determined by accurate mass measurements. Standard workup of an ethereal solution means washing with 5% HCl (aqueous), water, and 5% $KHCO_3$ (aqueous), drying with Na_2SO_4, and evaporation of the solvent in vacuo. Crystal data: $P2_1$, a = 12.962 (3) Å, (b = 6.260 (1) Å c = 15.711 (3) Å, β = 102.20 (2)°, Z = 2; $C_{27}H_{46}O$, M_r = 386.67, ρ_{calcd} = 1.03 g·cm^3, ρ_{obsd} = 1.023 (3) g·cm^{-3} (flotation in aqueous $ZnBr_2$), platelike crystal, 0.35 × 0.25 × 0.06 mm^3. Data collection:[35] Syntex $P2_1$, Cu Kα radiation (λ = 1.54178 Å), 2752 unique reflections in the $0 < 2\theta \leq 158°$ range, 1304 of them observed with $I > 1.96\sigma(I)$, room temperature, no absorption correction (μ = 4.13 cm^{-1}). Structure solution: direct methods and weighted Fourier syntheses, refinement by full-matrix least-squares to R = 0.089, R_w = 0.097 using MAGEX 80[36] and SHELX programs. Positions and anisotropic thermal parameters of non-H atoms together with positions and isotropic thermal parameters of H atoms refined in two blocks; average thermal parameters for hydrogens of CH_3, CH_2, and CH groups respectively were employed, methyl groups being treated as rigid bodies. No features greater than +0.17 and −0.20 e Å^{-3} were found in the final difference map. The atomic coordinates, anisotropic thermal parameters, and bond lengths and angles are available as supplementary material.

5α-Cholestane-5,19-diol (8). To a stirred solution of epoxide **7** (1.5 g) in ether (100 mL) was added lithium aluminum hydride (100 mg), the mixture was stirred at room temperature overnight and then quenched with saturated aqueous ammonium chloride. The organic layer was worked up as usual. The product was dissolved in benzene and filtered through a pad of aluminum oxide, and the solvent was evaporated in vacuo to yield diol **8** (1.1 g): $[\alpha]_D$ +18° (c 2.3); ^{1}H NMR 0.67 (s, 3 H), 3.78 (d, J = 12 Hz, 1 H), 4.07 (d, J = 12 Hz, 1 H).

Anal. Calcd for $C_{27}H_{48}O_2$: C, 80.14; 14; H, 11.96. Found: C, 80.03; H, 12.19.

5α-Cholestane-5,19-diol 19-Methanesulfonate (9). Diol **8** (1.0 g) was dissolved in pyridine (5 mL) and treated with methanesulfonyl chloride (0.5 mL) at 0 °C for 2 h. The mixture was then poured into ice, and the product was extracted with ether. Standard workup gave pure mesylate (**9** (1.05 g) as a colorless oil: $[\alpha]_D$ +24° (c 1.8); ^{1}H NMR 0.67 (s, 3 H), 2.98 (s, 3 H), 4.32 (d, J = 10 Hz, 1 H), 4.57 (d, J = 10 Hz, 1 H).

Anal. Calcd for $C_{28}H_{50}O_4S$: C, 69.66; H, 10.44; S, 6.64. Found: C, 69.52; H, 10.64; S, 6.89.

Acetolysis of 9. Mesylate **9** (500 mg) was refluxed with anhydrous sodium acetate (500 mg) in acetic acid (7 mL) and acetic anhydride (0.7 mL) for 30 min. The reaction mixture was cooled and diluted with water and the product taken up into ether. After standard workup the residue was crystallized from aqueous acetone[37] to afford pure ketone **11** (261 mg): mp 97–98 °C; $[\alpha]_D$ + 35° (c 1.6); IR 1697 cm^{-1}; ^{1}H NMR 0.66 (s, 3 H), 2.13 (ddd, J = 13.3, 10.0, and 2.0 Hz, 1 H), 2.55 (m, 2 H); ^{13}C NMR 12.15 (q), 18.70 (q), 22.53 (q), 22.60 (t), 22.80 (q), 23.87 (t), 24.67 (t), 25.44 (t), 26.57 (t), 27.98 (d), 28.45 (t), 29.40 (t), 30.78 (t), 33.72 (t), 35.68 (d), 36.20 (t), 36.45 (t), 39.50 (t, 2 C), 42.29 (d), 42.72 (s), 43.33 (t), 54.72 (d), 55.69 (d), 56.04 (d), 59.77 (s), 218.50 (s).

Anal. Calcd for $C_{27}H_{46}O$: C, 80.87; H, 11.99. Found: C, 80.65; H, 12.07.

^{1}H NMR spectrum of **10**: 0.71 (s, 3 H), 2.36 (m, 1 H), 2.85 (dd, J = 12.0 and 12.0 Hz, 1 H). ^{13}C NMR spectrum of **10**: 11.91 (q), 18.58 (q), 22.53 (q), 22.85 (q), 23.81 (t), 24.46 (t), 25.35 (t), 26.07 (t), 28.16 (t), 29.47 (t), 32.11 (t), 32.90 (t), 33.50 (t), 35.74 (d), 36.07 (t), 39.58 (t), 39.95 (t), 40.38 (t), 41.84 (d), 42.64 (s), 45.98 (t), 54.78 (d), 55.76 (d), 56.17 (d), 58.34 (s), 217.68 (s). The spectra were taken in a mixture with **11**.

Acknowledgment. We thank Dr. S. Vašíčková for measurement of IR spectra, J. Jelínková for measurement of 60-MHz ^{1}H NMR spectra, and the staff of the Analytical Laboratory of this Institute (Head Dr. J. Horáček) for elemental analyses.

Supplementary Material Available: Tables of atomic coordinates, anisotropic thermal parameters, and bond lengths and angles (5 pages). Ordering information is given on any current masthead page.

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(37) This single crystallization afforded material sufficient for the X-ray analysis.

Crown Ether Mediated Transport of Guanidinium Thiocyanate through a Bulk Liquid Membrane and the Correlation with the Complex Stability Constants

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A series of crown ethers with a ring varying between 18 and 33 ring atoms and possessing subunits of catechol and 1,3-xyleno have been synthesized. X-ray analysis of the 1:1 complex of guanidinium perchlorate and [2,8]dibenzo-30-crown-10 revealed complete encapsulation of the guanidinium cation by the crown ether. Association constants of guanidinium chloride and the synthesized crown ethers have been determined in methanol. Rates of transport of guanidinium thiocyanate through bulk liquid membranes of chloroform have been monitored by using the crown ethers as the carrier. The observed rates of transport could be correlated well to the determined association constants by the relation $J = (66.7 \times 10^{-8})(\alpha k K(CH_3OH)/[1 + \alpha k K(CH_3OH)])$ in which $\alpha = K(CHCl_3)/K(CH_3OH)$. The highest flux ($J(CHCl_3)$ = 38.9 × 10^{-8} mol cm^{-2} h^{-1}) was observed for benzo-30-crown-10, as carrier, which also showed the highest association constant in CH_3OH (K = 68 M^{-1}). It is concluded that the diffusion of the crown ether guanidinium thiocyanate complex is the rate-determining step in the overall transport process.

Introduction

Bulk liquid membranes are often used to investigate the complexation and transport properties of synthetic and natural ionophores with salts. The relation between the transport rate and the association constant was investigated initially by Reusch and Cussler[1] followed by Lamb et al.[2a] and Behr et al.[2b] The latter showed that with

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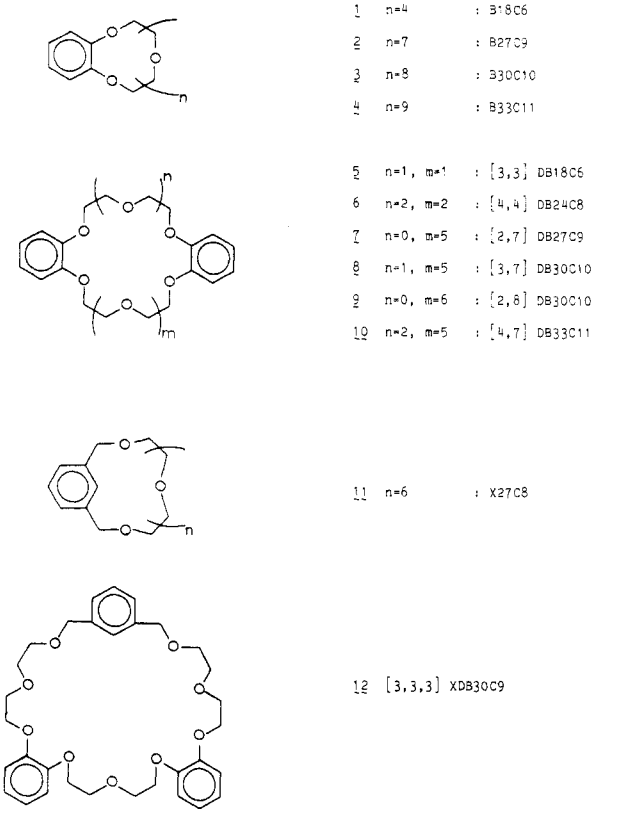
increasing association constants the transport rate goes through an optimum value. The observed decrease originates from a rate-determining decomplexation process. Synthetic ionophores such as crown ethers, cryptands, and podands are able to complex cations with a variable degree of selectivity and transport salts as ion pairs through bulk liquid membranes.[1,3,4] Generally, the observed transport selectivity reflects the preference of complexation of the ionophore.

In relation to our work on the selective complexation of urea and other polyfunctional molecules by synthetic macrocyclic receptors,[5] we are currently studying the possibility of the selective transport of such polyfunctional species through liquid membranes using crown ether molecules as synthetic carriers. The selective removal of urea from aqueous solutions by means of membranes would be of considerable importance in medical technology and in the treatment of waste water from the fertilizer industry.

Previously we have shown that urea forms a complex with 18-crown-6 in the solid state having a 5:1 stoichiometry.[5] X-ray analysis showed that in this complex two urea molecules are hydrogen-bonded to the crown ether in a perching position.[6] The remaining three urea molecules form layers in which they are mutually hydrogen-bonded. We have also shown that complexes of crown ethers and neutral molecules are much weaker than complexes formed with charged molecules.[7] These results prompted us to focus our attention on the complexation of the protonated form of urea, viz. uronium, to improve the association constant. Since guanidine is isoelectronic with urea and in contrast to urea is protonated in a more accessible pH range, we have carried out some transport and complexation experiments with guanidinium salts mimicking (the less basic) urea. We assume that such polyfunctional organic molecules are more strongly bound by crown ethers when they form encapsulated[6] complexes with the macrocycle, because in such complexes a maximum of all possible interactions between host and guest are used. From Corey–Pauling–Koltun (CPK) models, X-ray structure analysis, and extraction data we have found that (thio)uronium and guanidinium cations can only form encapsulated complexes with crown ethers having at least 27 ring atoms.[8-13] These polyfunctional cations have two

Chart I. Structures of Carrier Ligands[a]



[a] The following code was used in the abbreviated names: C = crown, B = benzo, D = di(or bis), X = 1,3-xylyl, [,] = code for the amount of hetero atoms between the functionalities (see also ref 16).

conjugated functional groups that share one positive charge, e.g. *S-tert*-butylisothiouronium[14] and guanidinium.[15] In the complexes binding occurs via linear $NH^+\cdots O$ hydrogen bonds, and further stabilization may come from electrostatic interactions with the ether oxygens. In encapsulated complexes the crown ether oxygens, which are not involved in hydrogen bonding, seem to have a considerable electrostatic interaction with the nitrogen atoms of the polyfunctional cation.[12] Behr et al. showed that the macrocyclic ring size selects the organic cation size: 18-membered crown ethers are selective for ammonium salts whereas 27-membered crown ethers prefer guanidinium salts.[15] To the best of our knowledge the bulk liquid membrane transport of such polyfunctional guest species has not been reported so far.

In this paper we report the results of a study on the membrane transport of guanidinium cations by crown ethers having a ring size varying between 18 and 33 ring

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atoms. The objective of the work was to correlate the observed transport rate with the independently determined corresponding association constants of guanidinium and crown ether.

Results

Synthesis of Crown Ether Carriers. The crown ether carriers investigated in this study are displayed in Chart I. The synthesis of **1–12** has been carried out by known procedures,[9,12,13,19] except **5** and **6**, which are commercially available. The benzo crown ethers (**1**, **2**, **3**, and **4**) were synthesized from catechol and polyethylene glycol ditosylates with potassium *tert*-butoxide (KO-*t*-Bu) as a base. The dibenzo crown ethers (**5**, **6**, **7**, **8**, **9**, and **10**) were prepared from 2,2′-[1,2-ethanediylbis(oxy)]bisphenol, 2,2′-[oxybis(2,1-ethanediyloxy)]bisphenol, or 2,2′-[1,2-ethanediylbis(oxy-2,1-ethanediyloxy)]bisphenol and the corresponding polyethylene glycol ditosylates with KO-*t*-Bu or cesium fluoride (CsF)[20] as a base. The 1,3-xyleno crown ether (**11**) was prepared from 1,3-bis(bromomethyl)benzene and heptaethylene glycol using sodium hydride (NaH) as a base. The 1,3-xylenodibenzo crown ether (**12**) was synthesized by reaction of 2,2-[oxybis(2,1-ethanediyloxy)]bisphenol and the ditosylate of 1,3-bis-((2-(2-hydroxyethoxy)ethoxy)methyl)benzene with CsF as a base.

Benzo-33-crown-11 (**4**) was synthesized according to the general procedure described by Kyba et al.[9] from catechol and decaethylene glycol ditosylate in a yield of 11%. [2,8]Dibenzo-30-crown-10 (**9**) was prepared according to the procedure described by de Boer et al.[12] starting from 2,2′-[1,2-ethanediylbis(oxy)]bisphenol and heptaethylene glycol ditosylate using CsF as a base in THF in a yield of 5% (oil). This crown ether was characterized as the corresponding guanidinium perchlorate complex (mp 126–127 °C; vide infra).

Liquid–Liquid Phase Transfer of Guanidinium Perchlorate. The complex formation of the crown ethers with guanidinium perchlorate was studied by means of two-phase liquid–liquid extraction experiments. A solution of 2 mL of 0.5 M crown ether in $CDCl_3$ was equilibrated at room temperature with an aqueous solution of 2 mL of 1 M lithium perchlorate and 0.5 M guanidinium sulfate. The amount of guanidinium perchlorate extracted to the organic phase was determined by ^1H NMR spectroscopy. More details of the extraction procedure are given in the Experimental Section.

Previously we have described[12,13] the results of extraction experiments for the benzo crown ethers **1**, **2**, **5**, **6**, **7**, **8**, **10**, **11**, and **12**. Crystal and molecular structures of several 1:1 complexes of crown ethers (**2**, **7**, **8**, and **11**) and guanidinium perchlorate showed that in all these complexes the cation is encapsulated in the crown ether cavity forming six hydrogen bonds to the oxygen atoms of the macrocyclic host.[12,13] On the other hand, Truter et al.[21] reported a perching complex of guanidinium nitrate and 18-crown-6 with a 2:1 stoichiometry. In their complex each guanidinium cation is associated to the crown ether via only one hydrogen bond from guanidinium to an oxygen atom of the crown ether. Our extraction experiments with the crown ethers **3**, **4**, and **9** resulted in an additional crystal structure of 1:1 complex of guanidinium perchlorate with **9**. This [2,8]dibenzo-30-crown-10–guanidinium perchlorate complex was obtained from the organic layer of an extraction experiment after evaporation of the solvent. Recrystallization from ethanol gave white crystals, mp 126–127 °C.

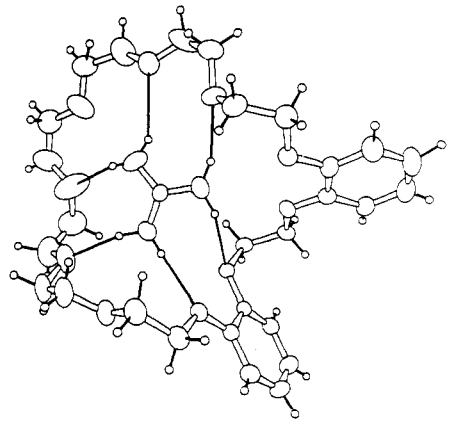

Figure 1. ORTEP[22] view of [2,8]dibenzo-30-crown-10–guanidinium perchlorate (1:1) complex (ClO_4^- not shown).

X-ray Analysis. The structure of the complex of guanidinium perchlorate and **9** has been determined by X-ray crystallography. Details of the structure determination are given in the Experimental Section. The ORTEP[22] view of the complex is given in Figure 1. The guanidinium ion is encapsulated within the macrocycle of this complex; i.e., all guanidinium hydrogen atoms take part in hydrogen bonding with oxygen atoms of the crown ether. In this complex hydrogen bonds between guanidinium and perchlorate ions do not exist. The N···O hydrogen bond distances vary between 2.83 and 3.15 Å, with N–H···O angles in the range of 135 to 171°. It is of interest to compare the crystal structure with the structure of [3,7]-dibenzo-30-crown-10–guanidinium perchlorate (1:1).[12] In both cases the macroring is wrapped in a fairly irregular way around the guanidinium ion. From the shape of the ring it can be said that the 30-membered ring is too large and does not have the proper symmetry for optimal hydrogen bonding between host and guest. A much better fit has been observed in the structures of the (1:1) complexes of guanidinium perchlorate with benzo-27-crown-9 and [2,7]dibenzo-27-crown-9.[12]

Stability Constants. Because we have no accurate method for the determination of association constants in chloroform, the stability constants of guanidinium chloride with the ligands studied were determined potentiometrically in methanol assuming that guanidium chloride will be completely dissociated into free ions. Because guanidinium-selective electrodes are not commercially available, we had to use a competition method. First, the binding constant of an indicator ion (K^+) with a crown ether was determined by using the Frensdorff method.[23] Subsequently, by repeating the titration in the presence of a known amount of guanidinium chloride, the corresponding association constant of the guanidinium complex could be calculated (Table I) by using the SUPERQUAD[24] computer program. For other ions similar procedures have been described previously, using Ag^+,[25] H^+,[26] or alkali[27] cations

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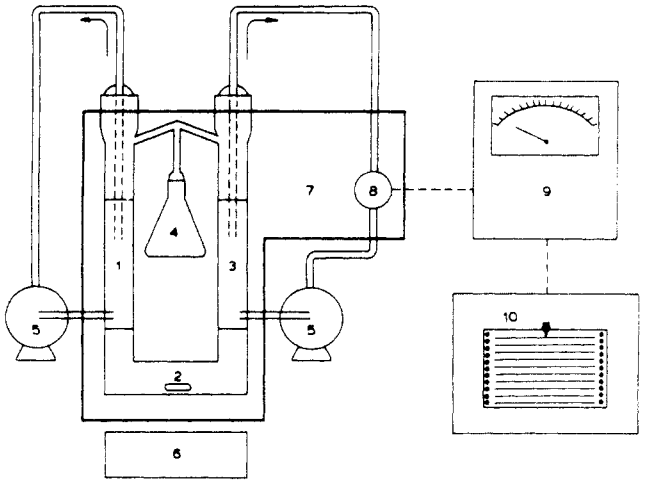

Figure 2. Measurement setup: (1) source phase, (2) membrane phase, (3) receiving phase, (4) chloroform to saturate the air above the two water phases, (5) peristaltic pump, (6) magnetic stirrer, (7) thermostated bath, (8) conductivity cell, (9) conductivity measuring bridge, (10) recorder.

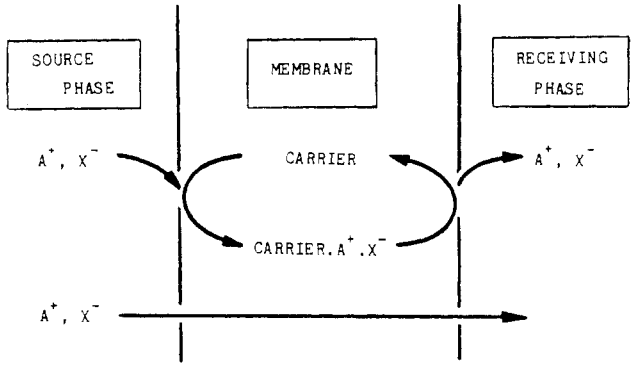

Figure 3. Simplified representation of the facilitated transport of a salt AX by a neutral carrier.

as indicator ions.

Bulk Liquid Membrane Transport. The transport experiments were carried out in a rectangular U-tube of well-defined shape and dimensions, at a constant temperature of 25.0 ± 0.5 °C (Figure 2). A detailed description of the measurement setup, its dimensions, and the conditions are given in the Experimental Section. The cell contained 15 mL of membrane phase (1.0 mM carrier in chloroform) which was stirred continuously, and two aqueous phases, viz. 15 mL of a 1.0 M aqueous solution of guanidinium thiocyanate (source phase) and 15 mL of distilled deionized water (receiving phase). Both the source and the receiving phase were continuously circulated. The amount of guanidinium thiocyanate transported through the membrane phase was monitored continuously by conductivity measurements of the receiving phase during 24 h. We found that, provided the amount of salt transported was small, the salt concentration in the receiving phase increased linearly with the time. After 24 h the receiving phase was also analyzed for guanidinium thiocyanate by a potentiometric titration in anhydrous acetic acid[28] (see Experimental Section). The results of both experiments are consistent within experimental error (±10%). A schematic drawing of a mobile carrier mechanism is given in Figure 3. Since in our study the membrane phase is stirred, the diffusion of the complex through the membrane phase will not be rate-determining. The reported values of the flux (Table I) are the average of two or three independent experiments with a maximum standard deviation of ±10%. Membrane leakage was also determined. Via blank experiments with no carrier present in the membrane phase it was found that the amount of guanidinium thiocyanate leakage was less than 1×10^{-8} mol h^{-1} cm^{-2}. After the measurements the receiving phase was analyzed for the presence of crown ether using UV spectroscopy. From this analysis we estimate that less than 1% (mol/mol) of the initial crown ether concentration was extracted from the membrane phase into the aqueous phases.

Table I. Rate of Guanidinium Transport Mediated by the Crown Ethers and Their Corresponding Association Constants in Methanol

crown ether	no.	$10^8 J$,[a] mol cm^{-2} h^{-1}	K(MeOH),[c,d] L mol^{-1}
B18C6	1	*b*	<10
[3,3] DB18C6	5	*b*	<10
[4,4] DB24C8	6	1.0	<10
B27C9	2	36.5	59
X27C8	11	4.0	<10
[2,7] DB27C9	7	6.5	<10
B30C10	3	38.9	68
[3,7] DB30C10	8	26.6	32
[2,8] DB30C10	9	30.5	42
[3,3,3] XDB30C9	12	3.3	<10
B33C11	4	24.8	31
[4,7] DB33C11	10	21.3	23

[a] The flux has been corrected for transport in a blank system. [b] Equal to transport in blank system. [c] CH_3OH, 25.0 °C. [d] Standard deviation ±10%.

Discussion

Relation between Structure and Complex Stability. X-ray studies have shown that, depending on ring size, guanidinium cations may be complexed in a perching or encapsulated way. In encapsulated complexes a maximum number of hydrogen bonds are present between host and guest.[12,13] The 24-membered and smaller ligands are not capable of encapsulating guanidinium, and consequently, if a complex is formed it must adopt a perching conformation. In comparison to the 27-, 30-, and 33-membered crown ethers, the association constants of the smaller ligands with guanidinium chloride in methanol were small ($K < 10$ L mol^{-1}). These observations are in full agreement with extraction[12] and membrane transport data.

From X-ray studies it is known that 27-membered ligands possess the best fitting cavities for guanidinium complexation. The cavities of 30- and 33-membered macrocycles seem too large. Therefore, based on solid state data, one would predict the association constants to decrease in the following order: K (27-crown-9) > K (30-crown-10) > K (33-crown-11). However, the following order is actually observed in solution (Table I): K (30-crown-10) > K (27-crown-9) > K (33-crown-11).

Recently we have found evidence from ^{13}C NMR T_1 relaxation time measurements[29] that the guanidinium complexes of 30-membered macrocycles have a larger conformational freedom for the ring atoms than the corresponding 27-crown-9 complexes. Therefore, the entropic contribution to the free energy of complexation is expected

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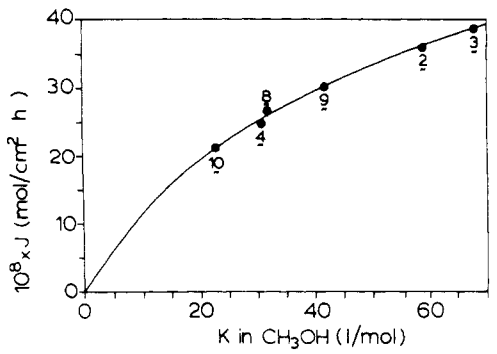

Figure 4. Flux of guanidinium thiocyanate vs. association constant of the complex between guanidinium and the corresponding benzo crown ether. The theoretical curve is calculated from eq 13.

to be less unfavorable for 30-membered crowns. Whereas the 27-membered crown ethers will probably show the tightest binding (enthalpic in origin), the 30-membered cycles have a more favorable balance between enthalpic and entropic effects. In general benzo crown ethers form more stable complexes with alkali and *tert*-butylammonium cations[30,31] compared with 1,3-xyleno crown ethers. The same trend is observed with guanidinium as the guest (Table I). Our recent ^{13}C NMR T_1 studies[29] show that the aromatic moiety of the larger ($n \geq 24$) xyleno crown ethers is occupying the cavity part of the time. Rotation out of the cavity of the xyleno moiety upon complexation will be an energetically unfavorable process. The association constants given in Table I show that the incorporation of more than one benzo moiety in the macrocyclic polyether ligands weakens the binding in the complexes in comparison with the monobenzo crown ethers. Apparently, it is more difficult for the rigid crown ethers to adopt the optimal conformation needed for complexation.[12] Another effect might be the enforced assistance of catecholic acceptor oxygen atoms in the hydrogen bonding scheme.[31] X-ray studies reveal that in complexes of monobenzo crown ethers a structure is adopted in which a minimum number of catecholic oxygen atoms are involved in the complementary binding.[12,13] That small variations in the structure of the host can have a substantial effect on the association constants can be learned from the two isomers of dibenzo-30-crown-10 (**8** and **9**). The difference in association constant between [3,7]dibenzo-30-crown-10 (**8**) and [2,8]dibenzo-30-crown-10 (**9**) may be rationalized in the following way. In the guanidinium perchlorate complex of [3,7]dibenzo-30-crown-10 only four oxygen atoms are used as acceptor atoms in two "linear" and four "bifurcated" hydrogen bonds.[12] The ligand [2,8]dibenzo-30-crown-10 exhibits four "linear" and two "catecholic" hydrogen bonds in the complex with guanidinium perchlorate (Figure 1). Obviously the cavity of [3,7]dibenzo-30-crown-10 is too large for the encapsulation of the guest molecule because none of the four catecholic oxygens is used in hydrogen binding. On the other hand [2,8]dibenzo-30-crown-10 uses two catecholic oxygen atoms in the hydrogen binding, this is energetically more favorable than using bifurcated bonds.

Relation between Association Constant and Flux. In Figure 4 the relation between the flux and the association constant with guanidinium as cation is plotted. Lamb, Christensen, and Izatt[2a] showed that for alkali and alkaline earth metal cations there is an optimum value of the complex stability constant for a maximum salt transport. They propose a cation transport model which correctly predicts the relation between the flux and log K (K is the association constant) over the whole range of log K values studied. In principle such a correlation is to be expected also for our system. However, because of the relatively small association constants of the complexes with guanidinium salts, the maximum flux is not nearly reached. It should be emphasized that the membrane solvent is different from the solvent in which we have determined the association constants. However, we can assume that the ratio of association constants in two different solvents is almost constant. From literature data it is deduced that the ratios between the association constants at 300 K of 18-crown-6 and 1,3-xyleno-18-crown-5 with *tert*-butylammonium cation in methanol, acetone, acetonitrile, and chloroform are 68, 87, 45, and 100, respectively.[30,32] Since the type of binding in the *tert*-butylammonium complex and the guanidinium complex is similar, our assumptions seem reasonable. For different crown ethers the corresponding association constant in chloroform will be increased by approximately the same factor.

Scheme I[a]

$$(GuH^+)_{aq} + (SCN^-)_{aq} \overset{k}{\rightleftharpoons} (GuHSCN)_{org} \quad (1)$$

$$(GuHSCN)_{org} + (CE)_{org} \overset{K}{\rightleftharpoons} (GuH^+\cdot CE\cdot SCN^-)_{org} \quad (2)$$

[a] GuH^+ = guanidinium cation; SCN^- = thiocyanate anion; CE = crown ether; GuHSCN = ion pair; $GuH^+\cdot CE\cdot SCN^-$ = complex.

The mechanism of transport is depicted in Figure 3 and Schemes I and II. From the equilibrium (eq 1) a value of the partition coefficient k is derived which gives the ratio of the concentration of guanidinium thiocyanate as an ion pair in the organic phase and the concentration of guanidinium thiocyanate as charge-separated ions in the aqueous phase (eq 3). The second equilibrium constant

Scheme II

$$k = \frac{[GuHSCN]_{org}}{[GuH^+]_{aq}[SCN^-]_{aq}} \quad (3)$$

$$K = \frac{[GuH^+\cdot CE\cdot SCN^-]_{org}}{[GuHSCN]_{org}[CE]_{org}^f} \quad (4)$$

$$kK = \frac{[GuH^+\cdot CE\cdot SCN^-]_{org}}{[GuH^+]_{aq}[SCN^-]_{aq}[CE]_{org}^f} \quad (5)$$

$$[CE]_{org}^f = [CE]_{org} - [GuH^+\cdot CE\cdot SCN^-]_{org} \quad (6)$$

$$[GuH^+\cdot CE\cdot SCN^-]_{org} = \frac{kK[GuH^+]_{aq}[SCN^-]_{aq}[CE]_{org}}{1 + kK[GuH^+]_{aq}[SCN^-]_{aq}} \quad (7)$$

(K) represents the complexation of the ion pair with the carrier in the organic phase (eq 4). The subscripts org and aq refer to the membrane phase and the aqueous source phase, respectively. Multiplying eq 3 and 4 gives expression 5 for kK. The concentration of the free crown ether ($[CE_{org}^f]$) in the membrane phase is equal to the initial crown ether concentration minus the complex concentration in the organic phase, assuming that no crown ether

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is transferred from the organic phase to the aqueous phase since our experiments showed that at most 1% (mol/mol) of the initial crown ether concentration was extracted from the membrane phase into the aqueous phases. Substitution of eq 6 into eq 5 gives expression 7 for the complex concentration in the organic phase. At the interface of the membrane phase and receiving phase decomplexation takes place. The amount of guanidinium cations transported to the source phase is negligible, since the concentration of guanidinium cations in the receiving phase is very small in our experiments. Using expression 7 for the concentration of guanidinium thiocyanate crown ether complex in the organic membrane phase and Fick's first law, expression 8 for the membrane flux (J) can be derived. Since all phases are stirred or circulated, concentration polarization is negligible. Concentration gradients are restricted to the unstirred boundaries (Nernst layer at the interface with a thickness of l cm). For transport of the alkali and alkaline earth cations by neutral carriers and synthetic ionophores, the rate limiting process is assumed mostly to be the diffusion through the Nernst layer.[1,2,33] We also assume that for our system: (i) the rates at which cation and anion partition into the receiving phase occur and the rates at which cation reacts with or is released from carrier ligand are fast compared to diffusion; (ii) the contribution to the flux of uncomplexed ion pairs is negligible; (iii) the diffusivities (D_L) in the membrane phase of the free ligand and of the ligand–guanidinium ion complex are equal; (iv) the bulk velocity of the water boundary layer normal to the membrane interface is zero; and (v) the salt concentration in the source phase is much larger than the salt concentration in the receiving phase. In a steady state the total flux is equal to the membrane flux (eq 8). A relationship between the flux and the association constant (eq 9) was obtained by a combination of eq 7 and 8. The

$$J = \frac{D_L}{l}[\mathrm{GuH^+{\cdot}CE{\cdot}SCN^-}]_{org} \quad (8)$$

$$J = \frac{D_L[\mathrm{CE}]_{org}}{l}\left\{\frac{kK[\mathrm{GuH^+}]_{aq}[\mathrm{SCN^-}]_{aq}}{1 + kK[\mathrm{GuH^+}]_{aq}[\mathrm{SCN^-}]_{aq}}\right\} \quad (9)$$

reciprocal value of the flux shows a linearity with the reciprocal value of the association constant (eq 10). As

$$\frac{1}{J} = \frac{l}{D_L[\mathrm{CE}]_{org}k[\mathrm{GuH^+}]_{aq}[\mathrm{SCN^-}]_{aq}}\frac{1}{K} + \frac{l}{D_L[\mathrm{CE}]_{org}} \quad (10)$$

mentioned before, the solvents in which the flux and the association constant were determined, are different.

In eq 10 $K(CHCl_3)$ must be used, while $K(CH_3OH)$ is determined. We assume (vide supra) a linear correlation between the association constant in methanol and in chloroform, respectively. In eq 11 the correlation is ex-

$$K(\mathrm{CHCl_3}) = \alpha K(\mathrm{CH_3OH}) \quad (11)$$

pressed with a constant factor α. The effect of charge separated ions in methanol vs. intimate ion pairs in chloroform on the association is discounted in α. Substituting eq 11 into eq 10 results in a relationship between the flux and the association constant in methanol (eq 12). From

$$\frac{1}{J} = \frac{l}{D_L[\mathrm{CE}]_{org}k\alpha[\mathrm{GuH^+}]_{aq}[\mathrm{SCN^-}]_{aq}}\frac{1}{K(\mathrm{CH_3OH})} + \frac{l}{D_L[\mathrm{CE}]_{org}} \quad (12)$$

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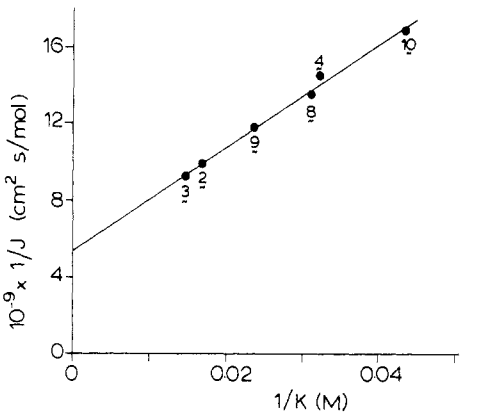

Figure 5. Reciprocal value of the flux vs. reciprocal value of the association constant according to eq 10.

Figure 5 ($1/J$ vs $1/[K(CH_3OH)]$) a value for $l/(D_L[CE]_{org})$ is derived from the intercept and a value for $l/(D_L[CE]_{org}k\alpha)$ from the slope: $(5.4 \pm 0.3) \times 10^9$ cm^2 s mol^{-1} and $(2.7 \pm 0.1) \times 10^{11}$ cm^2 s L^{-1}, respectively. The ratio between the intercept and slope gives a value for $k\alpha$ of 0.020 ± 0.002 M^{-1}. With the experimentally determined value of $k = (3.6 \pm 0.4) \times 10^{-5}$ M^{-1} (Experimental Section) α is computed: $\alpha = 560 \pm 120$. The relatively small value of α for the complexation of the guanidinium salts indicates the existence of loose ion pairs in chloroform. For the complexation of 18-crown-6 with *tert*-butylammonium salts a value of $\alpha > 10000$ has been reported.[30,32] A relation between the path length of the diffusion layer and the diffusion coefficient of the complex is derived from the intercept using the initial crown ether concentration (in mol cm^{-3}): $l/D_L = (5.4 \pm 0.3) \times 10^3$ (s cm^{-1}). The diffusion layer will have a length of 0.076 cm when an estimated value of D_L (1.4×10^{-5} cm^2 s^{-1})[2a] is used. This value is of the same order of magnitude as the thickness of the Nernst layer (0.005 – 0.030 cm)[2b] realizing that the value of the diffusion coefficient was estimated for a complex between an alkali or alkaline earth cation and a carrier with smaller dimensions. Equation 9 can be transferred into eq 13 by

$$J = 66.7 \times 10^{-8}\left(\frac{0.02\,K(\mathrm{CH_3OH})}{1 + 0.02\,K(\mathrm{CH_3OH})}\right) \quad (13)$$

using the values obtained from eq 12. The dimension of the flux in eq 13 is mol cm^{-2} h^{-1}. In Figure 4 eq 13 is used for drawing the curve. The maximum flux will be reached when the term between the brackets in eq 13 is equal to 1, which means that $K(CH_3OH)$ must be much larger than 100 M^{-1}. The flux measured with carrier 3 ($K(CH_3OH) = 68$ M^{-1}) is about 60% of the maximum flux. Equation 13 will be useful for the estimation of association constants of complexes between guanidinium thiocyanate and carriers by measuring the flux under the same conditions. Our description of the flux as a function of the association constant is compatible with the description reported by Reusch and Cussler.[1] But to the best of our knowledge they never showed the relation between the flux and the association constant experimentally. Lamb et al.[2a] suggested a cation-transport model based on similar principles which correctly predicts the change in the flux with log K over an extended range of log K values. The curve is fitted by estimating the values of the diffusion coefficients and by changing the values of some variables (partition coefficient, thickness of boundary layers). Behr et al.[2b] reported a model description for each transport mechanism ((i) carrier-mediated transport of a single substrate species and of an ion pair and (ii) carrier-mediated exchange diffusion of two substrates against a back-transported

species), resulting in an equation for the transport rate. They did not fit the theoretical curves (J vs. log K) with experimental results. Both Lamb and Behr found that the transport rate is limited by diffusion of the complex through a stagnant layer and that there is no need to invoke a mechanism where transport is limited by complexation kinetics.

Conclusions

The association constants of the complexes of 27-, 30-, and 33-membered crown ethers with guanidinium chloride in methanol are much larger than those of the complexes of 24-membered or smaller crown ethers, indicating that encapsulated complexes are more stable than perching complexes.

For membrane transport of guanidinium thiocyanate by crown ethers a theoretical model that predicts a relation between the flux and the association constant was confirmed experimentally. Diffusion of the complex through a stagnant layer (Nernst layer) is rate-determining; the ratio of the thickness of this layer (l) with the diffusion coefficient of the complex (D_L) is equal to $l/D_L = (5.4 \pm 0.3) \times 10^3$ s cm^{-1}. The ratio D_L/l is the mass transfer coefficient. The partition coefficient k of guanidinium thiocyanate has a value of $(3.6 \pm 0.4) \times 10^{-5}$ M^{-1} (chloroform/water). The conversion factor α for computing $K(CHCl_3)$ from $K(CH_3OH)$ is (560 ± 120) assuming that it is a proportional relation. Notwithstanding the optimal fit between guanidinium and the 27-crown ethers, benzo-30-crown-10 (**3**) has the largest association constant and the largest flux with guanidinium cation. The maximum flux measured for **3** is about 60% of the theoretical maximum flux. Structure, ring size, and basicity of the oxygen atoms in the ring have a great influence on the association constant and the flux. With these results and the model presented above either J or K can be estimated in certain ranges if the other of the two values is known. This method is especially useful for the determination of K, which is often difficult to measure in solvents like chloroform. This method, which requires only small amounts of ligands, is fast and simple.

Experimental Section

Melting points were determined with a Reichert melting point apparatus and are uncorrected. The ^{1}H and ^{13}C NMR spectra were recorded with a Bruker WP-80 and an NMC 1280 spectrometer respectively, in $CDCl_3$ with Me_4Si as an internal standard. Mass spectra were obtained with a Varian Mat 311 A. Elemental analyses were carried out by our department of chemical analysis.

Materials. Dibenzo-18-crown-6 (**5**) and dibenzo-24-crown-8 (**6**) were obtained from Aldrich and used without further purification. Benzo-18-crown-6 (**1**),[12] benzo-27-crown-9 (**2**),[9] benzo-30-crown-10 (**3**),[19] [2,7]dibenzo-27-crown-9 (**7**),[12] [3,7]dibenzo-30-crown-10 (**8**),[12] [4,7]dibenzo-33-crown-11 (**10**),[12] 1,3-xylyl-27-crown-8 (**11**),[13] and 1,3-xylyldibenzo-30-crown-9 (**12**)[12] were prepared according to literature procedures.

Polyethylene glycols and their ditosylates[9] and 2,2′-[1,2-ethanediylbis(oxy)]bisphenol[34] were prepared according to literature procedures. THF was freshly distilled from sodium/benzophenone prior to use. Guanidinium thiocyanate was obtained from Fluka and used without further purification. Potassium and guanidinium chloride were of the highest purity grade (Merck, suprapur). Tetraethylammonium chloride (Merck) was recrystallized 3 times from chloroform/diethyl ether and dried for 24 h at 120 °C under low pressure (10–12 mmHg). Triethylamine (BDH, anhydrous) and methanol (Merck, 99.8%) were pa grade. Anhydrous acetic acid and perchloric acid in anhydrous acetic acid were pa grade (Merck).

Benzo-33-crown-11 (**4**) was prepared according to the general procedure described by Kyba et al.[9] from catechol and deca(ethylene glycol) ditosylate. After filtration of the crude product, the filtrate was evaporated under vacuum, dissolved in CH_2Cl_2, and washed twice with 0.1 M sodium bicarbonate. After evaporation the residue was extracted with petroleum ether 60–80 for 12 h under reflux conditions and then concentrated in vacuo. Further purification was accomplished by chromatography on silica gel (EtOAc/EtOH 9/1 (v/v)) to give the product as a solid after evaporation of the eluents. Yield 11%: mp 33–35 °C; ^{1}H NMR δ 6.90 (s, 4 H, ArH), 4.23–3.87 (m, 40 H, OCH_2CH_2O); ^{13}C NMR δ 149.0 (ArC-1, ArC-2), 121.5 (ArC-4, ArC-5), 114.7 (ArC-3, ArC-6), 71.3–69.0 (CH_2); mass spectrum, m/e 532.290 (M^+; calcd 532.288). Anal. Calcd for $C_{26}H_{44}O_{11}$: C, 58.63; H, 8.33. Found: C, 58.97; H, 8.30.

[2,8]Dibenzo-30-crown-10 (**9**) was prepared according to the procedure described by de Boer et al.[12] from 2,2′-[1,2-ethanediylbis(oxy)]bisphenol[34] and hepta(ethylene glycol) ditosylate. After working up (vide supra) an oil was isolated: yield, 5%; ^{1}H NMR δ 6.94 (s, 8 H, ArH), 4.38 (s, 4 H, $ArOCH_2CH_2OAr$), 4.24–4.12 (m, 4 H, $ArOCH_2$), 3.90–3.60 (m, 24 H, OCH_2CH_2O); ^{13}C NMR δ 149.2, 148.9 (ArC-1, ArC-2), 121.9, 121.6 (ArC-4, ArC-5), 115.5, 115.2 (ArC-3, ArC-6), 70.9–68.3 (CH_2); mass spectrum, m/e 536.262 (M^+; calcd 536.262).

Extraction Experiments. $CDCl_3$ (2 mL) containing 1.0 mmol of crown ether and 2 mL of an aqueous solution containing 1.0 mmol of guanidinium sulfate and 2.0 mmol of lithium perchlorate were agitated vigorously for about 3 h. The $CDCl_3$ layer was separated off and subsequently dried over molecular sieves (4 Å). The ratio of crown ether:guanidinium perchlorate in the chloroform phase was determined from the intensities in the ^{1}H NMR spectra.

[2,8]Dibenzo-30-crown-10–Guanidinium Perchlorate (1:1). The complex was isolated from the organic layer, obtained in an extraction experiment, by subsequent evaporation of the solvent: mp 126–127 °C; ^{1}H NMR δ 6.94 (s, 8 H, ArH), 6.61 (s, 6 H, NH_2), 4.47 (s, 4 H, $ArOCH_2CH_2OAr$), 4.21–4.17 (m, 4 H, $ArOCH_2$), 3.89–3.59 (m, 24 H, OCH_2CH_2O); ^{13}C NMR δ 157.9 (C–NH_2), 148.0, 147.1 (ArC-1, ArC-2), 122.0, 121.5 (ArC-4, ArC-5), 113.6, 113.0 (ArC-3, ArC-6), 70.1–67.0 (CH_2). Anal. Calcd for $C_{29}H_{46}O_{14}N_3Cl$: C, 50.04; H, 6.66; N, 6.04. Found: C, 50.30; H, 6.73; N, 5.87.

X-ray Diffraction. X-ray measurements were performed on a single-crystal diffractometer (Philips PW1100) using the ω–2θ scanning mode. The most important data-collection parameters are presented in Table II. The solution (MULTAN[35a,b]) and refinement (block diagonal version of ORFLS[36]) was based on 4384 reflections with an intensity greater than the standard deviation from counting statistics. Most hydrogen atoms were found from difference Fourier syntheses and were subsequently refined. The number of parameters refined in the last cycles was 597 (scale factor, extinction parameter, positional parameters of all atoms, thermal parameters (isotropic for H-atoms, anisotropic for others)). Three H-atoms (at C18, C22, and C24) could not be located and were not included in the refinement.

Potentiometric Titration. For the determination of the guanidinium thiocyanate concentration in the receiving phase by a potentiometric titration, the water was evaporated, the residue was dissolved in anhydrous acetic acid, and the solution was titrated with 2.0 mM perchloric acid in anhydrous acetic acid.[28] Also the association constants of the guanidinium cation with the ligands studied, in methanol, were determined potentiometrically. The concentration of potassium ions was determined by measuring the EMF (±0.1 mV) of a K^+ ion selective electrode (Ingold, pK 271) with a Radiometer Copenhagen PHM 26. The reference electrode was a Ag/AgCl electrolyte electrode. Ionic strength was maintained at 0.10 M by addition of tetraethylammonium chloride. In order to prevent interference by H^+ ions, the pH of the solutions was kept above 8 by adding a small amount of tri-

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Table II. Data-Collection Parameters of the X-ray Structure Determination

formula	$C_{29}H_{46}O_{14}N_3Cl$
lattice type	triclinic
space group	$P\bar{1}$
T K	161(2)
cell dimensions:	
a, Å	12.876(9)
b, Å	12.978(8)
c, Å	11.723(3)
α, deg	66.16 (3)
β, deg	104.95 (1)
γ, deg	106.16 (4)
V, Å^3	1697 (3)
Z	2
D_c, g cm^{-3}	1.37
radiation (graphite monochromated)	Mo Kα
μ, cm^{-1}	1.77
θ-range, deg	$4 < \theta < 25$
no. of unique reflections measured	5953
no. of reflections with $F_0 > \sigma(F_0)$	4384
final no. of variables	597
final R, %	6.6
final R_w, %	5.5

ethylamine. Titrations were carried out in a thermostated cell at (25.0 ± 0.1) °C under a nitrogen atmosphere.

Liquid–Liquid Extraction: Determination of *k*. The partition coefficient of guanidinium thiocyanate k was determined using a liquid–liquid extraction. An extraction experiment was performed between 10 mL chloroform and 10 mL 1.0 M guanidinium thiocyanate in distilled deionized water. After 3 h the phases were separated and from 8 mL of the organic phase the solvent was evaporated. The residue was dissolved in 4 mL distilled deionized water and analyzed with UV spectroscopy. The partition coefficient k is defined as the ratio of the concentration guanidinium thiocyanate as ion pair in the organic phase and the concentration of guanidinium thiocyanate as charge-separated ions in the aqueous phase: $k = (3.6 \pm 0.4) \times 10^{-5}$ M^{-1}.

Measurement Setup. The bulk liquid membrane transport experiments were carried out in a U-tube of well-defined dimensions: the area between receiving phase and membrane phase and between source phase and membrane phase was 1.77 ± 0.05 cm^2; the volumes of the membrane phase, source phase, and receiving phase were equal: 15.0 mL; the path length in the membrane phase was 8.5 ± 0.3 cm. The U-tube was submerged in a thermostated water bath (Tamson, TC) at 25.0 ± 0.5 °C. The membrane phase consisted of freshly distilled chloroform containing 1.0 mM carrier and was stirred magnetically (Heidolph stirrer) at 200 rpm. The source phase consisted of a 1.0 M aqueous solution of guanidinium thiocyanate, while the receiving phase consisted of distilled deionized water. Both aqueous phases were circulated by a peristaltic pump (Deuster, München) with a flow of 10–12 mL/min. The receiving phase was analyzed continuously by means of conductivity measurements (electrodes, Radiometer CDC 114 with cell constants of 0.94 cm^{-1} and 1.06 cm^{-1}, respectively; measurement instrument, Radiometer Copenhagen CDM 2e) and after 24 h by means of a potentiometric titration (electrode, glass/calomel Metrohm EA121; titroprocessor, Metrohm E636).

Typical Transportation Experiment. The membranes consisted of 15.0 mL of a 1.0 mM solution of the carrier in chloroform placed at the bottom of a rectangular U-tube. The two aqueous phases were placed on both sides on top of the chloroform layer. The direction of circulation in these two aqueous phases had been selected in such a way that the interface between the membrane phase and the aqueous phase was stable: from the top of the aqueous phase via the peristaltic pump to the bottom of the aqueous phase. Advantages of circulating both aqueous phases are no concentration gradients in the aqueous phases, especially at the interfaces, and with a flow-cell electrode the receiving phase could be analyzed continuously by conductometric measurements. Two separate uniform U-tubes (of equal dimensions) were used for each guanidinium-macrocycle system to determine the reproducibility of the reported transport rates. A blank experiment was performed with the chloroform containing no crown ether to determine the amount of leakage of guanidinium across the chloroform membrane. With a pipet 10 mL of the receiving phase was withdrawn at the end of 24 h and analyzed for the amount of guanidinium thiocyanate which was transferred from the membrane phase to the receiving phase. For the detection of crown ether UV spectroscopy was used (Unicam SP 800 UV-spectrophotometer).

Registry No. 1·Gu·HSCN, 104946-45-4; 1·Gu·HCl, 104946-59-0; 2·Gu·HSCN, 104946-46-5; 2·Gu·HCl, 104946-60-3; 3·Gu·HSCN, 104946-47-6; 3·Gu·HCl, 104946-61-4; 4·Gu·HSCN, 104975-76-0; 4·Gu·HCl, 104946-63-6; 5·Gu·HSCN, 104946-48-7; 5·Gu·HCl, 104946-64-7; 6·Gu·HSCN, 104946-49-8; 6·Gu·HCl, 104975-77-1; 7·Gu·HSCN, 104946-51-2; 7·Gu·HCl, 104946-65-8; 8·Gu·HSCN, 104946-53-4; 8·Gu·HCl, 104946-66-9; 9·Gu·HSCN, 104946-55-6; 9·Gu·HCl, 104946-67-0; 9·Gu·$HClO_4$, 104946-71-6; 10·Gu·HSCN, 104946-56-7; 10·Gu·HCl, 104946-68-1; 11·Gu·HSCN, 104946-57-8; 11·Gu·HCl, 104946-69-2; 12·Gu·HSCN, 104946-58-9; 12·Gu·HCl, 104946-70-5.

Supplementary Material Available: Lists of positional and thermal parameters (anisotropic for non-hydrogen atoms, isotropic for hydrogens) and of bond lengths and bond angles for the solid [2,5]dibenzo-30-crown-10-guanidinium perchlorate (1:1) complex, as determined by X-ray diffraction (9 pages). Ordering information is given on any current masthead page.