# Neutral Anion Receptors with Multiple Urea-Binding Sites

**Bianca H. M. Snellink-Ruël,[a] Martijn M. G. Antonisse,[b] Johan F. J. Engbersen,[a] Peter Timmerman,[a] and David N. Reinhoudt*[a]**

**Keywords:** Neutral anion receptor / Hydrogen bonding / Urea moieties / Donor acceptor systems / Macrocycles

The synthesis of macrocyclic and acyclic cleft-like anion receptors in which four hydrogen bond donating urea moieties are present in a preorganized fashion is described. NMR spectroscopy shows the complex formation with $H_2PO_4^-$ and $Cl^-$. Cleft-like receptors bind $H_2PO_4^-$ in a 2:1 guest-host stoichiometry ($K_a$ = $10^7$ M$^{-2}$) in DMSO, whereas $Cl^-$ is bound in a 1:1 stoichiometry ($K_a$ = $10^3$M$^{-1}$). The macrocyclic receptors form a 1:1 complex with $H_2PO_4^-$ ($K_a$ = $10^3$ M$^{-1}$ in DMSO) with a 100-fold selectivity for $H_2PO_4^-$ over $Cl^-$.

## Introduction

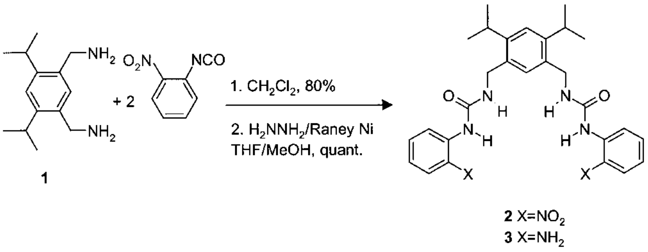
After the first synthetic receptor for anions had been developed by Park and Simmons several groups have contributed to this growing field of molecular recognition.[1] For most of these receptors the anion binding is due to Coulombic interactions (in positively charged receptors) and/or interactions with Lewis acidic sites (in organometallic receptors). However, in nature neutral anion binding proteins are known which bind the anions *only* via hydrogen bonding interactions.[2] Also synthetic anion receptors have been developed which bind anions via hydrogen bond donating (sulfon)amido substituents. In these receptors several scaffolds of spacers, e.g. tris(aminoethyl)amine,[3] cholic acid,[4] or calix[4]arenes,[5] are used to preorganize the amide moieties. Urea moieties are excellent hydrogen bond donors; *N*,*N′*-dimethylurea or *N*-butyl-*N′*-tolylurea form AA•DD type (acceptor-acceptor•donor-donor) complexes with carboxylates like acetate[6] and benzoate,[7] with appreciable stability in DMSO ($K_a$ = 50−150 M$^{-1}$). The binding strength and selectivity can be enhanced by preorganization of multiple urea moieties. There are a variety of multidentate anion receptors in which the geometry and flexibility of the spacer determines the selectivity. For example the rather flexible tris(2-aminoethyl)amine has been used for a tridentate receptor selective for $PO_4^{3-}$ ($K_a$ = 1.1 × $10^4$ M$^{-1}$ in DMSO),[8] rigid spacers like polycyclic diamines[7][9] and *p*-xylylenediamine[6] have been used to make receptors for dicarboxylates, calix[4]arene derivatives for $Cl^-$[10] and carboxylate[11] receptors and calix[6]arene derivatives for $Br^-$.[12] Recently, Umezawa et al.[13] published strong $H_2PO_4^-$ binding by a receptor in which two urea units are preorganized via a xanthene[14] spacer. Even in a polar solvent like DMSO the association constant is 2 × $10^5$ M$^{-1}$. Also based on the more accessible *m*-xylylenediamine, bisurea derivatives have been synthesized. Depending on the nature of the urea moities (aromatic, aliphatic, urea, or thiourea) they bind $H_2PO_4^-$ in DMSO with association constants ranging from 100 to 4600 M$^{-1}$ and with a 2−3 fold selectivity over $Cl^-$ binding.[13][15]

This paper describes neutral xylylenediamine based anion receptors. We have developed cleft-like receptors with firstly multiple urea moieties in order to *increase the number of hydrogen bond donating sites* and secondly, by ring closure of these clefts, we have decreased the flexibility of the hydrogen bond donating sites which *increases the preorganization*. For several anions the association constants and complex stoichiometry have been determined by $^1$H NMR spectroscopy in order to evaluate the effect of the modifications on the binding strength and selectivity.

## Results and Discussion

### Synthesis

Rigid aromatic diamine **1** is the preferred building block for our novel anion receptors. The isopropyl substituents increase the solubility of the receptors in solvents like THF and DMF compared to anion receptors derived from *m*-xylylenediamine or 1,2-diaminobenzene. Diamine **1** was reacted with two equivalents of 2-nitrophenyl isocyanate in $CH_2Cl_2$ and bisurea derivative **2** precipitated from the reaction mixture in 80% yield (Scheme 1).



Scheme 1

The two nitro substituents can be converted into a second pair of hydrogen bond donating moieties. The nitro substituents were reduced with Raney Nickel and hydrazine to give the diamino derivative **3** in quantitative yield. Reaction of **3** with two equivalents of propyl isocyanate in DMF

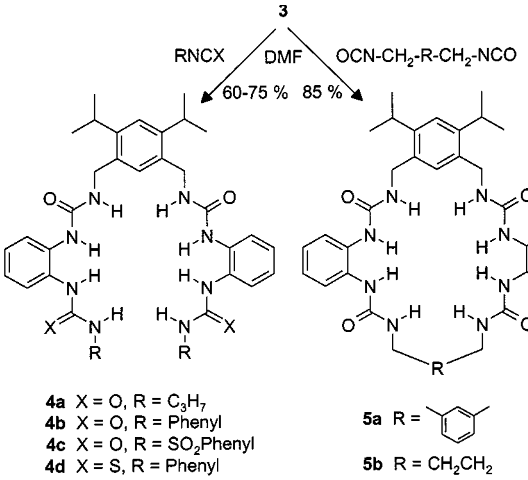
---

[a] Department of Supramolecular Chemistry and Technology, MESA Research Institute, University of Twente, P. O. Box 217, NL-7500 AE Enschede, The Netherlands

[b] Present address: DSM-Resins, Zwolle, The Netherlands

1434−193X/00/0101−165 $ 17.50+.50/0

yielded in 60% tetrakisurea cleft **4a**, which has eight hydrogen bond donating NH moieties (Scheme 2). Similarly, reaction of **3** with phenyl isocyanate or benzenesulfonyl isocyanate gave the receptors **4b** and **4c** in 75% yield. Reaction of diamine **3** with phenylisothiocyanate yielded the bisurea-bisthiourea **4d** in 60%. The increased acidity of the *thio*urea hydrogen atoms in **4d** might lead to a different anion association behavior.



Scheme 2

The $^{13}$C NMR spectrum of **4d** shows a characteristic C=S signal at δ = 180.7 for the thiourea moiety in addition to the C=O signal at δ = 155.0 of the urea moiety. In the $^1$H NMR spectrum of **4d** the thiourea NH hydrogen atoms, which are more acidic, resonate at lower field compared to the urea hydrogen atoms of **4a** (δ = 9.90 and 9.14 for **4d** vs. δ = 9.02 and 7.96 for **4b**).

According to CPK models, ring closure of diamine **3** with diisocyanates should yield macrocyclic tetrakisurea derivatives in which all eight urea hydrogen atoms point to the center of the macrocycle and therefore result in a highly preorganized anion binding site. Ideally, the distance between the amino substituents should be bridged by a *m*-xylylenediamine spacer and indeed we found that reaction of **3** with 1,3-bis(isocyanatomethyl)benzene gave macrocycle **5a** in 85% yield. Interestingly, the $^1$H NMR spectrum shows two broad triplets at δ = 6.85 and 6.78 for the CH$_2$NH urea hydrogen atoms. This double set of resonances might be due to the asymmetry induced by the isopropyl substituents. Also slow interconversion between two different conformers might explain the two sets of urea hydrogen atom signals. Steric interactions preclude a completely flat structure and the urea hydrogen atoms are slightly above or below the macrocycle plane. Even at 100 °C the two broad signals remain separated in the $^1$H NMR spectrum. Ring closure of diamine **3** with 1,4-diisocyanatobutane gave tetrakisurea macrocycle **5b** in 85% yield. In the $^1$H NMR spectrum of **5b** again two pairs of CH$_2$NH urea hydrogen atoms are present.

## Anion Binding Studies

The anion binding ability of the novel multidentate urea receptors in DMSO was investigated by $^1$H NMR spectroscopy. For this purpose the tetrakisurea clefts **4a−d** and macrocycles **5a**,**b** (2.5 mM solutions in [D$_6$]DMSO) were titrated with tetrabutylammonium salts of Cl$^-$, Br$^-$, NO$_3$$^-$, HSO$_4$$^-$, and H$_2$PO$_4$$^-$. The addition of one equivalent of H$_2$PO$_4$$^-$ resulted in large downfield shifts in the $^1$H NMR spectrum of tetrakisurea cleft **4a**. Both the low field aryl urea hydrogen atoms (ArNH) and the benzylic urea hydrogen atoms are strongly shifted downfield ( δ ≈ 0.7 and ≈ 0.5, respectively). This clearly indicates that all four urea moieties are involved in the anion binding. Moreover, large shifts were observed for the aromatic hydrogen atoms. The resonances at δ = 7.54 and 7.41 (hydrogen atoms *ortho* to the urea moieties) are shifted to δ = 7.62 and 7.68, respectively. Interestingly, the hydrogen atoms *meta* to the urea moieties are shifted *up*field by 0.07 ppm. A similar behavior was observed for the aromatic xylene hydrogen atoms. The resonance at δ = 7.16 broadens and is shifted 0.12 ppm downfield, whereas the singlet at δ = 7.28 shifts upfield to δ = 7.16. The latter signal has been used to determine the association constant for complex **4a**·H$_2$PO$_4$$^-$. The Job plot (Figure 1B) is not symmetric and shows a maximum when the mol fraction guest is 0.56, which indicates a mixed 1:1 and 2:1 guest-host stoichiometry. Consequently, it was not possible to obtain an accurate value for the association constants. In the presence of Cl$^-$, Br$^-$, NO$_3$$^-$, or HSO$_4$$^-$ the aryl urea and aromatic xylene hydrogens are hardly shifted and these effects are too small to determine the association constant.

The Job plot for the H$_2$PO$_4$$^-$ complexation by **4b** which has *N*-phenyl substituents instead of *N*-propyl substituents (Figure 2B) indicates that **4b** binds H$_2$PO$_4$$^-$ almost exclusively in a 2:1 guest-host stoichiometry. Assuming a 2:1 stoichiometry the association constant is $5 \times 10^7$ M$^{-2}$ (Figure 2A). Again, Cl$^-$, Br$^-$, NO$_3$$^-$, and HSO$_4$$^-$ do not induce shifts in the $^1$H NMR spectrum.

The *thio*urea moieties in cleft **4d** do not enhance the binding of H$_2$PO$_4$$^-$. The Job plot also shows a 2:1 guest-host stoichiometry and a similar association constant as for **4b**. However, upon the addition of one equivalent of Cl$^-$ a 0.025 ppm shift of the low field urea hydrogen atom singlets is observed and the Job plot indicates a 1:1 complex with an association constant of 250 M$^{-1}$.

The *N*-phenylsulfonyl-substituted receptor **4c** gives with H$_2$PO$_4$$^-$ a guest-host stoichiometry of 1.5:1 and no association constant could be determined accurately.

Upon the addition of H$_2$PO$_4$$^-$ to the *macrocyclic* receptors **5a** and **5b** pronounced effects on the $^1$H NMR spectrum were observed. The urea hydrogen atom resonances are broadened and shifted downfield over 1 ppm upon complexation of this anion. In contrast to the tetrakisurea clefts, macrocycle **5a** binds H$_2$PO$_4$$^-$ exclusively in a 1:1 stoichiometry (Figure 3B) with an association constant of $2.5 \times 10^3$ M$^{-1}$. Complexation of Cl$^-$ by **5a** induces a downfield shift of the aryl urea and aromatic hydrogen atoms. The Job

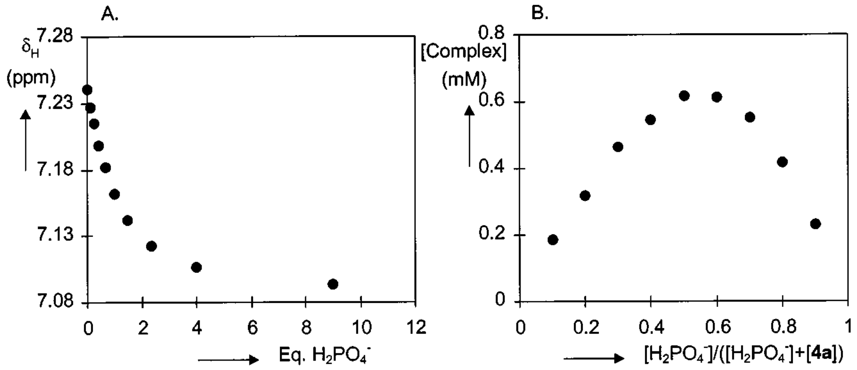


Figure 1. Complexation of $H_2PO_4^-$ by cleft **4a**. A. Effect on the chemical shift of an aromatic hydrogen atom. B. Corresponding Job plot.

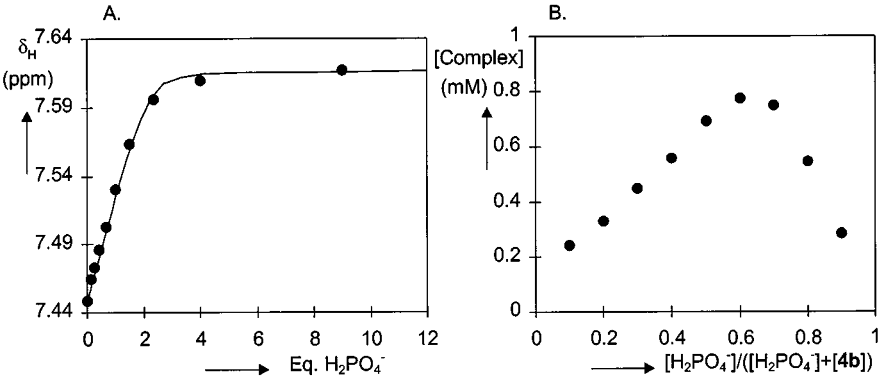
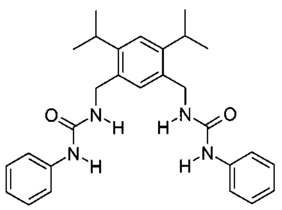


Figure 2. Complexation of $H_2PO_4^-$ by cleft **4b**. A. Effect on the chemical shift of an aromatic hydrogen atom. The curve is calculated for a $K_a$ of $5 \times 10^7$ $\mathrm{M}^{-2}$ and a $\delta_{complex}$ of 7.5; B. Corresponding Job plot.

plot clearly indicates a 1:1 stoichiometry ($K_a$ = 500 $\mathrm{M}^{-1}$). Also macrocycle **5b** binds $H_2PO_4^-$ in a 1:1 stoichiometry and the binding strength ($K_a = 4.0 \times 10^3$ $\mathrm{M}^{-1}$) is comparable with macrocycle **5a**. However, the $Cl^-$ binding is strongly reduced ($K_a$ < 50 $\mathrm{M}^{-1}$) and this means that **5b** binds $H_2PO_4^-$ with at least a 100-fold selectivity over $Cl^-$. $Br^-$, $NO_3^-$, and $HSO_4^-$ anions induce shifts that are too small to determine either the stoichiometry or association constant.

Bisurea derivative **6**, structurally related to the bis(thio)urea receptors developed by Umezawa *et al.*,[13][15] complexes $H_2PO_4^-$ with a association constant of 900 $\mathrm{M}^{-1}$. The addition of 1 equivalent of $Cl^-$ does not result in significant shifts in the $^1H$ NMR spectrum.



**6**

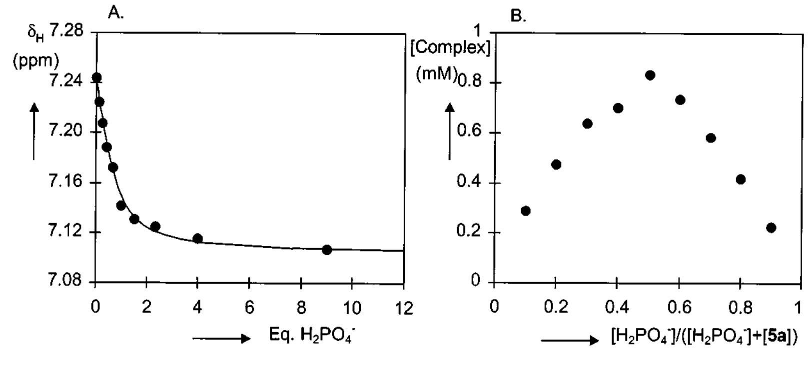


Figure 3. Complexation of $H_2PO_4^-$ by macrocycle **5a**. A. Effect on the chemical shift of an aromatic hydrogen atom. The curve is calculated for a $K_a$ of $2.5 \times 10^3$ $\mathrm{M}^{-1}$ and a $\delta_{complex}$ of 7.1; B. Corresponding Job plot.

## Discussion

The complexation of $H_2PO_4^-$ induces large shifts of all urea NH hydrogen atom signals for **4a−d**. Job plot analyses indicate the formation of complexes with a 2:1 guest-host stoichiometry and especially in the case of phenylurea derivatives **4b** and **4d** the termolecular complex is predominantly present with high association constants ($K_a = 5 \times 10^7$ M$^{-2}$) in [D$_6$]DMSO. This implies that binding of the first $H_2PO_4^-$ anion increases the affinity towards the second anion. For the $H_2PO_4^-$ complexes of **6** Umezawa *et al.*[15] suggested a structure in which one of the $H_2PO_4^-$ oxygen atoms forms two hydrogen bonds, whereas two other oxygen atoms have only one hydrogen bond interaction. The remaining polar hydroxyl is not involved in the binding due to the absence of properly oriented hydrogen bond acceptors. In the termolecular complex **4b**·$2H_2PO_4^-$ the first $H_2PO_4^-$ anion species can significantly contribute to the binding of a second $H_2PO_4^-$ anion (while bound by the second pair of urea moieties) as a result of *additional hydrogen bonding* between the hydroxyl groups of the two anions. This is in line with the previously reported dimerization of $H_2PO_4^-$ in uranyl salophene $H_2PO_4^-$ complexes.[16]

With **4a** and **4c** a considerable amount of 1:1 complex is present. The lower affinity for binding the second anion with these receptors might be related to the decreased acidity of the second pair of urea moieties in **4a** and **4c** or to increased *intra*molecular selfassociation of the urea moieties. In receptors **4b** and **4d** this will be prevented by the bulky phenyl substituents.

In the macrocyclic receptors **5a** and **5b** the flexibility and size of the binding cavity are smaller than in the clefts **4a−d**. $H_2PO_4^-$ is bound by the macrocycles exclusively in a 1:1 stoichiometry. The association constant of the complex of **5a**·$H_2PO_4$ is $2.5 \times 10^3$ M$^{-1}$ and comparable with $H_2PO_4^-$ complexation by uranyl salophene derivatives.[16] However, in this novel class of macrocyclic anion receptors only hydrogen bond formation contributes to the binding. Comparison of the association constants with the $H_2PO_4^-$ binding by the reference **6** ($K_a$ = 900 M$^{-1}$) shows that the increased number of hydrogen bond donating sites indeed results in stronger binding.

In contrast with $H_2PO_4^-$, $Cl^-$ is complexed by the cleft-like receptors **4a−d** in a 1:1 stoichiometry. However, complexation of $Cl^-$ generally induces only small shifts of the urea NH resonance signals of the cleft-like receptors **4a−d** (smaller than 0.05 ppm), and only for the bisurea-bisthiourea derivative **4d** an association constant of 250 M$^{-1}$ could be determined. In the $Cl^-$ complex probably only the second pair of urea moieties is involved in the anion binding and the urea moieties directly attached to the xylene linker are of minor importance. This has been confirmed in the complexation experiments with cleft **4a**, in which all the urea NH signals can be properly distinguished in the $^1$H NMR spectrum, and *only* the NH hydrogen atoms next to the phenylene moiety are (slightly) shifted. Moreover, bisurea **6** and bisurea derivatives of *m*-xylylenediamine reported in the literature show no indication for $Cl^-$ binding.[13][15]

The macrocyclic receptor **5a** also binds $Cl^-$ ($K_a$ = 500 M$^{-1}$) but the smaller ring size and higher flexibility of macrocycle **5b** reduces the binding of $Cl^-$ ($K_a$ <50 M$^{-1}$). Consequently, the selectivity for $H_2PO_4^-$ over $Cl^-$ binding is much higher (≥ 100).

Anions like $NO_3^-$ or $HSO_4^-$ form much weaker hydrogen bonds than $H_2PO_4^-$ (p$K_a$ = −1.4, −3.1, and 2.16, respectively),[17] and consequently the latter forms a stronger complex with the hydrogen bond donating hosts.[18]

In summary, this study shows that strong anion complexation in polar organic solvents can be achieved exclusively by hydrogen bond formation, i.e. without the use of Coulombic interactions (as in charged anion receptors) or interactions with strong Lewis acidic sites (as in organometallic receptors). The number and preorganization of the hydrogen bond donating moieties clearly influence the association constants and stoichiometry of the anion complex. The large number of urea moieties in the cleft-like receptors results in high association constants for the termolecular $2 \cdot H_2PO_4^-$ complex ($K_a = 10^7$ M$^{-2}$) and only minor indications of moderate $Cl^-$ binding is observed. The macrocyclic structure of receptor **5b** exhibits strong binding of $H_2PO_4^-$ ($K_a = 4.0 \times 10^3$ M$^{-1}$) with at least a 100-fold selectivity for $H_2PO_4^-$ over $Cl^-$.

## Experimental Section

**General:** NMR spectra were recorded in [D$_6$]DMSO on a Bruker AC 250 spectrometer. − DMF was freshly distilled from $CaCl_2$ and stored over molecular sieves (4 Å). − The reactions with isocyanates were carried out in a dry argon atmosphere. 1,3-Bis(aminomethyl)-4,6-diisopropylbenzene (**1**) was synthesized according to a literature procedure.[19]

**4,6-Diisopropyl-1,3-bis[methylene-(*N'*-2-nitrophenylureylene)]-*m*-xylene (2):** A solution of diamine **1** (2.3 mmol) and 2-nitrophenyl isocyanate (2.6 mmol, 0.43 g) in 200 mL of dry $CH_2Cl_2$ was stirred for 4 h. The precipitated yellow solid was collected by filtration and dried under vacuum to yield bisurea derivative **2**. Yield 1.0 g (80%). M.p. 258°C. − $^1$H NMR: δ = 9.40 (s, 2 H, ArNH), 8.34 (dd, 2 H, $J$ = 8.5 Hz, $J$ = 1.1 Hz, ArH), 8.03 (dd, 2 H, $J$ = 8.4 Hz, $J$ = 1.5 Hz, ArH), 7.89 (bt, 2 H, $CH_2NH$), 7.61 (m, 2 H, $J$ = 6.5 Hz, $J$ = 1.5 Hz, ArH), 7.26 (s, 1 H, ArH), 7.21 (s, 1 H, ArH), 7.15−7.05 (m, 2 H, ArH), 4.33 (s, 4 H, $CH_2$), 3.2−3.1 (m, 2 H, CH), 1.21 (d, 12 H, $J$ = 6.8 Hz, isopropyl $CH_3$). − $^{13}$C NMR: δ = 153.8 (s), 145.9 (s), 136.5 (s), 135.9 (s), 134.9 (d), 132.8 (s), 129.7 (d), 125.3 (d), 122.1 (d), 121.9 (d), 121.3 (d), 40.5 (t), 28.0 (d), 23.8 (q). − MS-FAB; *m/z*: 548.0 (M$^-$, calcd. 548.2). − $C_{28}H_{32}N_6O_6$: calcd. C 61.3, H 5.9, N 15.3; found C 61.2, H 5.9, N 15.1.

**4,6-Diisopropyl-1,3-bis[methylene(*N'*-2-aminophenylureylene)]-*m*-xylene (3):** A 1:1 mixture of THF and MeOH (100 mL) was used to dissolve the bisnitro derivative **2** (0.9 mmol). After the addition of 0.44 mL of hydrazine monohydrate (9 mmol) and a catalytic amount of Raney Nickel (50% slurry in water) the solution was refluxed overnight. The solution was filtered over Hyflo and the solvent was evaporated to afford the bisamino derivative **3** in quantitative yield. M.p. 290°C (dec). − $^1$H NMR: δ = 8.32 (s, 2 H, ArNH), 7.30 (dd, 2 H, $J$ = 7.9 Hz, $J$ = 1.3 Hz, ArH), 7.24 (s, 1 H, ArH), 7.20 (s, 1 H, ArH), 6.85−7.75 (m, 2 H, ArH), 6.68 (dd, 2 H, $J$ = 7.9 Hz, $J$ = 1.5 Hz, ArH), 6.55−6.5 (m, 2 H, ArH), 6.43 (t, 2 H, $J$ = 5.1 Hz, $CH_2N\mathit{H}$), 4.67 (br. s, 4 H, $NH_2$), 4.29 (d, 4 H, $J$ = 5.1 Hz, $CH_2$), 3.2−3.1 (m, 2 H, CH), 1.21 (d, 12 H, $J$ = 6.8 Hz, isopropyl $CH_3$). − $^{13}C$ NMR: δ = 155.4 (s), 145.7 (s), 140.4 (s), 133.4 (s), 129.5 (d), 125.4 (s), 123.8 (d), 123.2 (d), 122.0 (d), 116.8 (d), 115.7 (d), 40.6 (t), 28.0 (d), 23.9 (q). − MS-FAB; *m/z*: 489.6 [M + H]$^+$, calcd. 489.3. − $C_{28}H_{36}N_6O_2$: calcd. C 68.8, H 7.4, N 17.2; found C 69.0, H 7.5, N 17.4.

**General Procedure for the Preparation of Tetrakisurea Clefts 4a−c and Bisurea-Bisthiourea Cleft 4d:** To a solution of 0.10 g of diamine **3** (0.2 mmol) in 10 mL of dry DMF was added 0.5 mmol of iso(thio)cyanate (propyl isocyanate, phenyl isocyanate, benzenesulfonyl isocyanate, or phenylisothiocyanate for **4a**, **4b**, **4c**, and **4d**, respectively). After stirring the solution overnight at room temperature water was added to destroy the excess of isocyanate, and subsequently the solvent was evaporated. The crude product was triturated with MeOH. Filtration yielded **4a−d** as white solids.

**Tetrakisurea Cleft 4a:** Yield 0.08 g (60%). M.p. 245°C (dec). − $^1H$ NMR: δ = 7.82 (s, 2 H, ArNH), 7.71 (s, 2 H, ArNH), 7.56−7.52 (m, 2 H, ArH), 7.43−7.39 (m, 2 H, ArH), 7.23 (s, 1 H, ArH), 7.16 (s, 1 H, ArH), 6.95−6.91 (m, 4 H, ArH), 6.83 (bt, 2 H, $ArCH_2N\mathit{H}$), 6.45 (t, 2 H, $J$ = 5.5 Hz, propyl−NH), 4.27 (d, 4 H, $J$ = 4.9 Hz, $ArCH_2$), 3.2−3.1 (m, 2 H, CH), 2.99 (q, 4 H, $J$ = 6.5 Hz, $CH_3CH_2C\mathit{H}_2$), 1.44−1.36 (m, 4 H, $CH_3C\mathit{H}_2CH_2$), 1.19 (d, 12 H, $J$ = 6.7 Hz, isopropyl $CH_3$), 0.84 (t, 6 H, $J$ = 7.4 Hz, $C\mathit{H}_3CH_2CH_2$). − $^{13}C$ NMR: δ = 155.9 (s), 155.5 (s), 145.7 (s), 133.3 (s), 132.0 (s), 131.1 (s), 129.8 (d), 123.8 (d), 123.3 (d), 123.0 (d), 122.0 (d), 41.1 (t), 40.6 (t), 28.0 (d), 23.9 (q), 23.0 (t). − MS-FAB; *m/z*: 657.3 [M − H]$^+$, calcd. 657.3. − $C_{36}H_{50}N_8O_4\cdot MeOH$: calcd. C 64.3, H 7.9, N 16.2; found C 64.6, H 7.5, N 16.5.

**Tetrakisurea Cleft 4b:** Yield 0.11 g (75%). M.p. 247°C (dec). − $^1H$ NMR: δ = 9.02 (s, 2 H, ArNH), 7.96 (s, 2 H, ArNH), 7.87 (s, 2 H, ArNH), 7.60 (d, 2 H, $J$ = 9.1 Hz, ArH), 7.45−7.4 (m, 6 H, ArH), 7.3−7.15 (m, 6 H, ArH), 7.1−6.8 (m, 8 H, ArH and $ArCH_2N\mathit{H}$), 4.29 (d, 4 H, $J$ = 4.3 Hz, $CH_2$), 3.2−3.1 (m, 2 H, CH), 1.18 (d, 12 H, $J$ = 6.4 Hz, $CH_3$). − $^{13}C$ NMR ([D7]DMF): δ = 156.9 (s), 154.3 (s), 153.6 (s), 146.4 (s), 141.3 (s), 141.0 (s), 134.5 (s), 133.7 (s), 131.7 (s), 129.4 (d), 125.4 (d), 124.9 (d), 124.0 (d), 122.9 (d), 122.6 (d), 122.4 (d), 119.1 (d), 118.9 (d), 41.5 (t), 29.1 (d), 24.1 (q). − MS-FAB; *m/z*: 725.6 [M − H]$^+$, calcd. 725.4. − $C_{42}H_{46}N_8O_4\cdot 0.5MeOH$: calcd. C 68.7, H 6.5, N 15.1; found C 68.9, H 6.5, N 15.1.

**Tetrakisurea Cleft 4c:** Yield 0.13 g (75%). M.p. 208−210°C. − $^1H$ NMR: δ = 11.27 (br. s, 2 H, $SO_2NH$), 8.34 (s, 2 H, ArNH), 7.98 (s, 2 H, ArNH), 7.94 (d, 4 H, $J$ = 1.7 Hz, ArH), 7.7−7.6 (m, 6 H, ArH), 7.45−7.35 (m, 4 H, ArH), 7.27 (s, 1 H, ArH), 7.21 (s, 1 H, ArH), 7.1−7.0 (m, 4 H, ArH), 6.74 (bt, 2 H, $ArCH_2N\mathit{H}$), 4.34 (d, 4 H, $J$ = 4.7 Hz, $CH_2$), 3.2−3.1 (m, 2 H, CH), 1.21 (d, 12 H, $J$ = 6.7 Hz, $CH_3$). − $^{13}C$ NMR: δ = 155.6 (s), 149.8 (s), 145.9 (s), 140.0 (s), 133.3 (d), 133.1 (s), 132.0 (s), 129.7 (d), 129.1 (d), 127.3 (d), 125.5 (d), 125.0 (d), 124.2 (d), 123.7 (d), 123.6 (d), 122.2 (d), 40.8 (t), 28.0 (d), 23.9 (q). − MS-FAB; *m/z*: 853.4 [M − H]$^+$, calcd. 853.3. − $C_{42}H_{46}N_8O_8S_2\cdot 0.5MeOH$: calcd. C 58.6, H 5.6, N 12.9, S 7.4; found C 58.6, H 5.4, N 13.0, S 7.3.

**Bisureabisthiourea Cleft 4d:** Yield 0.09 g (60%). M.p. 173−166°C. − $^1H$ NMR: δ = 9.90 (s, 2 H, ArNH), 9.14 (s, 2 H, ArNH), 7.93 (s, 2 H, ArNH), 7.89 (d, 2 H, $J$ = 8.2 Hz, ArH), 7.51 (d, 4 H, $J$ = 7.9 Hz, ArH), 7.35−7.10 (m, 14 H, ArH and $ArCH_2N\mathit{H}$), 6.97 (t, 2 H, $J$ = 7.5 Hz, ArH), 4.26 (d, 4 H, $J$ = 3.7 Hz, $CH_2$), 3.2−3.1 (m, 2 H, CH), 1.21 (d, 12 H, $J$ = 6.7 Hz, $CH_3$). − $^{13}C$ NMR: δ = 180.7 (s), 155.0 (s), 146.1 (s), 139.2 (s), 136.1 (s), 133.1 (s), 130.2 (d), 128.9 (d), 128.4 (d), 126.7 (d), 124.5 (d), 123.6 (d), 122.2 (d), 121.8 (d), 120.7 (d), 40.7 (t), 28.1 (d), 23.9 (q). − MS-FAB; *m/z*: 749.3 [M$^+$], calcd. 759.0. − $C_{42}H_{46}N_8O_2S_2\cdot MeOH$: calcd. C 65.3, H 6.4, N 14.2, S 8.1; found C 65.1, H 6.1, N 14.3, S 8.3.

**General Procedure for the Preparation of Tetrakisurea Cycles 5a and 5b:** To a solution of 0.25 g (0.51 mmol) of diamine **3d** in 50 mL of dry DMF was added 0.51 mmol of 1,3-bis(isocyanatomethyl)benzene or 1,4-diisocyanatobutane (for **5a** and **5b**, respectively). After stirring the solution overnight the solvent was evaporated and the crude product was triturated with MeOH. Filtration yielded **5a** and **5b** as white solids.

**Tetrakisurea Cycle 5a:** Yield 0.29 g (85%). M.p. 230°C (dec). − $^1H$ NMR: δ = 7.93 (s, 2 H, ArNH), 7.89 (s, 2 H, ArNH), 7.60 (dd, 2 H, $J$ = 7.3 and 2.1 Hz, ArH), 7.43 (dd, 2 H, $J$ = 7.2 Hz, $J$ = 2.3 Hz, ArH), 7.3−7.1 (m, 6 H, ArH), 7.05−6.95 (m, 4 H, ArH), 6.85 (bt, 2 H, $ArCH_2N\mathit{H}$), 6.78 (bt, 2 H, $ArCH_2N\mathit{H}$), 4.3−4.2 (m, 8 H, $CH_2$), 3.2−3.1 (m, 2 H, CH), 1.21 (d, 12 H, $J$ = 6.7 Hz, $CH_3$). − $^{13}C$ NMR: δ = 155.9 (s), 155.4 (s), 145.7 (s), 140.0 (s), 133.1 (s), 132.5 (s), 130.7 (s), 129.5 (d), 128.3 (d), 126.9 (d), 126.5 (d), 124.4 (d), 123.9 (d), 123.0 (d), 122.9 (d), 122.0 (d), 43.3 (t), 40.4 (t), 28.0 (d), 23.9 (q). − MS-FAB; *m/z*: 677.5 [M + H$^+$], calcd. 677.3. − $C_{38}H_{44}N_8O_4$: calcd. C 67.4, H 6.6, N 16.6; found C 67.7, H 6.6, N 16.5.

**Tetrakisurea Cycle 5a:** Yield 0.30 g (85%). M.p. 280°C (dec). − $^1H$ NMR: δ = 7.92 (s, 1 H, ArNH), 7.85−7.65 (m, 3 H, ArNH), 7.65−7.3 (m, 2 H, ArH), 7.3−7.1 (m, 2 H, ArH), 7.05−6.85 (m, 4 H, ArH), 6.84 (bt, 1 H, $CH_2N\mathit{H}$), 6.77 (bt, 2 H, $CH_2N\mathit{H}$), 6.49 (bt, 1 H, $CH_2N\mathit{H}$), 6.38 (bt, 2 H, $CH_2N\mathit{H}$), 4.29 (bd, 4 H, $ArCH_2$), 3.3−3.0 (m, 6 H, CH and $NHC\mathit{H}_2CH_2$), 1.5−1.3 (bm, 4 H, $NHCH_2C\mathit{H}_2$), 1.20 (d, 12 H, $J$ = 6.7 Hz, $CH_3$). − $^{13}C$ NMR: δ = 156.0 (s), 155.4 (s), 145.8 (s), 133.1 (s), 132.6 (s), 130.8 (s), 130.0 (d), 124.5 (d), 123.8 (d), 123.0 (d), 122.7 (d), 122.0 (d), 40.5 (t), 39.3 (t), 28.0 (d), 27.0 (t), 23.9 (q). − MS-FAB; *m/z*: 629.3 [M + H]$^+$, calcd. 629.3. − $C_{34}H_{44}N_8O_4$: calcd. C 65.0, H 7.1, N 17.8; found C 65.2, H 7.2, N 18.1.

**NMR Experiments:** Complex stoichiometry and association constants were determined by $^1H$ NMR experiments (Job plot analysis). To this end, stock solutions were prepared of the host (2.5 mM in [D$_6$]DMSO) and of the tetrabutylammonium anion salts (2.5 mM in [D$_6$]DMSO). Ten NMR tubes were filled with 500 μL mixtures of the host and guest solutions in the volume ratios from 10:0 to 1:9. The $^1H$ NMR spectra were recorded and the complex concentration was calculated as follows: $[\text{complex}] = [\text{host}]_{\text{tot}}\cdot(\delta_{\text{obs}} - \delta_{\text{host}})/(\delta_{\text{complex}} - \delta_{\text{host}})$, in which $[\text{host}]_{\text{tot}}$ is the total host concentration, $\delta_{\text{obs}}$ the observed chemical shift, $\delta_{\text{host}}$ the estimated chemical shift of the free host, and $\delta_{\text{complex}}$ the chemical shift of the complex. Association constants were determined by a nonlinear fit of the observed chemical shifts in the ten NMR measurements, assuming exclusively 1:1 or 2:1 guest-host complexation.

## Acknowledgments

The Technical Foundation (STW), Technical Science Branch of The Netherlands Organization for Scientific Research (NWO) is gratefully acknowledged for financial support.

---

[1] For recent reviews dealing with anion receptors see: [1a] M. M. G. Antonisse, D. N. Reinhoudt, *Chem. Commun.* **1998**, 443−448. − [1b] F. P. Schmidtchen, M. Berger, *Chem. Rev.* **1997**, *97*, 1609−1646. − [1c] J. Scheerder, J. F. J. Engbersen, D. N. Reinhoudt, *Recl. Trav. Chim. Pays-Bas* **1996**, *115*, 307−320.

[2] [2a] F. A. Quiocho, J. S. Sack, N. K. Vyas, *Nature* **1987**, *329*, 561−564. − [2b] J. W. Pflugrath, F. A. Quiocho, *J. Biol. Chem.* **1988**, *200*, 163−180.

[3] [3a] S. Valiyaveettil, J. F. J. Engbersen, W. Verboom, D. N. Reinhoudt *Angew. Chem. Int. Ed. Eng.* **1993**, *32*, 900−901. − [3b] C. Raposo, M. Almaraz, M. Martin, V. Weinrich, L. Mussons, V. Alcazar, C. Caballero, J. R. Mosan, *Chem. Lett.* **1995**, 759−760.

[4] [4a] A. P. Davis, J. F. Gilmer, J. J. Perry, *Angew. Chem. Int. Ed. Eng.* **1996**, *35*, 1312−1315. − [4b] A. P. Davis, J. J. Perry, R. P. Williams, *J. Am. Chem. Soc.* **1997**, *119*, 1793−1794.

[5] [5a] Y. Morzherin, D. M. Rudkevich, W. Verboom, D. N. Reinhoudt, *J. Org. Chem.* **1993**, *58*, 7602−7605. − [5b] P. D. Beer, M. G. B. Drew, R. J. Knubley, M. I. Ogden, *J. Chem. Soc., Dalton Trans.* **1995**, 3117−3123.

[6] E. Fan, S. A. van Arman, S. Kincaid, A. D. Hamilton, *J. Am. Chem. Soc.* **1993**, *115*, 369−370.

[7] T. R. Kelly, M. H. Kim, *J. Am. Chem. Soc.* **1994**, *116*, 7072−7080.

[8] C. Raposo, M. Almaraz, M. Martin, V. Weinrich, L. Mussons, V. Alcazar, C. Caballero, J. R. Mosan, *Chem. Lett.* **1995**, 759−760.

[9] K.-S. Jeong, J. W. Park, Y. L. Cho, *Tetrahedron Lett.* **1996**, *37*, 2795−2798.

[10] J. Scheerder, M. Fochi, J. F. J. Engbersen, D. N. Reinhoudt, *J. Org. Chem.* **1994**, *59*, 7815−7820.

[11] A. Casnati, M. Fochi, P. Minari, A. Pochini, M. Reggiani, R. Ungaro, D. N. Reinhoudt, *Gazz. Chim. Ital.* **1996**, *126*, 99−106.

[12] J. Scheerder, J. F. J. Engbersen, A. Casnati, R. Ungaro, D. N. Reinhoudt, *J. Org. Chem.* **1995**, *60*, 6448−6454.

[13] P. Bühlmann, S. Nishizawa, K. P. Xiao, Y. Umezawa, *Tetrahedron* **1997**, *53*, 1647−1654.

[14] B. C. Hamann, N. R. Branda, J. Rebek, Jr., *Tetrahedron Lett.* **1993**, *34*, 6837−6840.

[15] S. Nishizawa, P. Bühlmann, M. Iwao, Y. Umezawa, *Tetrahedron Lett.* **1995**, *36*, 6483−6486.

[16] D. M. Rudkevich, W. Verboom, Z. Brzozka, M. J. Palys, W. P. R. V. Stauthamer, G. J. van Hummel, S. M. Franken, S. Harkema, J. F. J. Engbersen, D. N. Reinhoudt, *J. Am. Chem. Soc.* **1994**, *116*, 4341−4351.

[17] D. D. Perrin, *Pure Appl. Chem.* **1969**, *20*, 133−236.

[18] Recently, a bicyclic cyclophane has been reported which binds $NO_3^-$ more strongly than $H_2PO_4^-$. − A. P. Bisson, V. M. Lynch, M.-K. C. Monahan, E. V. Anslyn, *Angew. Chem.* **1997**, *109*, 2435−2437; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2340−2342.

[19] C. T. Seto, J. P. Mathias, G. M. Whitesides, *J. Am. Chem. Soc.* **1993**, *115*, 1321−1329.

Received June 18, 1999
[O99365]