) urea in 2 mL 20% $HClO_4$. After separation of the layers, the chloroform layer was dried over $MgSO_4$ and evaporated. The crystalline residue was triturated with chloroform. Mp 99-101 °C. ^1H NMR δ 7.6 (bs, 5H, NH_2 and OH), 6.94 (s, 4H, ArH), 4.30-3.65 (m, 32H, OCH_2).

Benzo-21-crown-7.Uronium Picrate (1:1). In 2 mL of a mixture of chloroform/methanol (1:1) were dissolved 226 mg (0.63 mmol) of benzo-21-crown-7 and 182 mg (0.63 mmol) uronium picrate, under heating. After cooling to room temperature diethyl ether was added until the mixture was slightly turbid, and the complex started to precipitate. A yellow 1:1 complex could be isolated in 67% yield. Mp 120-121 °C. ^1H NMR ($CDCl_3$/DMSO-d_6) δ 8.82 (s, 2H, ArH), 7.65 (s, 4H, ArH), 4.78 (bs, 4H, NH_2), 4.23-3.60 (m, 24H, OCH_2). Anal. calcd for $C_{25}H_{35}N_5O_{15}$: C, 46.51; H, 5.46; N, 10.85. Found: C, 46.43; H, 5.68; N, 10.91.

X-ray Diffraction. X-ray diffraction measurements on solid benzo-27-crown-9.$UrHClO_4$ (1:1) were made at T = 269 K on a Philips PW 1100 diffractometer using graphite monochromated Mo K_α radiation (λ = 0.71069 Å). Crystal data: triclinic, space group P1, a = 13.866(5) Å, b = 12.585(7) Å, c = 9.926(6) Å, α = 99.59(3), β = 74.91(6), γ = 116.52(3)°, Z = 2, d_c = 1.350 g cm^{-3}. Measurement: ω-2θ scan mode, $3 < \omega < 25°$; number of reflections measured: 5253. Measured intensities were corrected for the decrease in intensity during data collection, using the intensities of three standard reflections measured every hour.

The structure was solved by direct methods[21] and refined by full-matrix least-squares analysis,[22] using 3145 reflections with $I > \sigma(I)$. Hydrogen atoms were found in difference-Fourier syntheses. The number of parameters refined was 526: overall scale factor, isotropic secondary extinction parameter, positional parameters of all atoms, anisotropic thermal parameters for non-hydrogen atoms, and isotropic thermal parameters for hydrogens. The weight for each reflection was taken to be $w = [\sigma(F_o) + 0.01\,|F_o|]^{-2}$, where $\sigma(F_o)$ is the estimated standard deviation of the observed structure factor (F_o) derived from counting statistics. Scattering factors for non-hydrogen atoms were taken from ref 23; for H the scattering factors of Stewart, Davidson, and Simpson[24] were used. No absorption corrections were applied. The refinement resulted in an unweighted R-factor of 8.3%, whereas R_w was 5.6%.

Atomic coordinates for this structure have been deposited with the Cambridge Crystallographic Data Centre. The coordinates can be obtained on request from The Director, Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, U.K..

Complete lists of positional parameters for all atoms, anisotropic thermal parameters for heavy atoms and isotropic thermal parameters for hydrogens, and lists of bond lengths and bond angles have been deposited as Supplementary Material with the British Library Lending Division, Boston Spa, Wetherby, West Yorks LS23 7BQ, U.K..

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(19) "s" (synperiplanar) denotes an OCCO torsion angle of almost 0°, imposed by the benzo-moiety.

(20) An additional extraction experiment was carried out with benzo-21-crown-7 and guanidinium perchlorate, under conditions as described by de Boer et al. in ref. 6 for 18 and 24 or more membered rings. Under the standard conditions A and B the guanidinium salt could be extracted into the organic phase with a ratio salt to crown ether of 0.13 and 0.14, respectively.
The extractions with uronium perchlorate were carried out again for the benzo-18-crown-6 and the benzo-21-crown-7 under conditions as mentioned in this paper, but with an additional amount of lithium perchlorate, equimolar to the amount of urea, in the aqueous phase. In this case the extraction efficiency appeared to be 0.13 and 0.11, respectively, values in agreement with the guanidinium salt extractions. This shows that the benzo-21-crown-7 prefers a lithium ion as guest above a uronium ion.

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