Articles

(Thio)urea Resorcinarene Cavitands. Complexation and Membrane Transport of Halide Anions

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Reaction of aminomethylcavitands with iso(thio)cyanates gives (thio)urea-functionalized resorcinarene cavitands, which represent a novel class of neutral anion receptors. The complexation of halide anions has been studied both with infrared and ^{1}H NMR spectroscopy. The receptors have a small *preference for chloride* over the other halides; *p*-fluorophenylthiourea cavitand **8a** gives the highest association constant ($K_{ass} = 4.7 \times 10^5$ M^{-1} with chloride in $CDCl_3$). A cooperative effect of the ligating (thio)urea moieties is indicated by the lower affinity of the corresponding tris(thio)urea-functionalized cavitands. For the first time facilitated membrane transport of halide anions through supported liquid membranes is achieved.

Introduction

The complexation of anions by synthetic receptors is important because of its analogy with anion binding and transport in biological processes. There are two different types of synthetic anion receptors, positively charged and neutral.[1] Positively charged ligands comprise porphyrins,[2] (poly)ammonium receptors, and guanidinium[3] or cobalticinium[4] based receptors. The neutral ligands can be classified according to the type of interactions with the anion, e.g. ion−dipole interactions,[5] hydrogen bonding, or combinations of both.[1,6]

Urea and thiourea moieties are powerful hydrogen-bond donors[7] that can bind anions solely via hydrogen bonding. Rebek et al.[8] reported receptors based on xanthenedicarboxylic acid derivatized with two urea moieties with an asymmetric center; these complex asymmetric carboxylates. Both 1,4-[9] and 1,3-bis[propylthioureamethyl]benzene[10] complex *di*carboxylic acids and dihydrogen phosphate in DMSO-d_6.

Reinhoudt et al. studied the (halide) anion complexation in $CDCl_3$ of *p-tert*-butylcalix[4]arenes functionalized with (thio)urea functions at the 1,3-positions of the lower rim.[11] The bidentate *N*-butyl-*N*′-phenylurea calix[4]arene showed the strongest complexation ($K_{ass} = 7.1 \times 10^3$ M^{-1}) for chloride because of strong intramolecular hydrogen bond formation; however, the complexation decreased for a calix[4]arene with four butylphenylurea groups ($K_{ass} = 2.7 \times 10^3$ M^{-1} for chloride). Ungaro et al.[12] reported upper-rim mono- and di(thio)urea-functionalized calix[4]arenes that complex carboxylate anions in DMSO-d_6 although with very low associations for chloride ($K_{ass} < 10$ M^{-1}). Ditopic receptors based on a di- and tetra-urea-functionalized tetraethyl ester calix[4]arene are capable of solubilizing sodium halide salts in $CHCl_3$.[13]

Several tetraureacalix[4]arenes form dimers in apolar solution via an array of eight (thio)urea moieties,[14] which also diminishes the ability to complex (halide) anions.

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Compared to the calix[4]arenes, resorcinarene cavitands[15] are more rigid platforms that are suitable for further functionalization.[16,17] Substitution of the cavitand template with (thio)urea moieties may provide receptors that cannot form such intramolecular hydrogen bonds. Also, the formation of dimers by a cyclic array of eight (thio)urea moieties of two tetra(thio)urea cavitands, similar to the calix[4]arenes, is prevented by the methyleneoxy bridges of the cavitand. Therefore, (thio)urea-derivatized cavitands were expected to associate more strongly with halide anions.[18]

In this paper we present the synthesis of neutral (thio)urea-functionalized resorcinarene cavitands and their complexation with halide anions. In addition, we describe the first carrier-mediated transport through supported liquid membranes (SLMs)[19] with neutral carriers that complex halide anions exclusively by hydrogen bonds.[20]

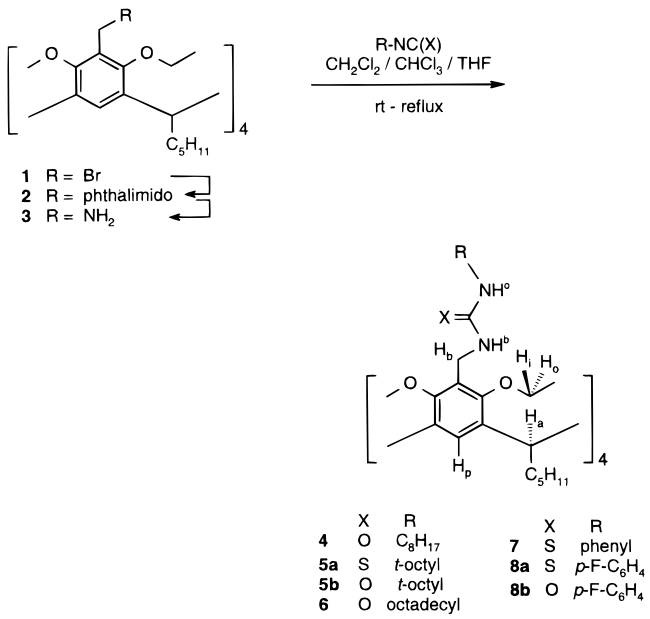
Results and Discussion

Synthesis. Thiourea- and urea-derivatized resorcinarene cavitands **4**−**8** were synthesized in three steps starting from tetrakis(bromomethyl)cavitand **1** (Scheme 1). Reaction of bromomethylcavitand **1**[16] with potassium phthalimide in toluene afforded tetrakis(phthalimidomethyl)cavitand **2**, which after subsequent treatment with hydrazine hydrate in refluxing ethanol/THF gave tetrakis(aminomethyl)cavitand **3** in 67% overall yield.[16]

The tetrakis[(thio)ureamethyl]cavitands **4**−**8** were synthesized by subsequent reaction of tetraamine **3** with the appropriate iso(thio)cyanates. Despite the reactivity of iso(thio)cyanates,[21] the reactions proceeded slowly, as amine **3** and most (thio)ureacavitands (and the partially reacted intermediates) are moderately soluble in CH_2Cl_2. The solubility of the products was increased by using isocyanates with longer or branched aliphatic chains, e.g. octyl (**4**) vs octadecyl (**6**), and octyl (**4**) vs *tert*-octyl (1,1,3,3-tetramethylbutyl) (**5b**).

The solubility of the (thio)ureacavitands was further enhanced for the use in transport (SLM) experiments, by introducing long aliphatic chains that resemble the membrane solvent (vide infra: *o*-nitrophenyl *n*-octyl ether; NPOE). For the synthesis of NPOE-side-chain-containing thioureacavitand **11a**, aminocavitand **3** was first converted to tetrakis(isothiocyanatomethyl)cavitand **9a** using thiophosgene in 54% yield (Scheme 2). Subsequent reaction of cavitand **9a** with NPOE-amine **10** afforded tetrakis(*o*-nitrophenyloctylthioureamethyl)cavitand **11a** in 55% yield. Similarly, aminocavitand **3** was converted to tetrakis(isocyanatomethyl)cavitand **9b** using triphosgene, which was directly reacted with NPOE-amine **10** to give tetrakis(*o*-nitrophenyloctylureamethyl)-cavitand **11b** in 11% overall yield.

Scheme 1



Cavitands with three ligating sites (**13** and **14**) were synthesized by reaction with the appropriate iso(thio)-cyanates from the tris(aminomethyl)cavitand **12** (Chart 1), which can be obtained in three steps from tetrakis-(bromomethyl)cavitand **1**.[22]

All new cavitands show two broad signals for the NH hydrogens in the ^{1}H NMR spectra. The benzylic NH^b hydrogens absorb downfield from the outer NH^o hydrogens. The hydrogens of *tert*-octylureacavitand **5b** are present at 4.80 (NH^b) and 4.73 ppm (NH^o) and those of the corresponding *tert*-octyl*thio*ureacavitand **5a** are at 6.12 (NH^b) and 5.23 ppm (NH^o). The downfield shift of the thiourea hydrogens reflects the higher acidity of the thiourea (pK_a values in DMSO are 21.0 and 26.9 for thiourea and urea, respectively[23]).

The model compounds *p*-fluorophenyloctyl(thio)ureas **15a**,**b** were synthesized by reaction of octylamine with *p*-fluorophenyl isothiocyanate and isocyanate in essentially quantitative and 89% yield, respectively (Chart 1).

Determination of Association Constants of Anion Complexation. **Dimerization.** In contrast to (thio)-urea-functionalized calix[4]arenes[11,14] the corresponding (thio)ureacavitands cannot form *intra*molecular hydrogen bonds,[24] but in solution they form intermolecular hydrogen bonds. ^{1}H NMR dilution experiments with hosts **6**

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(24) Weak intramolecular NH hydrogen bonds (ca. 4−5 Å) were estimated. However, these effects are negligible compared to the anion complexation.

Scheme 2

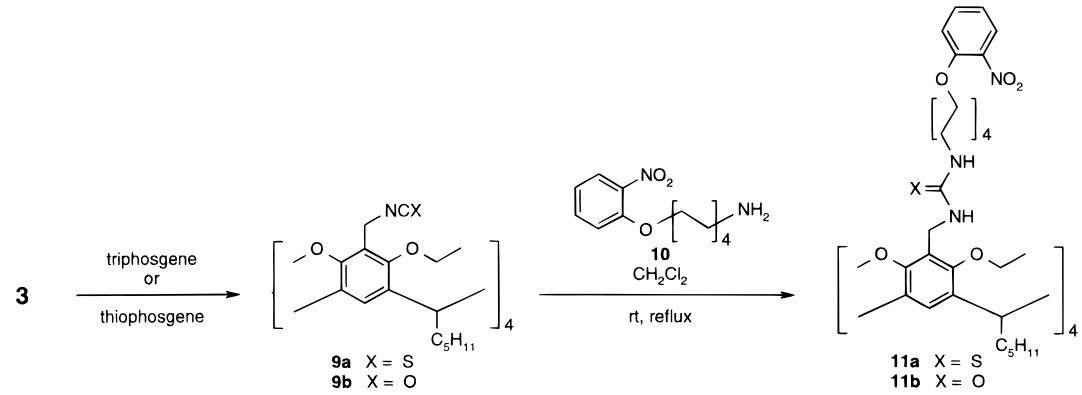
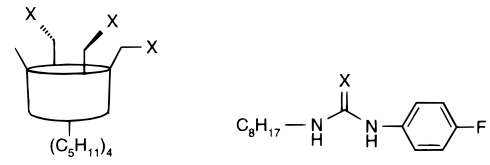


Chart 1



12 X = NH_2
13 X = *t*-octylthiourea
14 X = octadecylurea

15a X = S
15b X = O

and **8a** in the 0.5−5 mM concentration range gave dimerization constants (K_{dim}) of 225 and 165 M^{-1}, respectively.[25] Infrared spectroscopy did not indicate that self-association occurs for cavitands **7**, **8a**, **11b**, and model compound **15a** in the concentration range <0.5 mM.

As the self-association constants are much smaller than the K_{ass} values (vide infra) and the resulting changes in chemical shift are negligible, this process was neglected for the K_{ass} determination of the anion complexation. Only in the determination of the K_{ass} value for **15a** the dimerization was considered, as the contribution of the chemical shift from the dimer was not negligible.[26]

The association constants of a selection of the new cavitand-based anion receptors and the model compounds with tetraalkylammonium halide salts were independently determined with ^{1}H NMR and infrared spectroscopy. On the basis of ^{31}P NMR experiments carried out with ligand **11b** and tetraethyl, tetrabutyl-, and tetraphenylphosphonium chlorides,[27] we can exclude alkylammonium cation−host interactions. The $R_4P^+X^-$ salts were used as ^{31}P NMR is more sensitive than ^{15}N NMR spectroscopy and because of the geometric similarity with the tetraalkylammonium salts.

NMR Studies. The association constants of the complexes of a number of these new receptors were determined via ^{1}H NMR titration experiments (see Experimental Section) with chloride in $CDCl_3$ (Table 1). The signals of the methylene hydrogens (H_a) were used as a probe (see Scheme 1) for all cavitands evaluated. For reasons of comparison, in Table 1 K_{ass}-values determined with other probes are also included. In all cases

Table 1. Association Constants for 1:1 Complexes of Selected Ligands with Chloride Anions in $CDCl_3$ Determined with ^{1}H NMR Spectroscopy at a Total Molar Content of 5 mM

compd	ligating sites	K_{ass} [M^{-1}][a] ($-\Delta G$ [kJ/mol])[b]		other probe
	Tetrasubstituted			
5a	*t*-octylthiourea	6.1×10^4 (27.0)	7.0×10^4 (27.4)	H_i
5b	*t*-octylurea	1.3×10^4 (23.2)	1.8×10^4 (24.0)	H_o
6	octadecylurea	3.0×10^4 (25.3)	3.0×10^4 (25.3)	H_b
8a	*p*-fluorophenylthiourea[c]	4.7×10^5 (32.0)	4.0×10^5 (31.6)	phenyl
	Trisubstituted			
13	*t*-octylthiourea	4.2×10^3 (20.5)	2.2×10^3 (18.9)	ArH
14	octadecylurea	3.3×10^3 (19.9)	1.2×10^3 (17.4)	H_o
	Monofunctionalized			
15a	*p*-fluorophenylthiourea[d]	2.0×10^3 (18.7)		
15b	*p*-fluorophenylurea[d]	1.8×10^3 (18.4)		

[a] Determined with the methylene hydrogens (H_a) as probe. [b] At $T = 295$ K. [c] K_{ass} values for bromide and iodide are 2.9×10^5 and 2.8 M^{-1}, respectively. [d] Determined with benzylic NH as a probe.

analysis of the Job plots indicated 1:1 host to guest stoichiometries for complexation.[28]

The complexation of chloride with the thioureacavitands is slightly stronger (K_{ass} values are ca. 1.5−4 times higher; $\Delta\Delta G$ = 0.3−3.8 kJ/mol) than that with the ureacavitands (e.g. **5a** vs **5b**, **13** vs **14**, and **15a** vs **15b**), due to the higher acidity of the thiourea hydrogens (vide supra). The trifunctionalized cavitands **13** and **14** exhibit 9−15 times ($\Delta\Delta G$ = 2.7−5.4 kJ/mol) *lower* affinity for chloride, compared to their tetrafunctionalized analogues, indicating a strong cooperative effect. With the corresponding (thio)ureacalix[4]arenes, an increase in the number of (thio)urea moieties results in lower K_{ass} values (vide supra).[14] The association constants of the "simple" linear (thio)ureas **15a**,**b** are only slightly lower than those of the tris(thio)ureacavitands **13** and **14**.

The highest association constant was found with *p*-fluorophenyl-substituted cavitand **8a** for chloride (K_{ass} = 4.7×10^5 M^{-1}). The related di- and tetraureacalix[4]-arenes are ~10^2 times weaker receptors for chloride (K_{ass} = 7.1×10^3 and 2.7×10^3 M^{-1}, respectively).[11] The cholic

(25) For 1,3-bis[propyl(thio)ureamethyl]benzene in $CDCl_3$, Umezawa et al. found a dimerization constant (K_{dim}) of 130 M^{-1}; see ref 10a.

(26) For the procedure followed, see: Higler, I.; Verboom, W.; Van Veggel, F. C. J. M.; De Jong, F.; Reinhoudt, D. N. *Liebigs Ann./Recueil* **1997**, 1577.

(27) Both ligand **11b** and the phosphonium salts were 5 mM. Upon increasing the ratio of the phosphonium guest, no significant δ_P was observed.

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Table 2. Association Constants for 1:1 Complexes of Selected Ligands with Halide Anions in $CHCl_3$ Determined with Infrared Spectroscopy at a Total Molar Content of 1 mM

	K_{ass} [M^{-1}][a,b] ($-\Delta G$ [kJ/mol])[c]			
guests[d]	**7**	**8a**[e]	**11b**	**15a**[e]
F^-	–[f]	1.2×10^5 (28.7)	–[f]	–[f]
Cl^-	1.5×10^5 (29.2)	$>2 \times 10^5$ (>29.9)	8.6×10^4 (27.9)	2.2×10^3 (18.8)
Br^-	1.2×10^4 (23.6)	1.8×10^5 (29.7)	1.3×10^4[g] (23.2)	8.6×10^3[h] (22.2)
I^-	1.0×10^4 (22.6)	1.5×10^5 (29.2)	1.4×10^4 (23.4)	–[f]

[a] Spectral region 3500−3200 cm^{-1}. [b] Determined with nine samples. [c] At $T = 295$ K. [d] Guests as tetrabutylammonium salts. [e] Determined with five samples. [f] Not determined. [g] Determined with seven samples. [h] Spectral region 3525−3250 cm^{-1}.

acid based receptors reported by Davis et al.[29] also complex chloride more weakly (K_{ass} values up to 9.2×10^4 M^{-1} in $CDCl_3$).

Infrared Studies. The association in $CHCl_3$ with infrared spectroscopy was measured from the NH stretching vibrations of the (thio)urea moiety. The nonassociated NH moieties give a complex band profile with a maximum at 3408 cm^{-1}. On complexation of (thio)-ureacavitands **7**, **8a**, and **11b** and thiourea **15a** with a halide ion, a second broad band emerges at a lower wavenumber. Both the position and bandwidth of this band indicate complexation of the halide by hydrogen bonding. The association constant K_{ass} was assessed by a multivariate regression procedure.[30] The spectral region selected for regression covered the NH stretching absorption of both host and complex species.

The data for the complexation of hosts **7**, **8a**, **11b**, and **15a** with halide anions is summarized in Table 2. The complexation of cavitand **8a** with chloride could not be processed straightforwardly assuming a 1:1 association. The association may not be purely 1:1, as we observed that the data for the larger host fractions are higher than expected on the basis of 1:1 association. The influence of another stoichiometry in this case prohibits accurate determination of the first-order association constant.[31]

The association constants determined with infrared and ^1H NMR spectroscopy are in excellent agreement. The K_{ass} values of **15a** are essentially the same, while the values determined with ^1H NMR for **8a** with bromide and iodide (2.9×10^5 and 2.8×10^5 M^{-1}) are only slightly higher (~2 times).

The effect of the electron-withdrawing fluoro substituent[32] on the phenyl ring is clear from the increase in K_{ass} value of 1 order of magnitude ($\Delta\Delta G = 6.1-6.6$ kJ/mol) for cavitand **8a** compared to cavitand **7**.

The K_{ass} values for the complexation of both bromide and iodide are comparable for cavitands **7**, **8a**, and **11b**, with a preference for chloride. The bromide and iodide anions are weaker complexed because of their "softer" nature, despite the increased size. The association with fluoride is weaker although fluoride is "harder". Probably, the anion is too small to fit satisfactorily in the cavity formed by the eight thiourea hydrogens, or the fluoride anion might be hydrated resulting in weaker association.

Table 3. Supported Liquid Membrane Transport of Salts in the Absence and the Presence of Different (Thio)Urea Based Receptors

entry	salt[a]	receptor	concn [mM]	initial flux J_0 [10^{-8} mol/m^2 s]
1	Pr_4NCl			0.8
2	Pr_4NBr			4
3	Pr_4NCl	**5a**	15	38
4	Pr_4NBr	**5a**	15	45
5	Pr_4NCl	**11b**	15	44
6	Pr_4NBr	**11b**	15	48
7	Pr_4NCl	**15a**	15	11
8	Pr_4NBr	**15a**	15	18
9	Pr_4NCl	**15a**	60	24
10	Pr_4NBr	**15a**	60	74
11	KCl[b]	**11b**	15	3
12	KCl[b]	**5a**	15	8.5
13	KBr[b]	**5a**	15	13

[a] The aqueous salt concentrations were 0.1 M. [b] Transport through the membrane phase in absence of the carrier is negligible.

For model compound **15a**, K_{ass} values for bromide and chloride of 2.2×10^3 and 8.6×10^3 M^{-1}, respectively, were found. The K_{ass} value for the "simple" thiourea **15a** is $>10^2$ times ($\Delta\Delta G > 11.1$ kJ/mol) lower than for its tetrakis(*p*-fluorophenylthioureamethyl)cavitand analogue **8a**.

Membrane Transport. Cation facilitated transport of salt by neutral cation carriers has been investigated extensively.[19] Facilitated halide transport is considered to take place following this sequence of steps: (i) partition of the salt from the aqueous phase to the organic membrane phase, which consists of a solution of the carrier in a solvent (NPOE) that is immobilized in a polymeric support,[33] (ii) complexation of the halide anion by the carrier molecule, (iii) diffusion of the complex through the membrane phase, (iv) decomplexation, and (v) partition of the salt from the organic membrane phase to the aqueous receiving phase. A cation is cotransported for reasons of electroneutrality.

In Table 3 the results of the transport experiments with carriers **5a**, **11b**, and **15a** and various salts are summarized. Transport of the tetrapropylammonium salts (Pr_4NX; X = Cl or Br) in the absence of the carrier is low (entries 1 and 2) and is solely based on the partitioning from the aqueous phase to the membrane phase. The blank transport of Pr_4NBr is much higher than of Pr_4NCl (entries 1 and 2), due to the increased lipophilicity of the bromide anion compared to chloride, as can be seen from the initial transport ratio ($J_{Cl}/J_{Br} = 0.2$). Both in the case of NPr_4Cl and NPr_4Br, a large increase of the flux was observed upon addition of (15 mM[34]) anion carrier (entries 3−8). Since tetraalkylammonium cations are not complexed by the anion carrier (vide supra), transport in the presence of a receptor can be attributed solely to the anion complexation in the membrane.

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(30) A more detailed account of the procedure will be given elsewhere: Nissink, J. W. M.; Boerrigter, H.; Verboom, W.; Reinhoudt, D. N.; Van der Maas, J. H. *J. Chem. Soc., Perkin Trans. 2* In press.

(31) Nevertheless, from a close inspection of the data we estimate the 1:1 K_{ass} value to be much larger than 2×10^5 M^{-1}.

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(34) At carrier concentrations in NPOE of >15 mM, gelation or crystallization of the carrier or the complex from the membrane phase may occur.

Despite the higher blank flux of bromide, the facilitated transport of both bromide and chloride salts is almost equal with the rigid carriers thioureacavitand **5a** (entries 3 and 4) and NPOE-ureacavitand **11b** (entries 5 and 6). The initial transport rates (J_0) are higher in comparison with that of the simple monotopic thiourea **15a** (entries 7 and 8). The noncompetitive transport ratios (J_{Cl}/J_{Br}) of the cavitands are increased from initially 0.2 to 0.84 and 0.92, for **5a** and **11b**, respectively, indicating that selectivities can be changed by preorganization of the associating (thio)urea moieties.[35] This in contrast to the frequently used charged receptors, where selectivities are solely governed by hydrophilicity of the anions.[36] The observed increased selectivity for chloride over bromide is in accordance with the ^{1}H NMR and IR data.

Facilitated transport of bromide and chloride with the "simple" thiourea **15a** (at 60 mM) resulted in a transport ratio of $J_{Cl}/J_{Br} = 0.32$ (entries 9 and 10), which is closer to the ratio of transport in the absence of a carrier. For the cavitands with potassium cations, facilitated transport decreased drastically (entries 11−13) as expected on the basis of the hydrophilic nature of the potassium ion.[37]

Conclusions

The new resorcinarene cavitand-based anion receptors (**4**−**8** and **11**) with four (thio)urea moieties complex halide anions exclusively by hydrogen bonding. The association constants for the complexation of halide anions, determined independently with ^{1}H NMR and infrared spectroscopy, are ∼10^2 times higher than for the corresponding tetra(thio)ureacalix[4]arenes.

All cavitands have a small preference for chloride over bromide, iodide, and fluoride. The tetrafunctionalized cavitands bind ca. 9−15 times ($\Delta\Delta G = 2.7-5.4$ kJ/mol) stronger than the cavitand-based ligands with three (thio)urea groups (**13** and **14**). Also, in SLM transport experiments an increased selectivity for chloride over bromide was observed. The initial noncompetitive transport ratios of J_{Cl}/J_{Br} increased from 0.2 in blank experiments to 0.84−0.92 with carriers **5a** and **11b**.

Experimental Section

THF was freshly distilled from sodium/benzophenone before use, DMF was dried over molecular sieves (3/4 Å) for at least 3 days, Et_3N was distilled and kept on KOH pellets, and CH_2Cl_2 was distilled from $CaCl_2$ and kept on molecular sieves (3/4 Å). Toluene was distilled from sodium and kept on molecular sieves (3/4 Å). Other chemicals were of reagent grade and used without further purification. For the infrared and NMR spectroscopic titration experiments, the solvents were used as received, unless otherwise stated.

All reactions were carried out under an argon atmosphere, unless otherwise stated. Flash column chromatography was performed with Merck silica gel 60 (0.040−0.063 mm, 230−400 mesh). Melting points are uncorrected. Unless otherwise indicated, the ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$, and the chemical shifts were expressed relative to $CDCl_3$ as internal standard (7.26 and 76.91 ppm, respectively). The ^{31}P NMR spectra were recorded in $CDCl_3$. FAB mass spectra were recorded using *m*-nitrobenzyl alcohol as a matrix. The presence of solvent molecules in the analytical samples was confirmed by ^{1}H NMR spectroscopy.

Compounds **1**−**3**,[16] **10**,[37b] and **12**[22] were prepared according to literature procedures.

Tetrakis(*n*-octylureamethyl)cavitand (4). A solution of aminomethylcavitand **3** (198 mg, 0.21 mmol) and *n*-octyl isocyanate (0.30 mL, 1.70 mmol) in CH_2Cl_2 (50 mL) was stirred at room temperature for 3 h. After evaporation of the solvent and column chromatography (SiO_2, CH_2Cl_2/MeOH 98/2), **4** was isolated as a yellow solid: yield 108 mg (33%); mp 213-215 °C (CH_2Cl_2/MeOH); MS (FAB) *m*/*z* 1554.1 (100%, M^+, calcd for $C_{92}H_{144}N_8O_{12}$ 1554.1); ^{1}H NMR δ 7.05 (s, 4 H), 6.00 (d, 4 H, J = 7.4 Hz), 5.43 (s, 4 H), 5.12 (s, 4 H), 4.73 (t, 4 H, J = 7.9 Hz), 4.43 (d, 4 H, J = 7.4 Hz), 4.17 (s, 8 H), 3.07 (q, 8 H, J = 5.0 Hz), 2.2−2.0 (m, 8 H), 1.4−1.25 (m, 72 H), 0.91 (t, 12 H, J = 6.8 Hz), 0.86 (t, 12 H, J = 6.8 Hz); ^{13}C NMR δ 158.4, 153.5, 138.0, 125.6, 120.0, 100.3, 32.1. No satisfactory elemental analysis could be obtained.

Tetrakis(*tert*-octylthioureamethyl)cavitand (5a). A solution of aminomethylcavitand **3** (183 mg, 0.20 mmol) and *tert*-octyl isothiocyanate (0.20 mL, 1.37 mmol) in $CHCl_3$ (25 mL) was refluxed for 22 h. After evaporation of the solvent and column chromatography (SiO_2, CH_2Cl_2/MeOH 99/1), **5a** was isolated as a yellow solid: yield 201 mg (63%); mp 156−158 °C (CH_2Cl_2/MeOH); MS (FAB) *m*/*z* 1619.5 (20%, $[M + H]^+$, calcd 1619.0); ^{1}H NMR (acetone-d_6) δ 7.55 (s, 4 H), 6.94 (s, 4 H), 6.63 (s, 4 H), 5.93 (d, 4 H, J = 7.6 Hz), 4.67 (t, 4 H, J = 8.0), 4.34 (s, 8 H), 4.31 (d, 4 H, J = 7.8 Hz), 2.3−2.2 (m, 8 H), 2.01 (s, 8 H), 1.37 (s, 24 H), 1.35−1.2 (m, 24 H), 1.0−0.8 (m, 48 H); ^{13}C NMR (acetone-d_6) δ 179.5, 153.0, 138.5, 123.3, 120.1, 99.5, 32.1. Anal. Calcd for $C_{92}H_{144}N_8O_8S_4 \cdot CH_2Cl_2$: C, 65.58; N, 6.58; H, 8.64. Found C, 65.66; N, 6.35; H, 8.53.

Tetrakis(*tert*-octylureamethyl)cavitand (5b). A solution of aminomethylcavitand **3** (505 mg, 0.541 mmol) and *tert*-octyl isocyanate (0.59 mL, 3.25 mmol) in $CHCl_3$ (30 mL) was stirred at room temperature for 18 h. After the addition of 1 mL of water, the solution was evaporated to dryness. Purification of the residue with column chromatography (SiO_2, CH_2Cl_2/MeOH 98/2) afforded **5b** as a white solid: yield 360 mg (43%); mp 180−182 °C (CH_2Cl_2/MeOH); MS (FAB) *m*/*z* 1576.5 (95%, $[M + Na]^+$, calcd 1576.1); ^{1}H NMR δ 7.04 (s, 4 H), 5.96 (d, 4 H, J = 7.0 Hz), 4.80 (s, 4 H), 4.75−4.65 (m, 4 + 4 H), 4.36 (d, 4 H, J = 7.0 Hz), 4.05 (d, 8 H, J = 5.5 Hz), 2.2−2.1 (m, 8 H), 1.68 (s, 8 H), 1.32 (s, 48 H), 0.91 (s, 48 H); ^{13}C NMR (DMSO-d_6) δ 156.7, 152.8, 138.0, 125.8, 120.9, 99.3. Anal. Calcd for $C_{92}H_{144}N_8O_{12} \cdot CH_2Cl_2$: C, 68.15; N, 6.94; H, 8.98. Found: C, 68.12; N, 6.95; H, 9.30.

Tetrakis(octadecylureamethyl)cavitand (6). A solution of aminomethylcavitand **3** (147 mg, 0.16 mmol) and *n*-octadecyl isocyanate (372 mg, 1.26 mmol) in THF (25 mL) was refluxed for 19 h. After evaporation of the solvent and column chromatography (SiO_2, CH_2Cl_2/MeOH 99/1), the residue was subsequently triturated with EtOH and recrystallized from CH_2Cl_2/EtOH to give **6** as a white solid: yield 70 mg (21%); mp 114−115 °C (CH_2Cl_2/EtOH); MS (FAB) *m*/*z* 2115.7 (40%, $[M + H]^+$, calcd 2115.7); ^{1}H NMR δ 7.05 (s, 4 H), 5.99 (d, 4 H, J = 7.4 Hz), 5.36 (s, 4 H), 5.23 (s, 4 H), 4.73 (t, 4 H, J = 7.9 Hz), 4.43 (d, 4 H, J = 7.4 Hz), 4.18 (s, 8 H), 3.15−3.0 (m, 8 H), 2.25−2.1 (m, 8 H), 1.4−1.2 (m, 152 H), 0.91 (t, 12 H, J = 6.8 Hz), 0.87 (t, 12 H, J = 6.8 Hz); ^{13}C NMR δ 158.5, 153.5, 138.0, 125.2, 119.5, 100.0, 32.1. Anal. Calcd for $C_{132}H_{244}N_8O_{12} \cdot 2H_2O$: C, 73.70; N, 5.21; H, 10.68. Found C, 73.30; N, 5.16; H, 10.99.

Tetrakis(phenylthioureamethyl)cavitand (7). A solution of aminomethylcavitand **3** (0.70 g, 0.75 mmol) and phenyl isothiocyanate (0.81 g, 6.0 mmol) in CH_2Cl_2 (50 mL) was refluxed for 2 h. After evaporation of the solvent, column chromatography (SiO_2, CH_2Cl_2/MeOH 93/7) and recrystalliza-

(35) From transport experiments at different salt concentrations in the receiving phase, it has become apparent that at a salt concentration of 15 mM all carrier in the membrane phase is involved in complexation and the maximum flux is reached. In this case, the diffusion coefficient of the cavitand carrier solely determines the overall rate of transport, hence a flux ratio $J_{Cl}/J_{Br} \approx 1$ is expected.

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tion (2×) from hot CH_2Cl_2 gave **7** as a white powder: yield 0.30 g (27%); mp 168−170 °C (CH_2Cl_2); MS (FAB) *m*/*z* 1473.7 (85%, M^+, calcd 1473.6); ^{1}H NMR ($CDCl_3$/MeOD 9/1) δ 8.34 (bs, 4 H), 7.4−7.15 (m, 20 H), 7.01 (s, 4 H), 6.7 (bs, 4 H), 5.65 (d, 4 H, J = 7.0 Hz), 4.64 (t, 4 H, J = 7.9 Hz), 4.58 (s, 8 H), 4.29 (d, 4 H, J = 7.3 Hz), 2.11 (q, 8 H, J = 5.7 Hz), 1.4−1.15 (m, 24 H), 0.83 (t, 12 H, J = 6.7 Hz); ^{13}C NMR ($CDCl_3$/MeOD 9/1) δ 181.2, 181.1, 154.8, 139.6, 138.4, 131.1, 128.0, 126.0, 124.5, 121.5, 101.3, 38.2. Anal. Calcd for $C_{84}H_{96}N_8O_8S_4\cdot 1.5H_2O$: C, 67.22; N, 7.47; H, 6.65. Found: C, 67.18; N, 7.41; H, 6.33.

Tetrakis(*p*-fluorophenylthioureamethyl)cavitand (8a). A solution of aminomethylcavitand **3** (226 mg, 0.24 mmol) and *p*-fluorophenyl isothiocyanate (223 mg, 1.45 mmol) in a 1/1 mixture of CH_2Cl_2 (20 mL) and THF (20 mL) was refluxed for 22 h. After evaporation of the solvents and column chromatography (SiO_2, CH_2Cl_2/MeOH gradient 100/0 to 98/2) **8a** was isolated as a yellowish solid: yield 203 mg (54%); mp 300 °C (dec) (CH_2Cl_2/MeOH); MS (FAB) *m*/*z* 1543.4 (100%, $[M - H]^-$, calcd 1543.6); ^{1}H NMR (acetone-d_6) δ 8.73 (s, 4 H), 7.64 (s, 4 H), 7.5−7.4 (m, 4 H), 7.22 (s, 4 H), 7.1−7.0 (m, 4 H), 6.01 (d, 4 H, J = 7.5 Hz), 4.77 (t, 4 H, J = 8.0 Hz), 4.75−4.65 (m, 4 H), 4.46 (d, 4 H, J = 7.6 Hz), 2.35−2.25 (m, 8 H), 1.4−1.3 (m, 24 H), 0.89 (t, 12 H, J = 6.7 Hz); ^{13}C NMR (acetone-d_6) δ 180.2, 153.2, 138.3, 122.5, 120.2, 99.8, 36.7. Anal. Calcd for $C_{84}H_{92}F_4N_8O_8S_4\cdot H_2O$: C, 64.51; N, 7.16; H, 6.06. Found: C, 64.45; N, 7.33; H, 6.08.

Tetrakis(*p*-fluorophenylureamethyl)cavitand (8b). A solution of aminomethylcavitand **3** (214 mg, 0.23 mmol) and *p*-fluorophenyl isocyanate (0.21 mL, 1.84 mmol) in DMF (25 mL) was stirred at 70 °C for 16 h. After evaporation of the solvent, column chromatography (SiO_2, CH_2Cl_2/MeOH 99/1), and trituration of the residue with EtOH, **8b** was isolated as a white solid: yield 82 mg (24%); mp 280 °C (dec) (EtOH); MS *m*/*z* 1503.5 (100%, $[M + Na]^+$, calcd for $C_{84}H_{92}F_4N_8O_{12}\cdot$Na 1503.7]; ^{1}H NMR (DMSO-d_6) δ 8.54 (s, 4 H), 7.57 (s, 4 H), 7.3−7.2 (m, 8 H), 7.0−6.9 (m, 8 H), 6.27 (s, 4 H), 6.03 (d, 4 H, J = 7.5 Hz), 4.75−4.65 (m, 4 H), 4.34 (d, 4 H, J = 7.5 Hz), 4.14 (s, 8 H), 2.4−2.2 (m, 8 H), 1.35−1.25 (m, 24 H), 0.88 (t, 12 H, J = 6.7 Hz); ^{13}C NMR (DMSO-d_6) δ 162.4, 158.1, 143.2, 141.4, 130.5, 126.4, 124.8, 120.5, 105.5. No satisfactory elemental analysis could be obtained.

Tetrakis(isothiocyanatomethyl)cavitand (9a). To a stirred solution of tetrakis(aminomethyl)cavitand **3** (0.50 g, 0.536 mmol) in toluene (50 mL) was added thiophosgene (0.82 mL, 10.72 mmol), followed by the addition of Et_3N (1.49 mL, 10.72 mmol). Subsequently the temperature was raised to 70 °C and the solution was stirred for 4 h. After evaporation of the solvent, the residue was redissolved in CH_2Cl_2 (25 mL) and the solution was filtered over a short column (2 cm) of silica eluted with CH_2Cl_2. The solvent was concentrated to 25 mL and the solution was washed with 0.5 M NaOH (2 × 10 mL) and 0.5 M HCl (10 mL), and dried over Na_2SO_4. After removal of the solvent and recrystallization of the residue from MeOH, **9a** was obtained as a brownish powder, the purity of which was sufficient to be used in the subsequent reaction: yield 0.32 g (54%); MS (FAB) *m*/*z* 1042.4 (100%, $[M - NCS]^+$, calcd for $C_{60}H_{68}N_4O_8S_4$−NCS 1042.3); ^{1}H NMR δ 7.16 (s, 4 H), 5.99 (d, 4 H, J = 7.1 Hz), 4.76 (t, 4 H, J = 8.1 Hz), 4.61 (s, 8 H), 4.41 (d, 4 H, J = 7.1 Hz), 2.22 (q, 8 H, J = 6.1 Hz), 1.6−1.2 (m, 24 H), 0.92 (t, 12 H, J = 6.8 Hz); ^{13}C NMR δ 153.5, 138.3, 132.8, 121.2, 120.4, 99.9, 39.0, 36.9.

***o*-Nitrophenyl-*n*-octylamine (10)**. The HCl-salt of *o*-nitrophenyl-*n*-octylamine (NPOE-amine) **10**[37b] was dissolved in CH_2Cl_2, washed with 1 N NaOH (2×) and H_2O, and dried over Na_2SO_4 to give free amine **10** after removal of the solvent.

Tetrakis(*o*-nitrophenyl-*n*-octylthioureamethyl)cavitand (11a). A solution of isothiocyanatocavitand **9a** (0.12 g, 0.11 mmol) and NPOE-amine **10** (0.25 g, 0.83 mmol) in CH_2Cl_2 (50 mL) was stirred at room temperature for 24 h. Subsequently the mixture was washed with 0.5 M HCl (2 × 25 mL) and H_2O and dried over Na_2SO_4. After removal of the solvent, the crude product was purified by flash column chromatography (SiO_2, CH_2Cl_2/MeOH, gradient 100/0 to 98/2) to give **11a** as a light-brown powder: yield 0.13 g (55%); mp 88−90 °C (CH_2Cl_2/MeOH); MS (FAB) *m*/*z* 2167.1 [60%, M^+, calcd 2166.8]; ^{1}H NMR δ 7.81 (d, 4 H, J = 6.8 Hz), 7.51 (t, 4 H, J = 7.2 Hz), 7.10−6.95 (m, 4 + 8 H), 6.41 (bs, 4 H), 6.27 (bs, 4 H), 6.00 (d, 4 H, J = 7.1 Hz), 4.71 (t, 4 H, J = 7.9 Hz), 4.43 (d, 4 H, J = 7.1 Hz), 4.32 (bs, 8 H), 4.10 (t, 8 H, J = 6.2 Hz), 3.47 (bs, 8 H), 2.25−2.1 (m, 8 H), 1.82 (pentet, 8 H, J = 6.4 Hz), 1.6−1.15 (m, 56 H), 0.90 (t, 12 H, J = 6.6 Hz); ^{13}C NMR δ 180.9, 153.1, 152.6, 139.7, 138.4, 134.3, 125.6, 120.0, 114.5, 99.9, 69.6, 32.0. Anal. Calcd for $C_{116}H_{156}N_{12}O_{20}S_4\cdot 2H_2O$: C, 63.25; N, 7.63; H, 7.32. Found: C, 63.29; N, 7.33; H, 7.22.

Tetrakis(*o*-nitrophenyl-*n*-octylureamethyl)cavitand (11b). Aminomethylcavitand **3** (2.00 g, 2.14 mmol) was dissolved and evaporated to dryness three times from toluene (50 mL). After redissolving the residue in toluene (100 mL), triphosgene (848 mg, 2.86 mmol) was added in portions and the mixture was refluxed for 4 h. The solvent was removed in vacuo and the crude **9b** was dissolved in CH_2Cl_2 (100 mL). To the well-stirred solution was added dropwise a solution of NPOE-amine **10** (3.89 g, 12.86 mmol) in CH_2Cl_2 (100 mL). The mixture was stirred overnight at room temperature and subsequently at reflux temperature for 4 h. The solution was washed with 0.5 M HCl (2 × 25 mL), H_2O (25 mL), and dried over Na_2SO_4. After removal of the solvent and column chromatography (SiO_2, CH_2Cl_2/MeOH gradient 100/0 to 95/5), **11b** was isolated as a slightly yellow powder to yield 492 mg (11%). After basicifying of the collected aqueous layers with 2 M NaOH (till pH >10) and extraction with CH_2Cl_2, 16% of the NPOE-amine **10** was recovered. **11b**: mp 114−116 °C (CH_2Cl_2/MeOH); MS (FAB) *m*/*z* 2125.3 (60%, $[M + Na]^+$, calcd 2125.5); ^{1}H NMR δ 7.82 (d, 4 H, J = 8.0 Hz), 7.49 (t, 4 H, J = 7.3 Hz), 7.05−6.95 (m, 4 + 8 H), 5.98 (d, 4 H, J = 7.2 Hz), 5.15 (bs, 4 H), 5.04 (bs, 4 H), 4.72 (t, 4 H, J = 7.6 Hz), 4.44 (d, 4 H, J = 7.4 Hz), 4.17 (bs, 8 H), 4.07 (t, 8 H, J = 6.1 Hz), 3.08 (q, 8 H, J = 5.0 Hz), 2.3−2.05 (m, 8 H), 1.79 (pentet, 8 H, J = 6.6 Hz), 1.6−1.15 (m, 56 H), 0.99 (t, 12 H, J = 6.7 Hz); ^{13}C NMR δ 158.4, 153.5, 152.6, 139.8, 138.0, 134.2, 125.1, 120.0, 114.4, 125.6, 120.0, 100.3, 69.6, 32.1. Anal. Calcd for $C_{116}H_{156}N_{12}O_{24}$: C, 66.27; N, 7.99; H, 7.48. Found: C, 65.93; N, 7.45; H, 7.90.

Tris(*tert*-octylthioureamethyl)cavitand (13). A solution of tris(aminomethyl)cavitand **12** (160 mg, 0.174 mmol) and *tert*-octyl isothiocyanate (0.15 mL, 1.05 mmol) in $CHCl_3$ (25 mL) was stirred at room temperature for 2 d. After evaporation of the solvent and column chromatography (SiO_2, CH_2Cl_2/MeOH 95:5), **13** was isolated as a yellow solid: yield 190 mg (76%); mp 166−168 °C (CH_2Cl_2/MeOH); MS (FAB) *m*/*z* 1429.3 (30%, M^-, calcd 1429.9); ^{1}H NMR δ 7.10 (s, 3 H), 6.96 (s, 1 H), 6.09 (s, 6 H), 6.00 (d, 2 H, J = 7.0 Hz), 5.93 (d, 2 H, J = 7.0 Hz), 4.8−4.7 (m, 4 H), 4.42 (s, 6 H), 4.35 (d, 2 H, J = 7.0 Hz), 4.31 (d, 2 H, J = 7.0 Hz), 2.25−2.1 (m, 8 H), 1.96 (s, 3 H), 1.81 (s, 6 H), 1.46 (s, 18 H), 1.4−1.3 (m, 24 H), 0.95−0.85 (m, 39 H); ^{13}C NMR δ 180.0, 153.3, 153.2, 152.9, 152.8, 139.1, 138.6, 138.1, 137.7, 124.0, 123.0, 120.4, 99.4, 99.0. Anal. Calcd for $C_{83}H_{126}N_6O_8S_3\cdot 1.5CH_2Cl_2$: C, 65.08; N, 5.39; H, 8.34. Found: C, 65.17; N, 5.35; H, 8.32.

Tris(octadecylureamethyl)cavitand (14). A solution of tris(aminomethyl)cavitand **12** (87 mg, 0.095 mmol) and octadecyl isocyanate (113 mg, 0.38 mmol) in $CHCl_3$ (15 mL) was stirred at room temperature for 1 h. After evaporation of the solvent and recrystallization of the residue from CH_2Cl_2/MeOH, **14** was isolated as a white solid: yield 130 mg (76%); mp 95−97 °C (CH_2Cl_2/MeOH); MS (FAB) *m*/*z* 1804.9 (60%, $[M + H]^+$, calcd 1804.4); ^{1}H NMR δ 7.06 (s, 3 H), 6.93 (s, 1 H), 5.93 (d, 2 H, J = 7.3 Hz), 5.90 (d, 2 H, J = 7.0 Hz), 5.0−4.8 (m, 9 H), 4.75−4.65 (m, 4 H), 4.38 (dd, 4 H, 2 × J = 7.0 Hz), 4.3−4.05 (m, 6 H), 3.2−3.0 (m, 6 H), 2.17 (s, 8 H), 1.96 (s, 3 H), 1.5−1.20 (m, 120 H), 1.0−0.8 (m, 21 H); ^{13}C NMR δ 158.3, 153.5, 153.4, 153.3, 153.2, 138.6, 138.1, 137.9, 137.5, 125.2, 124.1, 120.2, 120.0, 100.5, 99.1. Anal. Calcd for $C_{113}H_{186}N_6O_{11}\cdot CH_2Cl_2$: C, 72.46; N, 4.45; H, 10.03. Found: C, 72.36; N, 4.47; H, 10.28.

***p*-Fluorophenyl-*n*-octylthiourea (15a)**. A solution of *n*-octylamine (0.32 mL, 1.93 mmol) and *p*-fluorophenyl isothiocyanate (593 mg, 3.87 mmol) in $CHCl_3$ (25 mL) was stirred at

room temperature for 19 h. After evaporation of the solvent and column chromatography (SiO_2, CH_2Cl_2/MeOH 99/1), **15a** was isolated as a white solid: yield 553 mg (100%); mp 75−77 °C (CH_2Cl_2/MeOH); MS (EI) *m*/*z* 282.1 (35%, M^+, calcd 282.2); ^{1}H NMR (acetone-d_6) δ 8.71 (s, 1 H), 7.5−7.35 (m, 2 H), 7.1−7.0 (m, 3 H), 3.58 (q, 2 H, J = 7.0 Hz), 1.6−1.5 (m, 2 H), 1.4−1.25 (m, 8 H), 0.87 (t, 3 H, J = 6.8 Hz); ^{13}C NMR δ 180.7, 161.4, 132.1, 127.8, 117.0, 45.5. Specific coupling constants were observed for J_{CF}. Anal. Calcd for $C_{15}H_{23}FN_2S$: C, 63.93; N, 9.92; H, 8.21. Found C, 63.93; N, 10.09; H, 8.58.

***p*-Fluorophenyl-*n*-octylurea (15b)**. A solution of *n*-octylamine (0.26 mL, 1.55 mmol) and *p*-fluorophenyl isocyanate (0.34 mL, 3.10 mmol) in $CHCl_3$ (25 mL) was stirred at room temperature for 17 h. After evaporation of the solvent and column chromatography (SiO_2, CH_2Cl_2/MeOH 95/5), **15b** was isolated as a white solid: yield 366 mg (89%); mp >300 °C (dec) (CH_2Cl_2/MeOH); MS (FAB) *m*/*z* 267.1 (100%, M^+, calcd 267.2); ^{1}H NMR (acetone-d_6) δ 8.68 (s, 1 H), 7.5−7.35 (m, 2 H), 7.15−7.0 (m, 3 H), 3.58 (q, 2 H, J = 7.2 Hz), 1.7−1.5 (m, 2 H), 1.4−1.25 (m, 10 H), 0.87 (t, 3 H, J = 6.7 Hz); ^{13}C NMR (acetone-d_6) δ 158.5, 156.3, 138.0, 120.5, 115.7, 40.5. Specific coupling constants were observed for J_{CF}. Anal. Calcd for $C_{15}H_{23}FN_2O$: C, 67.64; N, 10.52; H, 8.70. Found C, 67.41; N, 10.54; H, 8.96.

Determination of Association Constants. **Dimerization.** In ^{1}H NMR dilution experiments in the 0.5−5 mM concentration range (maximum concentration was ~5 mM due to limited solubility of the receptors), the dimerization constants (K_{dim}) were determined based on the NH^o shifts following the procedure of Horman and Dreux.[38] The signals of the other hydrogens only gave very small shifts upon dilution. Due to the limited solubility of the *p*-fluorophenyl-substituted model compounds **15a**,**b,** the dimerization constants could not satisfactorily be determined in the 2.5−25 mM range using ^{1}H NMR spectroscopy. For the compounds **15a**,**b** the literature values[39] of unsubstituted *N*-butyl-*N*′-phenylthiourea and *N*-butyl-*N*′-phenylurea (K_{dim} = 28 and 1.5 M^{-1}, respectively) were therefore used.

^{1}H NMR Titrations. Stock solution of the host in $CDCl_3$ (5 mM) and of the tetrabutylammonium salts (5 mM) in $CDCl_3$ were prepared. NMR spectra were recorded of 500 μL mixtures of the host and guest solutions in volume ratios varying from 10:0 to 9:1 to 1:9. The K_{ass} values were evaluated with a nonlinear least-fit two-parameter fit of the chemical shift of the complex and the association constant.[40] With these values the complex concentrations in solution were calculated and plotted against the mole fraction of the host (Job plot).

Infrared Spectroscopy. Spectra were recorded at ambient temperature in cells with path lengths of 0.5, 1, or 2 mm. Scanning parameters: resolution of 4 cm^{-1}, 16 scans, medium Norton Beer apodization. Freshly prepared solutions in ethanol-free chloroform with host fraction covering the range 0.9−0.1 and a constant total molar content [0.5 mM for the cavitands and 6 mM for the "simple" (thio)ureas] were measured for the hosts with tetrabutylammonium halide guests (Bu_4NX, with X = F, Cl, Br, and I). Addition of molecular sieves to stock solutions should be avoided as severe adsorption of the hosts to the sieves was observed. Association constants were determined by application of regression analysis.[30]

Transport Measurements. The transport experiments were carried out in a permeation cell consisting of two identical cylindrical compartments (half-cell volume, 50 mL; effective membrane area, 12.4 cm^2) as described previously.[33] The supported liquid membrane consisted of a thin, microporous polypropylene film (Accurel; thickness d = 100 μm, porosity Θ = 64%) immobilizing the solution of carrier in NPOE. Aqueous tetrapropylammonium halide solutions were used as source phase, and doubly distilled and deionized water was used as receiving phase. The measurements were performed at a constant temperature of 25 °C. The transported salts were determined by monitoring the conductivity of the receiving phase as a function of time. The standard deviation in the transport measurements is about 15%.

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