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Phosphate selective alkylenebisurea receptors: structure-binding relationship

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ABSTRACT

New host molecules for anions, adamantane, and alkyl urea derivatives substituted by naphthalene chromophores, were synthesized. Their binding with F^-, Cl^-, Br^-, OAc^-, HSO_4^-, NO_3^-, and $H_2PO_4^-$ was investigated by UV–vis, fluorescence and NMR spectroscopy. The anion binding ability of adamantyl bisurea derivatives was compared with the analogous host molecules, wherein the urea moieties are separated by flexible alkyl linkers of the same length, and adamantane monourea derivative. The host molecules show the highest selectivity toward F^- and $H_2PO_4^-$. The binding stoichiometry and the values of the association constants depend on the basicity of anions, availability of H-bonding sites, preorganization, and rigidity of the hosts, as well as solvent polarity and H-bonding availability. Rigid adamantane receptors, compared to flexible analogues show increased selectivity for $H_2PO_4^-$, whereas binding of OAc^- is better with flexible receptors. The binding of OAc^- and $H_2PO_4^-$ was investigated by microcalorimetry. The stoichiometries and the stability constants of the corresponding complexes obtained by this method were in good agreement compared to those determined by UV–vis titrations. In both cases the enthalpic contribution to the overall complex stability was predominant.

1. Introduction

Anions play an important role in a range of biological processes.[1] They are essential in the formation of a variety of enzyme–substrate and enzyme–cofactor complexes, as well as in the interaction between proteins and nucleic acids. ATP and other high-energy phosphate derivatives provide energy for most biological processes. On the other hand, mis-regulation of anion transporting mechanisms results in serious complications and diseases, such as cystic fibrosis. Consequently, it is essential to develop reagents that can detect the presence of various anionic analytes and regulate their transport in the biological systems. This demand sparked significant progress in the field of anion supramolecular chemistry.[2] However, the quest for good anion host molecules is not over. Many scientific groups work on the development of novel hosts characterized by desired selectivity.[3]

One way in which host molecules can recognize anionic guests is based on electrostatic interactions.[4] However, due to non-directional properties of electrostatic interactions host molecules that operate on that principle often suffer from the lack of selectivity.[5] On the other hand, a very important motif for anion recognition is hydrogen bonding. Contrary to electrostatic interactions, hydrogen bonding is directional, which is extremely useful in designing selective hosts for anions with different geometries. Urea and thiourea groups are very often used as binding units in anion supramolecular chemistry.[6] They have two H-bond donating sites that point in the same direction and hence provide the possibility of constructing highly preorganized molecular hosts. The urea (or thiourea) moiety has been used as a host by attachment to *o*-phenylene,[7] *m*-phenylene and xanthene,[8] *p*-phenylene,[9] naphthalene,[10] anthracene,[11] pyrene,[12] chiral cyclohexanediamine,[13] calix[4]arenes,[14] and anthraquinone.[15] Although some of the prepared host molecules are characterized by exceptional selectivity, there are not many reports where structure and selectivity were correlated.[16] Many questions remain unanswered, particularly those related to the number of H-bonding sites and molecular preorganization that are required for the selective recognition of particular oxo-anions of different geometries.

Incorporation of urea moieties in rigid spacers, such as norbornene[17] prompted us to prepare a new class of anion receptors that would have two urea moieties as a binding site, separated by an adamantane rigid spacer and different chromogenic and fluorogenic groups.[18] Herein we report an anion binding study of 1,3-adamantylenebisureas substituted with a naphthalene chromophore, **3** and **4**. The anion binding ability and selectivity of **3** and **4** were compared to the analogous derivatives **1** and **2**, wherein the urea groups are separated by flexible alkyl chains of the same length. In addition, we investigated the anion binding of monourea derivative **5**. This investigation on specifically designed new host molecules for anions was undertaken to increase general knowledge in supramolecular anion chemistry regarding the relationship

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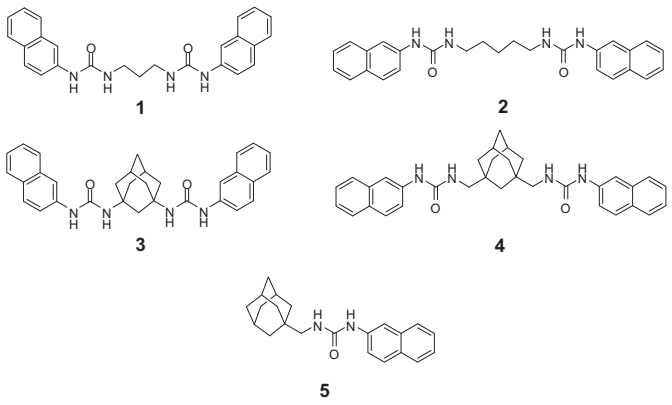
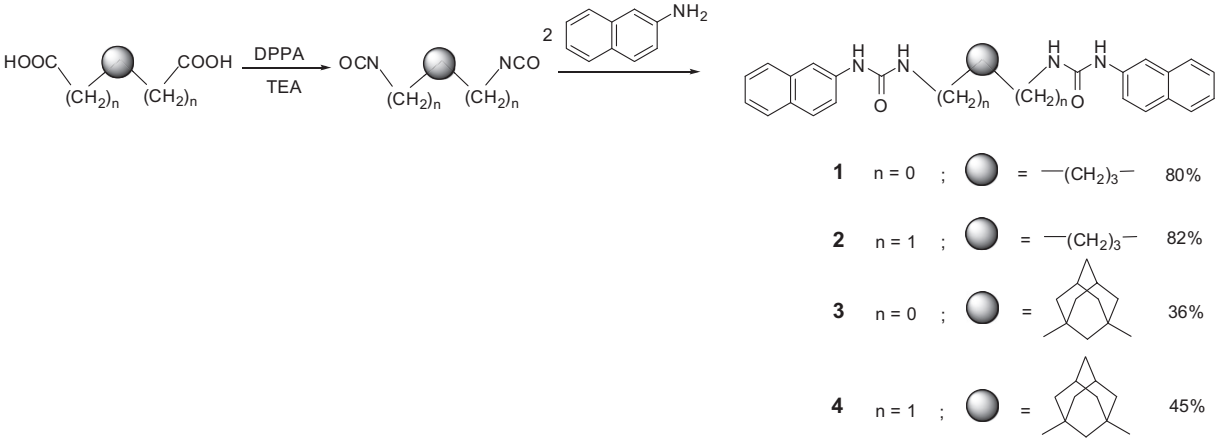
between selectivity and the number of available binding sites, as well as to probe for the possibility of cooperativity and allosteric effects. The results should be of special importance for the rational design of new receptors characterized by better selectivity.



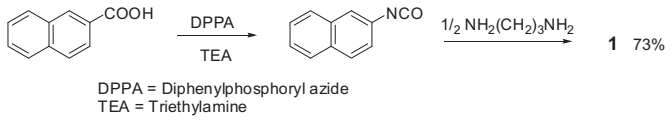
2. Results and discussion

2.1. Synthesis

Urea derivatives **2**–**5** were prepared in moderate to good yields according to a modification of the published procedure[19] from the corresponding carboxylic acids that were transformed to isocyanates *in situ* and reacted with β-naphthylamine (Scheme 1). However, in the preparation of **1**, the same pathway afforded a mixture of products. Therefore **1** was prepared by another pathway, from naphthalene-2-carboxylic acid and propylene diamine (Scheme 2), giving product **1** of higher purity.



Scheme 1.



Scheme 2.

2.2. Anion binding

The anion binding ability of the urea receptors in the solution was investigated by UV–vis, fluorescence, NMR, and microcalorimetric titrations. Anions used in the study were in the form of tetrabutylammonium salts. The following anions, characterized by different size, basicity, and geometry were used: F^-, Cl^-, Br^-, OAc^-, HSO_4^-, NO_3^-, and $H_2PO_4^-$. The data obtained by UV–vis and fluorescence titrations were analyzed by the SPECFIT program,[20] whereas for the analysis of NMR data we used EQNMR.[21] The UV–vis titrations were performed in CH_3CN and DMSO, whereas NMR titrations were performed in DMSO-d_6 due to the low solubility of the compounds in CH_3CN. The estimated binding constants are compiled in Tables 1 and 3.

2.2.1. UV–vis titrations. UV–vis titrations of the receptors with anions in CH_3CN or DMSO after the correction for dilution generally show an increase in absorbance, with a rather small bathochromic shift of the maxima. For example, shifts of absorption maxima of only ~5 nm were seen in titrations with OAc^-, and $H_2PO_4^-$ (Fig. 1). This finding is in accordance with the formation of H-bonded complexes that do not significantly perturb the electronic excitation of the naphthalene chromophore. The observed small bathochromic shift indicates that the negative charge on the nitrogen atom increases only slightly, that is, there is no deprotonation of the urea moiety. The observed findings are in accordance with the experimental and theoretical investigation performed by Lee and Nam.[10d, 22]

Dependences of absorption spectra on anion concentrations were processed by multivariate non-linear regression analysis to determine the complex stoichiometries and the association constants (see Supplementary data). In some cases, fitting was difficult since the addition of anions induced relatively small changes in absorbance, particularly when the titrations were performed in DMSO. Therefore, the constants were not determined precisely, especially in cases where complexes of several stoichiometries were formed. Moreover, in the titration experiments with Cl^- and NO_3^- in DMSO, small changes of absorbance were observed (<0.05) on addition of huge excess of anion (100 equiv), so the UV–vis data could not be used to reveal the association constants. Receptors formed mostly 1:1 complexes, except with F^- and $H_2PO_4^-$. To additionally verify the complexes stoichiometries Job plots were performed (see Supplementary data). They indicated that 1:1 complexes prevailed in the solution. The constants compiled in Table 1 reveal that receptors generally form more stable complexes in CH_3CN than in DMSO (except for F^-). This finding is in accordance with the stronger ability of the urea receptors to solvate with DMSO. Since DMSO can engage as a hydrogen bonding acceptor, solvent participation plays an important role in enthalpic and enthropic contribution to the association of the complex.[9b] Thus, DMSO competes for the hydrogen bonding with receptor molecules

Table 1
Cumulative stability constants of the complexes with anions determined by UV–vis titrations [log (β_{11}/M^{-1})] or [log (β_{12}/M^{-2})][a]

Ion/Rec.	1	2	3	4	5
F^-	~5 (1:1)[c,d]	~5 (1:1)[c,d]	3.1 ± 0.1 (1:1)[b] ~4 (1:1)[c,d]	2.8 ± 0.1 (1:1)[b] ~5 (1:1)[c,d]	3.1 ± 0.1 (1:1)[b] ~5 (1:1)[c,d]
Cl^-	—[c,e]	—[c,e]	3.08 ± 0.02 (1:1)[b] —[c,e]	3.87 ± 0.02 (1:1)[b] —[c,e]	2.57 ± 0.04 (1:1)[b] —[c,e]
Br^-	—	—	2.29 ± 0.03 (1:1)[b]	3.08 ± 0.02 (1:1)[b]	—
$H_2PO_4^-$	5.5 ± 0.7 (1:1)[c] 8.7 ± 0.7 (1:2)[c]	3.47±0.04 (1:1)[c]	5.2 ± 0.2 (1:1)[b] 9.4 ± 0.1 (1:2)[b] 2.96 ± 0.08 (1:1)[c] 6.04 ± 0.08 (1:2)[c]	6.2 ± 0.1 (1:1)[b] 10.6 ± 0.1 (1:2)[b] 4.2 ± 0.1 (1:1)[c] 7.2 ± 0.3 (1:2)[c]	3.16 ± 0.01 (1:1)[b] 2.91 ± 0.09 (1:1)[c]
HSO_4^-	—	—	—[b,e]	2.87 ± 0.02 (1:1)[b]	—
OAc^-	3.30 ± 0.03 (1:1)[c]	3.39±0.04 (1:1)[c]	4.9 ± 0.2 (1:1)[b] 2.93 ± 0.02 (1:1)[c]	4.29 ± 0.05 (1:1)[b] 3.18 ± 0.04 (1:1)[c]	3.64 ± 0.02 (1:1)[b] 2.73 ± 0.06 (1:1)[c]

[a] The anion is added in the form of tetrabutylammonium salt. Stoichiometries of the complexes are indicated in the parentheses (receptor:anion).
[b] Titration performed in CH_3CN.
[c] Titration performed in DMSO.
[d] The titration performed in DMSO strongly indicated formation of complexes of different stoichiometries but titration curves could not be well-fitted. The reported value was obtained by fitting only the spectra corresponding to anion:receptor molar ratio from 0 to 3.
[e] Very small changes were observed in the UV–vis spectra and the data could not be used to estimate the association constants.

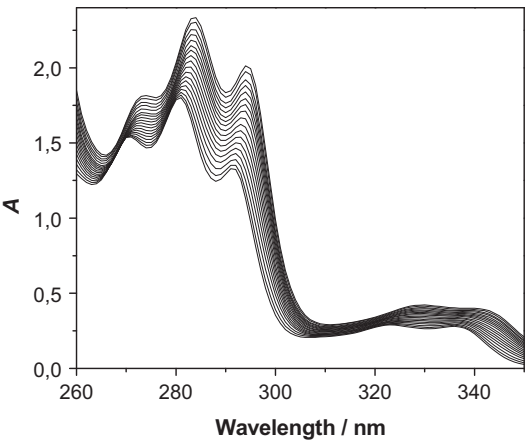


Fig. 1. UV–vis titration of **3** with $H_2PO_4^-$ in CH_3CN. The bottom curve corresponds to the solution of **3**, whereas the curves from bottom to top correspond to the solutions with increasing concentration of $Bu_4NH_2PO_4$.

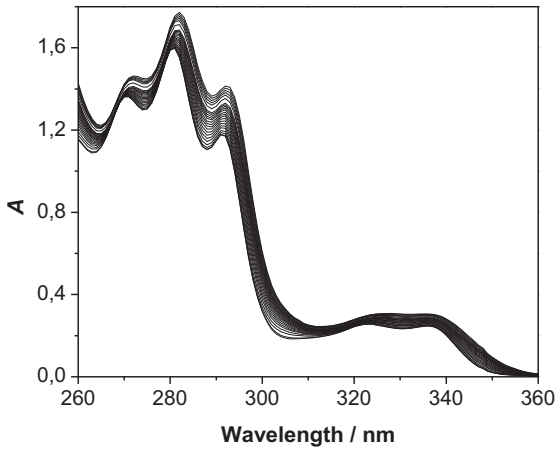


Fig. 2. UV–vis titration of **3** with F^- in CH_3CN. The bottom curve corresponds to the solution of **3**, whereas the curves from bottom to top correspond to the solutions with increasing concentration of Bu_4NF.

decreasing the affinity for the binding of the anions. In general, all receptors showed the strongest binding with $H_2PO_4^-$, and F^-. Although these are very basic anions, the association constants cannot be correlated only to basicity.

It is well known that the addition of basic F^- can in principle induce deprotonation of the urea moiety and the formation of HF_2^- species.[23] In the examples reported by Fabbrizzi et al. the first F^- forms an H-bonded complex and the second induces deprotonation due to the formation of a very stable HF_2^- species (ΔH_{form}=39 kcal/mol).[23] The deprotonation is usually well-visualized by the formation of red-shifted bands in the absorption spectra.[23] Titration of our receptors with F^- in CH_3CN and DMSO, on the other hand, only induced an increase in absorbance (Fig. 2), and very small bathochromic shifts were observed. This result suggests that the β-naphthyl NH on the urea moiety is not acidic enough to be deprotonated by the second equivalent of F^- and that only H-bonded complexes are formed. Namely, the pK_a value of the naphthyl urea NH is probably similar to the one of the unsubstituted diphenyl urea in DMSO (pK_a=19.5).[24] Hence, in bidentate host molecules **1**–**4**, the formation of 1:1 (host:anion) and 1:2 complexes should be possible in principle. It is interesting to note that **3**–**5** in CH_3CN form complexes with F^- characterized only by stoichiometry 1:1 and similar association constants (log K ~3). This finding suggests that only one urea moiety in **3** and **4** forms a complex with the anion, that is, the second urea moiety does not participate in the binding. On the other hand, in DMSO, the receptors formed in addition to 1:1 stoichiometry other complexes, as clearly pointed from the titration data (see the Supplementary data). However, precise determination of the association constants was not possible since the data could not be fitted to any model. Possible reason for such a behavior may be aggregation of the molecules, which may be dependant on the F^- concentration. Since deprotonation can be excluded based on the small bathochromic shifts in the spectra, it is very likely that both urea moieties participate in the formation of the complex, each binding one F^-. Although differences in the observed stoichiometries in CH_3CN and DMSO cannot be rationalized at this point, they are probably due to different solvations of the receptors in two investigated solvents, and possibly due to varying trace amounts of moisture in Bu_4NF and solvent.

All investigated receptors form 1:1 complexes with Cl^- characterized by the association constants that are in some cases similar or higher than the comparable association constants with more basic F^- (comparing 1:1 complexes in CH_3CN). Formation of stable complexes with Cl^- in DMSO was in previous reports explained by strong ion-dipole coupling with that solvent.[8c] In our case, however, the association constants with Cl^- in DMSO could not be estimated by UV–vis titration. The stability of the complex is not only a function of the solvation and the basicity of anions. Comparison of the association constants with Cl^- (Table 2) can be related to the molecular structure. The bidentate receptor **4** forms a complex,

Table 2
Thermodynamic parameters for the complexation of Bu_4NOAc and $Bu_4NH_2PO_4$ with receptor **4**[a]

Ion	log (K/M^{-1})	Δ_rG° kJ mol^{-1}	Δ_rH° kJ mol^{-1}	$T\Delta_rS^\circ$ kJ mol^{-1}
OAc^-	4.6 ± 0.1 (1:1)	− 26.36 ± 0.05 (1:1)	− 18.8 ± 0.7 (1:1)	7.5 ± 0.5 (1:1)
$H_2PO_4^-$	5.89 ± 0.05 (1:1)	−33.6 ± 0.3 (1:1)	−22.0 ± 0.1 (1:1)	9.7 ± 0.2 (1:1)
	4.19 ± 0.02 (1:2)	−23.93 ± 0.03 (1:2)	−26.2 ± 0.4 (1:2)	−18 ± 4 (1:2)

[a] Titration performed in CH_3CN at 25 °C. The association constants [log (K/M^{-1})] and the thermodynamic parameters correspond to successive (not cumulative) equilibria. Stoichiometries of the complexes are indicated in the parentheses (receptor:anion). The standard errors of the mean (N=3) are reported.

which is 20 times more stable than the corresponding complex of the monodentate receptor **5**, suggesting that both urea moieties can participate in the binding, thus making the complex more stable. It is interesting to note that the most stable complex with Cl^- is formed with **4** wherein the urea moieties are separated from the adamantane by the methylene spacers. This finding indicates that both urea moieties in **4** participate in the binding, whereas the binding by two urea moieties in **3** is probably hindered due to steric reasons. The value of the association constant of **4** with Cl^- is in accordance with both ureas participating in the binding since it is higher than the value for some tetradentate urea cyclic ligands,[8e] or bidentate urea ligands on anthracene,[11f,g] or *o*-phenylenediamine.[7a]

Complexation with Br^- was analyzed only for receptors **3** and **4** in CH_3CN. The receptors form 1:1 complexes with association constants lower than for Cl^-. This finding is in accordance with the lower basicity and hydration energy of Br^-. However, it is interesting to note that **4** forms a rather stable complex with Br^-. That suggests that both urea moieties participate in the binding of one Br^-, similar to the complexes with Cl^-.

The investigated compounds form very stable complexes with $H_2PO_4^-$. Receptors **2** and **5** form only 1:1 complexes, whereas other receptors form both 1:1 and 1:2 stoichiometries. For **5** the finding is logical since two urea moieties in a molecule are required for the formation of a 1:2 complex, as seen with **1**, **3**, and **4**. However, why does receptor **2** form only a 1:1 complex? It is interesting to note that receptor **2** forms only 1:1 stoichiometries with all anions. Although structural evidence is not available at the moment (vide infra, NMR section) the observed stoichiometry may be due to the flexibility of **2**.[25] Furthermore, it is interesting to note that **3** and **4** form more stable complexes than **1** and **2**, respectively, indicating that adamantane preorganizes the host for binding with $H_2PO_4^-$. Receptor **4** forms the most stable complexes, suggesting that good preorganization for binding is achieved when the urea moieties are separated from the adamantane by methylene groups. Very high association constants for the complexes with $H_2PO_4^-$ make the receptor **4** among the strongest $H_2PO_4^-$ binders. However, it should be recalled that UV–vis titration is not reliable for determining high association constants (K>10^6 M^{-1}). Formation of 1:2 complexes with $H_2PO_4^-$ and urea bidentate ligands has already been reported in several examples, albeit with lower stability constants.[8e,10f,11d,e] Umezawa suggested that $H_2PO_4^-$ forms a complex with *m*-phenylenemethylene urea derivative wherein one of the oxygen atoms of the $H_2PO_4^-$ forms two hydrogen bonds, whereas the other oxygen atoms have only one H-interaction with the urea and one hydroxyl group does not participate in the binding.[8b,c] Furthermore, in Fabbrizzi's example of a bisurea receptor, two $H_2PO_4^-$ are bound in a complex wherein each $H_2PO_4^-$ forms 2H-bonds with the urea, and 2H-bonds are formed between the anions.[13b] In our case, in the 1:2 complex, the first $H_2PO_4^-$ can also probably contribute to the binding of the second ion as a result of secondary hydrogen bonding between the hydroxyl groups of the two anions (see Scheme 8).[8e] The positive allosteric effects and cooperativity of anion binding by urea derivatives have already been reported by Gunnlaugsson et al.[26] However, in Gunnlaugsson's example, the binding of the first anion by urea induced the binding of the second by an amide function.[26] In our host molecules the first anion probably induces binding of the second to the same binding site (vide infra).

UV–vis titrations with HSO_4^- were performed for receptors **3** and **4**. However, the observed changes in the spectra of **3** were too small to estimate the binding constant. Although $H_2PO_4^-$ and HSO_4^- have similar geometry, the binding of the latter with **4** was accomplished only in 1:1 stoichiometry with the association constants weaker by four orders of magnitude. Lower stability of the complex is in line with lower basicity of the HSO_4^-. The lack of 1:2 stoichiometry is probably due to the inability of HSO_4^- to form H-bonded dimeric structures and additionally stabilize the complex, as in the case of $H_2PO_4^-$. In addition, HSO_4^- has a lower tendency of forming H-bonds than $H_2PO_4^-$, based on their hydration energies in the gas phase (5.9 and 7.6 kcal/mol, respectively).[27]

It is well known that urea receptors form strong complexes with acetate due to its Y-shaped geometry and formation of the contact with the urea moiety with two well-positioned H-bonds. Can our bidentate receptors form stable complexes with OAc^- wherein the anion would be bound by both urea moieties? The association constant of **4** in CH_3CN is 4.5 times higher than for **5** (in DMSO 2.8 times higher). This suggests that both urea moieties in **4** participate in the binding. In addition, the association constants with OAc^- are higher than those for flexible *m*-phenylene bidentate urea ligands,[8b] or similar to those of bidentate norbornene[17b] or anthracene urea ligands,[11g] wherein it was shown that acetate is bound by two urea moieties.[11g] However, much smaller binding constants than for some other bidentate urea ligands, such as *o*-phenylenediamine[7b] or xanthene[8a] (K=1–3×10^5 M^{-1}), suggest that acetate does not form a perfect fit with the clefts of receptors **1**–**4**. In addition, flexible receptors **1** and **2** form slightly more stable complexes than adamantane receptors **3** and **4**. It is probably the adamantane moiety in **3** and **4** that hinders the molecular motion necessary for adopting optimal geometry for the complexation with OAc^-.

Binding of NO_3^- was investigated for adamantane receptors **3** and **4**. However, very small changes were seen in the UV–vis spectra, precluding further analysis and estimation of association constants.

2.2.2. Fluorescence titrations. A fluorescence titration was performed for receptors **3** with F^- in DMSO. The emission spectrum of **3** in DMSO has maximum at 370 nm and does not have a vibronic structure. The excitation spectrum overlaps the absorption with a vibronically structured band with the maximum at 285 nm and a much weaker, broader band at ~350 nm. The addition of the anion to the DMSO solution quenched the fluorescence without shifts to the maxima in the excitation and fluorescence spectra (Fig. 3). Multivariate non-linear regression analysis of the fluorescence spectra suggested the same complex stoichiometry as indicated by the UV–vis titration. However, we observed slow equilibration of the fluorescence intensity upon addition of the anion aliquots. Usually fluorescence decreased in the intervals of 3–5 min. Therefore, fluorescence titrations could not be used to precisely estimate the association constants. Similarly slow equilibration of the fluorescence intensity due to slow formation of the complexes was observed in fluorescence titration of **3** with $H_2PO_4^-$. Contrary to the fluorescence titration, slow kinetics of the complex formation was not observed with other techniques (UV–vis and NMR) where the concentration of the substrates was higher.

2.2.3. Calorimetry. UV–vis titration with $H_2PO_4^-$ indicated the formation of 1:1 and 1:2 complexes and very high association constants (e.g., with **4** K>10^6 M^{-1}, Table 1). Therefore, calorimetric titrations were performed to additionally verify these observations,

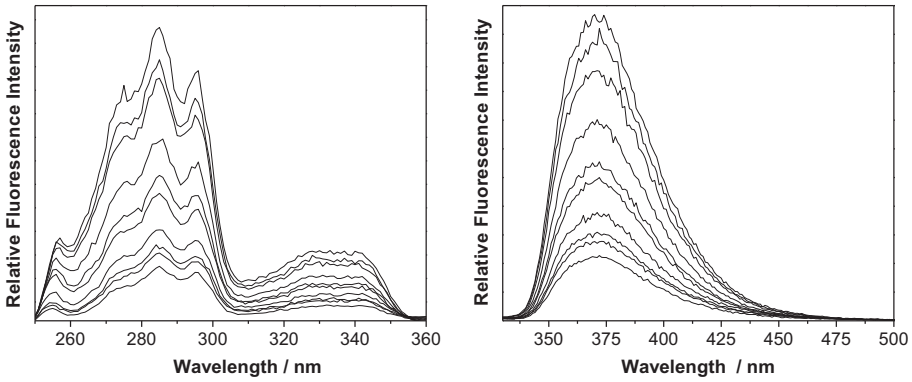


Fig. 3. Fluorescence titration of **3** with F^- in DMSO (left: excitation spectra, λ_{em}=370 nm, right: emission spectra, λ_{ex}=295 nm). The top curve corresponds to the solution of **3**, whereas the curves from top to bottom correspond to the solutions with increasing concentrations of Bu_4NF.

and get further insight into the thermodynamics of the complexation. The complexation of two anions, $H_2PO_4^-$ and OAc^- with **4** was investigated by microcalorimetric titrations. The addition of both $Bu_4NH_2PO_4$ or Bu_4NOAc into the solution of **4** in CH_3CN resulted in exothermic changes as a consequence of the complexation. The calorimetric titration curves were processed by nonlinear regression analysis to determine the stability constants of the complexes and the reaction enthalpies. As an example, the experimental and fitted data corresponding to the titration of **4** with Bu_4NOAc are shown in Fig. 4 (for the titration with $Bu_4NH_2PO_4$ see the Supplementary data).

2.2.4. NMR titrations. To verify the results obtained by UV–vis titrations and get more information about the geometry of the complexes in solution, NMR titrations were carried out. The titrations were performed for receptors **1**, **3**, and **4** with the following anions: F^-, Cl^-, OAc^-, and $H_2PO_4^-$. Generally, in all titrations the addition of anions induced significant downfield shifts of both signals assigned to the urea NH protons, indicating that anions formed H-bonded complexes with the urea moiety. Fitting the dependence of the chemical shift of the aromatic NH signal on the anion concentration by using the EQNMR program revealed the complex stoichiometries and the association constants (compiled

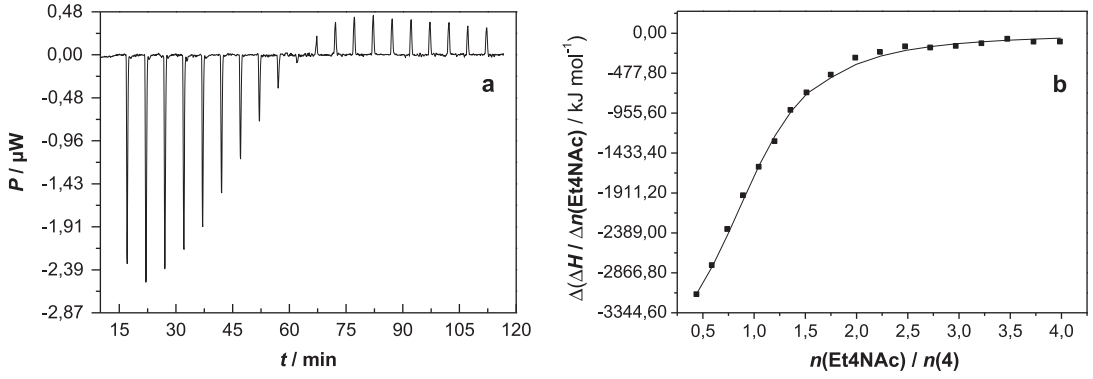


Fig. 4. Calorimetric titration of **4** ($c = 1.598\times10^{-4}$ M) with Bu_4NOAc (c=3.327×10^{-3} M) in CH_3CN, T=25 °C. (a) Raw ITC data. (b) Dependence of successive enthalpy change per mole of titrant on Bu_4NOAc/4 M ratio. ■ experimental values; —calculated values.

The stoichiometry of the complex of **4** with OAc^- was found to be 1:1, whereas in the case of $H_2PO_4^-$ the formation of complexes with both 1:1 and 1:2 (receptor:anion) stoichiometries was observed. These findings are in agreement with the results of the above described UV–vis titrations. The values of the stability constants (Table 2) agree relatively well with those obtained by UV–vis titrations. Standard reaction Gibbs energies and entropies were calculated using equations $\Delta_rG^\circ = RT\ \ln\ K$ and $\Delta_rG^\circ = \Delta_rH^\circ - T\ \Delta_rS^\circ$, respectively. By inspecting the data given in Table 2 it can be easily concluded that for both anions the enthalpic and entropic contributions to the overall stability of their 1:1 complexes with **4** are favorable, with the enthalpic one being predominant. On the other hand, formation of the complex comprising compound **4** and two $H_2PO_4^-$ anions is completely enthalpy driven, with unfavourable reaction entropy (Table 2). The Δ_rH° value for the 1:2 complex formation is higher than the one corresponding to the 1:1 complex. That can be tentatively rationalized by taking into account the possibility of an additional energetical stabilization caused by hydrogen bonding interactions between the two $H_2PO_4^-$ anions bound to **4**, whereas the preorganization of the receptor, which accompanies the binding process leads to the decrease in entropy.

in Table 3). In some cases characterized by the presence of complexes of several stoichiometries, the fitting could not reveal association constants accurately, so only approximate values are reported. The values of the estimated constants are generally lower

Table 3
Cumulative stability constants of the complexes with anions determined by NMR titrations [log (β_{11}/M^{-1})] or [log (β_{12}/M^{-2})][a]

Ion/Receptor	1	3	4
F^-	~2 (1:1) ~6 (1:2)[d]	2.36 (1:1)[b] ~4 (1:2)[c]	~2 (1:1) ~5 (1:2)[d]
Cl^-	1.54 (1:1)	2.29 (1:1)	1.66 (1:1)
OAc^-	3.32 (1:1) ~ 5 (1:2)	2.60 (1:1)	2.77 (1:1)
$H_2PO_4^-$	3.13 (1:1) ~ 6 (1:2)	~1 (1:1) ~4 (1:2)	~3 (1:1) ~5 (1:2)

[a] Titration performed in DMSO-d_6. The anion is added in the form of tetrabutylammonium salt. The error is estimated at±10%. Stoichiometries of the complexes are indicated in the parentheses (receptor:anion).
[b] Estimated H_2O content 0.14 M.
[c] Estimated H_2O content 0.02 M.
[d] Both complex stoichiometries were formed, 1:1 and 1:2; estimated H_2O content 0.02 M.

by 1–3 orders of magnitude than those obtained from the UV–vis titration. That is probably due to concentration of the receptor in the NMR experiment higher by two orders of magnitude wherein there is probably strong intermolecular interaction between the urea moieties resulting in the formation of weaker complexes with anions. In addition, the formation of higher molecular aggregates than simple stoichiometries cannot be disregarded.

To investigate if aggregation of the receptors takes places, NMR spectra were taken at different concentrations. For example, a 10-fold increase of the concentration of **2** induced downfield changes of the urea NH chemical shifts by 0.005 ppm (see Supplementary data). The observed downfield shift is in accordance with intermolecular interactions between the urea moieties.

The addition of F^-, the most basic anion, to the solutions of **1**, **3**, and **4** induced the most pronounced shifts of the urea NH signals, in accordance with the formation of stable complexes. However, it is interesting to note that almost negligible changes in the spectra were observed until the addition of the second equivalent of F^-. The fitting of the dependence of the $\Delta\delta$ on the F^- concentration indicated the formation of weak 1:1 complexes and much more stable 1:2 complexes. The titration with F^- can be demonstrated on the example of receptor **4**. Upon addition of the first equivalent of F^- negligible changes were observed, which became more pronounced on further increase of the F^- concentration. Since we observed only shifts in signals without the appearance of new signals, the finding indicates that there is a fast exchange between the complexed and the noncomplexed species. Finally, on approaching the F^- concentration equivalent to the ratio 1:4, the changes became smaller with a tendency of reaching a plateau. Thus, upon the addition of the fourth equivalent of F^-, the signal of the urea NH at the naphthalene moiety shifted from the value of δ 8.63 ppm (corresponding to the neat receptor) to ~11.8 ppm. The signal of the urea NH connected to the CH_2 group shifted from 6.25 to ~7.8 ppm (Fig. 5). Since the addition of 4 equivalents of basic F^- did not result in the disappearance of the NH signals, deprotonation of the urea probably does not take place. Shifting of both NH signals suggests that F^- is being bound by two H-bonds to one urea moiety. Besides the shifting of the NH signals, a smaller downfield shift of the C–H signal corresponding to the naphthalene position 3 was observed ($\Delta\delta$ ~0.1 ppm), suggesting its through-space interaction with the F^-. The other signals of the aromatic part of the spectrum exhibited no change or very small upfield shifts (up to $\Delta\delta$ ~0.05 ppm), in accordance with a small increase in electron density on the naphthalene moiety due to the partial formation of negative charge on the N atom in the complex.

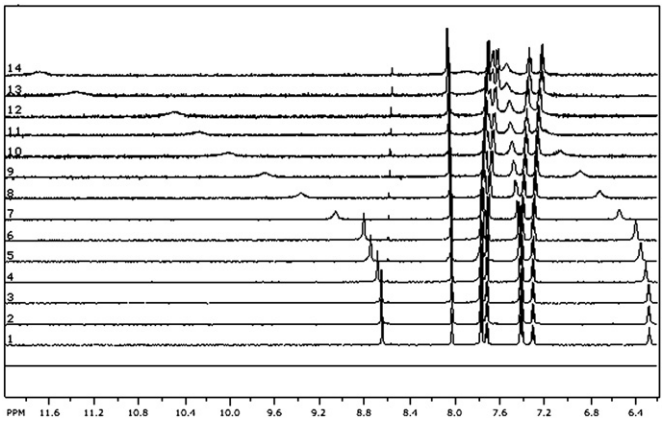


Fig. 5. Aromatic part of the NMR spectra obtained on titration of **4** with Bu_4NF. The bottom spectrum corresponds to ^1H NMR spectrum of **4** in DMSO, whereas spectra from bottom to top correspond to **4** with the increased concentration of Bu_4NF reaching the maximal ratio of anion:receptor=4:1.

In the aliphatic part of the spectrum of **4**, the addition of F^- resulted in upfield shifts in signals by up to 0.1 ppm (Fig. 6). The most pronounced difference in the aliphatic part of the spectrum due to the complexation was observed in the chemical shifts of the adamantane signals, which are assigned to the *endo*- and *exo*-H on the C4,9 and C8,10. For the neat receptor they appear as an 'AB quartet' (at δ 1.47 and 1.40 ppm, with the typical geminal coupling constant of 11.7 Hz). In the complex they appear as a broad singlet, that is, they become magnetically equivalent. This finding suggests that there is a free rotational mobility of the arms bearing a urea naphthalene moiety in the complex (Scheme 3). However, since there is an upfield shift of the methylene signal at the position 2 of the adamantane, we presume that A-**4**·2F^- conformation is more populated than B-**4**·2F^-. In the B-**4**·2F^- conformation, the F^- would probably induce anisotropic deshielding (downfield shift) of the signal corresponding to the C–H at the position 2. In addition, in B-**4**·2F^- there would probably be electronic repulsion between two F^- moieties that are close.

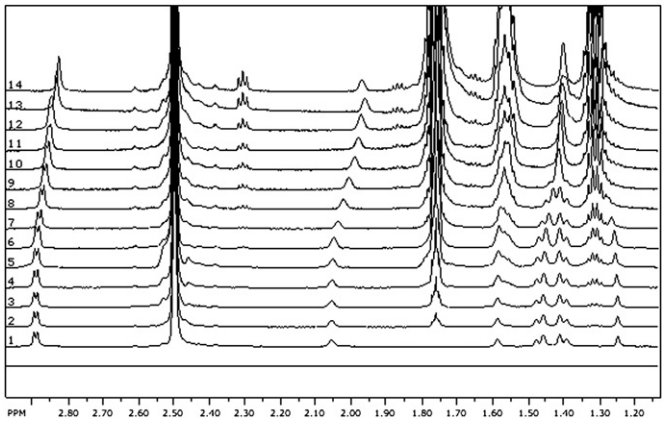
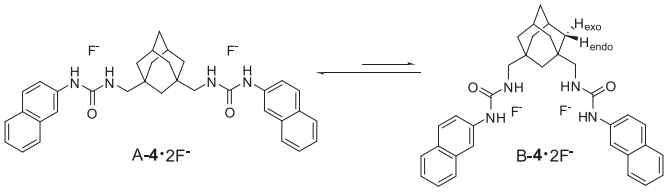


Fig. 6. Aliphatic part of the NMR spectra obtained on titration of **4** with Bu_4NF. The bottom spectrum corresponds to ^1H NMR spectrum of **4** in DMSO, whereas spectra from bottom to top correspond to **4** with the increased concentration of Bu_4NF reaching the maximal ratio of anion:receptor=4:1.



Scheme 3.

Titration of the other two receptors, **1** and **3**, with F^- resulted in similar spectral changes. However, it should be noted that changes of the chemical shifts upon addition of F^- (and accordingly, the estimated stoichiometry and the association constants), depend strongly on H_2O content. For example, titration of **3** with F^- was performed in DMSO containing different H_2O content. Changes in chemical shifts of the urea NH signals on F^- concentration are presented in Fig. 7, being much smaller in moist DMSO than in dry DMSO. The fitting of the data revealed the formation of a 1:1 complex in moist DMSO, whereas in dry DMSO 1:2 complex was formed. This finding clearly shows the large influence of the solvent polarity and the H-bonding ability to the complexation with ureas. The influence of solvation and ability of the solvent to participate in H-bonding to the complex stoichiometry has also been found for adamantane dipyrromethane anion receptors.[28]

To get further evidences about the structures of the complexes with F^-, NOESY spectra of the 1:1 complexes with **2** and **3** were

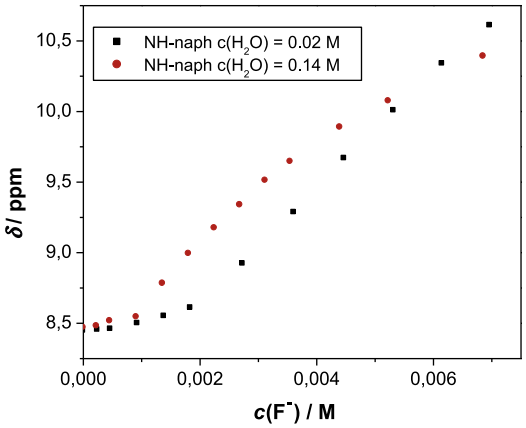
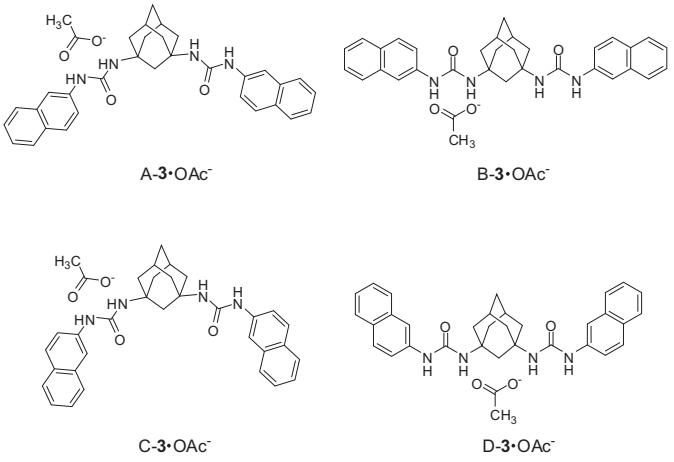


Fig. 7. Dependance of the chemical shift of the signal of the urea NH attached to the naphthalene in **3** on F^- concentration in DMSO at different H_2O content (estimated from the integral in ^1H NMR spectra).

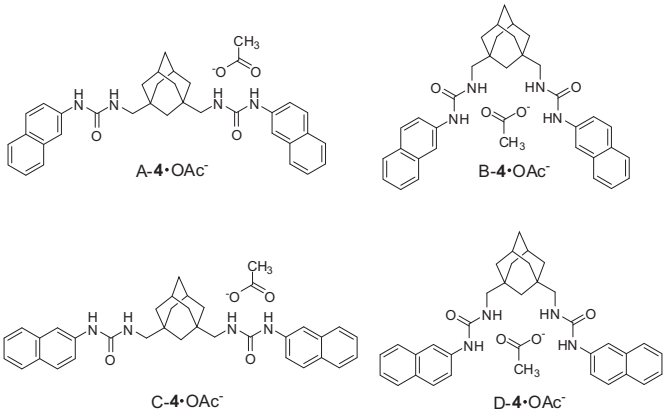
taken. However, no interaction was observed between the signals of the NH with the signals of the aliphatic or the aromatic part of the molecule. In addition, the signals of the tetrabutylammonium group and THF covered practically all aliphatic signals of the complexes.

Titration of **1**, **3**, and **4** with Cl^- induced very small changes in the NMR spectra (see Supplementary data). The urea NH signals of **1**, **3**, and **4** shifted downfield by $\Delta\delta$ 0.2, 0.1, and 0.2 ppm, respectively. The additions of Cl^- almost did not affect the other signals and only a weak influence to the adamantane *exo*- and the *endo*-H signals was observed, which became more magnetically equivalent. The fitting with the EQNMR revealed rather small values of the association constants of the complexes (Table 3).

The addition of OAc^- to the solutions of **1**, **3**, and **4** resulted in downfield shifts of the urea NH signals by $\Delta\delta \sim 1$–1.2 ppm. The fitting of the data indicated the presence of 1:1 complexes (except for **1**). Furthermore, since both NH signals exhibited similar differences in chemical shifts upon addition of OAc^-, it is reasonable to assume that one urea moiety is forming a complex with OAc^-, whereas the other one is not involved in the binding (contrary to the findings from the UV–vis titrations). The finding is additionally supported by the changes in the aliphatic part of the spectra wherein the signals for **3** and **4** corresponding to the adamantane *exo*- and *endo*-H changed the appearance from 'AB quartet' to singlet. That is, conformation B-**3**·OAc^- is more likely than D-**3**·OAc^- (Scheme 4). In addition, the observed changes in the aliphatic region of the spectrum suggest free rotation of the urea naphthalene moiety. In the aromatic region, in addition to the shifts of the NH signals, smaller downfield shifts of the C–H signals corresponding to the position C1 (0.06 ppm) and C4 (0.1 ppm) of the naphthalene moiety were observed. This suggests that OAc^- interacts through-space with both C–H, that is, there is a free rotation around the N–C bond between the urea and the naphthalene (giving rise to the conformations A and C of the complexes **3**·OAc^- and **4**·OAc^-, Schemes 4 and 5, respectively). The flexible receptor **1** can form a more stable complex with OAc^- than rigid adamantane derivatives **3** and **4**, as shown by the NMR and UV–vis titration data. Probably a relatively small OAc^- could not fit well into a cleft of the rigid skeleton of the conformers D of the complex **3**·OAc^-, or conformers B and D of the complex **4**·OAc^-, and hence, does not form very stable complexes ($K<10^3$ M^{-1}).

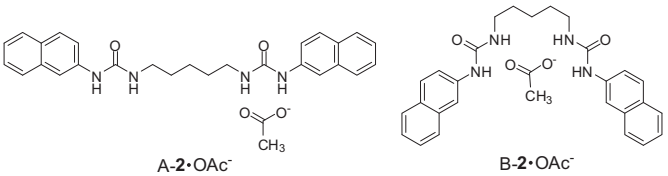


Scheme 4.



Scheme 5.

NOESY spectra of the complexes **2**·OAc^- and **3**·OAc^- support the findings observed in the titration experiments. For both complexes, the NOE interactions were observed between the urea NH proximal to the naphthalene and the naphthalene CH atoms at the positions 1 and 3. The finding is in agreement with free rotation of the naphthalene moiety and the existence of the conformers A-**3**·**OAc**$^-$ and C-**3**·**OAc**$^-$. Furthermore, in a spectrum of **3**·AcO^-, a stronger NOE interaction was observed between the urea NH (connected to the adamantane moiety) and the adamantane *endo*- and *exo*-H atoms than between the urea NH and the adamantane H-atoms at the position 2. The finding is in agreement with the geometry of the complex where one arm holds anion as in A-**3**·**OAc**$^-$ and C-**3**·**OAc**$^-$ (or the corresponding A-**4**·OAc^- and C-**4**·OAc^-). In the NOESY spectrum of **2**·OAc^-, the interactions were observed between the NH connected to the aliphatic chain and the CH_2 at the α- and the β-position to the urea moiety. In addition, a NOE interaction was observed between the acetyl group and the urea NH connected to the naphthalene. The latter interaction strongly suggests a folded conformation of the complex, as in B-**2**·OAc^-. Such an interaction would be less likely in a complex A-**2**·OAc^- (Scheme 6).



Scheme 6.

The NMR titration with $H_2PO_4^-$ induced different changes in the spectra than titration with other anions. In the aromatic part of the spectra, similarly to previous examples, the signal of the urea NH connected to the naphthalene shifted to the lower magnetic field

~2 ppm, whereas the signal of the NH connected to the aliphatic part of the molecule shifted ~1 ppm (Fig. 8 and the Supplementary data). In the aromatic part of the spectrum pronounced difference was also observed in the signal of the C–H at the position 3 of the naphthalene, whereas other signals exhibited almost no change. The finding suggests prevalence of conformers A and D (compared to C and B, respectively) for the complex **3**·$H_2PO_4^-$ (Scheme 7), and **4**·$H_2PO_4^-$ (Scheme 8).

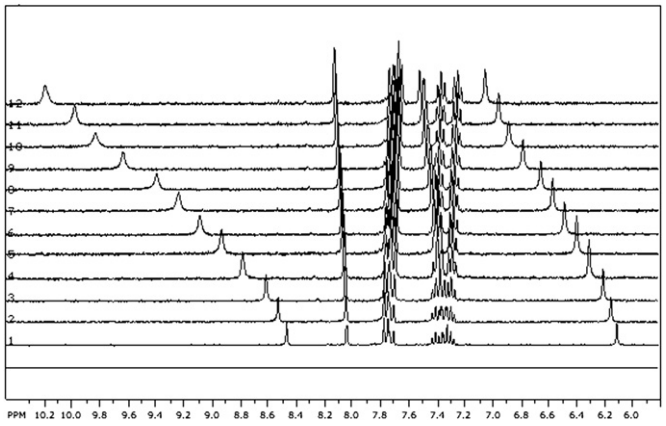
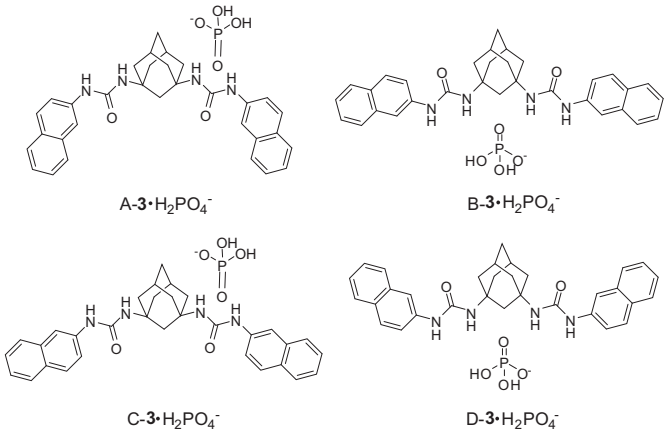
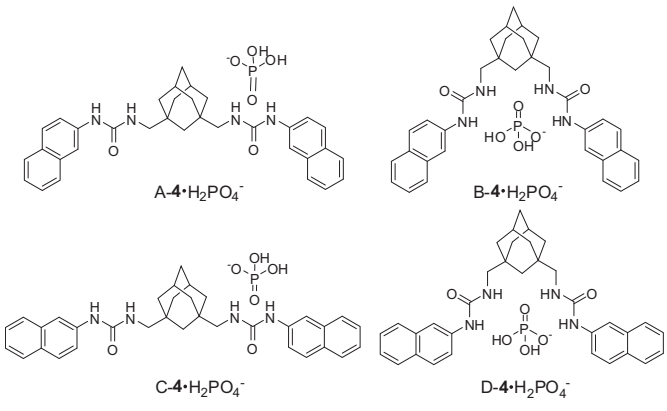


Fig. 8. Aromatic part of the NMR spectra obtained on titration of **3** with $Bu_4NH_2PO_4$. The bottom spectrum corresponds to ^{1}H NMR of **3** in DMSO, whereas spectra from bottom to top correspond to **3** with increased concentration of $Bu_4NH_2PO_4$ reaching the maximal ratio of anion:receptor=4:1.



Scheme 7.



Scheme 8.

The aliphatic part of the spectra observed on titration of **3** and **4** with $H_2PO_4^-$ clearly indicated the formation of different complex species depending on the $H_2PO_4^-$ concentration. At lower $H_2PO_4^-$, up to the addition of 0.5 equiv of the anion, signals corresponding to the *exo*- and the *endo*-H atoms of the C4,9 and C8,10 of the adamantane moiety become more magnetically equivalent (spectra 1–3, Fig. 9). Further increase in $H_2PO_4^-$ concentration induced differentiation of the signals, which started to appear as an 'AB quartet', and finally upon addition of four $H_2PO_4^-$ equivalents, as two doublets with very large difference in chemical shifts (0.7 ppm). Fitting of the dependence of the NH chemical shifts on the $H_2PO_4^-$ concentration indicated the formation of 1:1 and 1:2 stoichiometries.

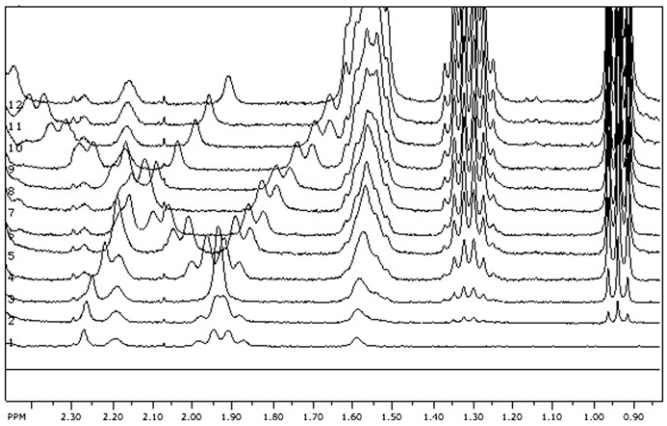
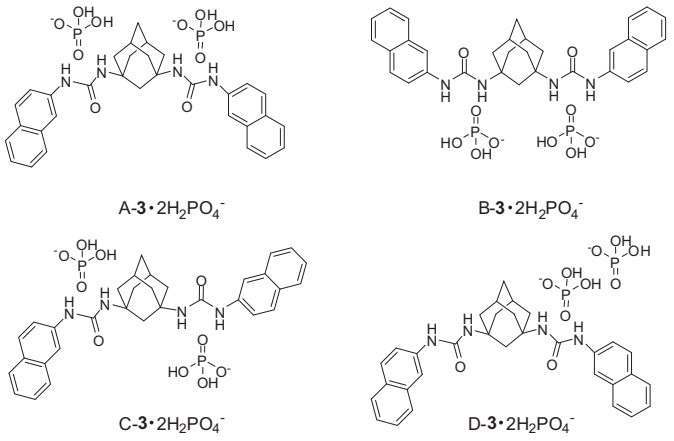


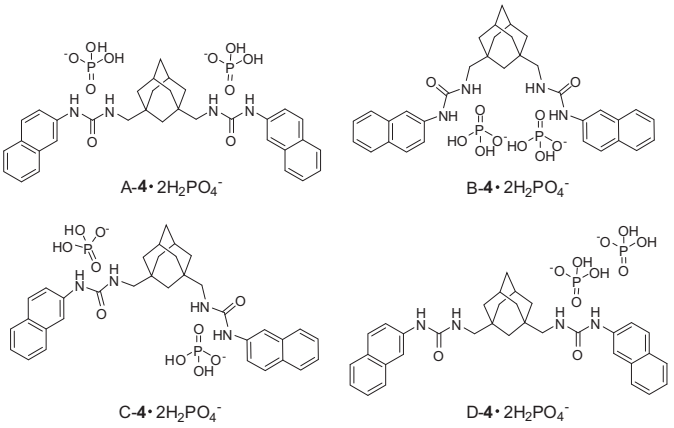
Fig. 9. Aliphatic part of the NMR spectra obtained on titration of **3** with $Bu_4NH_2PO_4$. The bottom spectrum corresponds to ^{1}H NMR of **3** in DMSO, whereas spectra from bottom to top correspond to **3** with increased concentration of $Bu_4NH_2PO_4$ reaching the maximal ratio of anion:receptor=4:1.

What is the geometry of the $H_2PO_4^-$ complexes? The observed changes in the aliphatic part of the spectrum at low $H_2PO_4^-$ concentration strongly suggest that the anion is being bound by two urea moieties forming a symmetric structure (conformers B and D of the complex **3**·$H_2PO_4^-$, Scheme 7, or **4**·$H_2PO_4^-$, Scheme 8). The other less likely option that cannot be disregarded is binding of the anion by one urea moiety (conformations A and C) and fast exchange between all conformations (Schemes 7 and 8). Large shifts in signals corresponding to the *endo*- and *exo*-H of the adamantane on the increase of anion concentration after addition of the first anion equivalent indicate that **3**·$2H_2PO_4^-$ or **4**·$2H_2PO_4^-$ are characterized by different geometry than the corresponding 1:1 complexes. In addition to changes in the chemical shift of the *endo*- and *exo*-H signals there is also a large upfield shift of the adamantane C–H signal at the position 2 (0.4 ppm). These findings suggest that two anions are not being bound in the cleft formed by two urea moieties resulting in a symmetric structure like B-**3**·$2H_2PO_4^-$ or B-**4**·$2H_2PO_4^-$ (wherein the anions would induce a downfield shift due to the anisotropic effect). Furthermore, taking into account that $H_2PO_4^-$ has a tendency to form dimeric structures,[8c] the results from NMR titration suggest that two $H_2PO_4^-$ form complexes with **3** and **4** wherein one urea binds two $H_2PO_4^-$ giving a bulky arm with restricted rotation (structure D, Schemes 9 and 10). On the other hand, the geometry of the complex represented by B-**4**·$2H_2PO_4^-$ is suggested due to very high stability of the 1:2 complexes of **3** and **4** with $H_2PO_4^-$. Namely, in conformation B, the complex should be very stable due to multiple H-bonds between the anion and the ureas, as well as between the anions themselves. However, the geometry wherein each $H_2PO_4^-$ is being bound by one urea arm (e.g., C-**4**·$2H_2PO_4^-$) is also possible in principle, although less likely.

To get answers to topological questions that arose from the NMR titrations with $H_2PO_4^-$ the NOESY spectra of the complexes



Scheme 9.



Scheme 10.

2·$H_2PO_4^-$, **3**·$H_2PO_4^-$, and **3**·$2H_2PO_4^-$ were taken. In the NOESY spectrum of **3**·$H_2PO_4^-$, a stronger interaction was observed between the urea NH atom (connected to the adamantane) and the adamantane CH at the position 2, than with the adamantane *endo*- and *exo*-H atoms. The finding suggests a prevalence of the conformers B-**3**·$H_2PO_4^-$ and D-**3**·$H_2PO_4^-$ (Scheme 7). In addition, NOESY spectrum showed interaction of the NH connected to the naphthalene with the naphthalene CH atoms at the position 1 and 4. The latter finding is in accordance with the free rotation of the naphthalene moiety. Similar to **3**·$H_2PO_4^-$, in the NOESY spectrum of **3**·$2H_2PO_4^-$, a stronger interaction was observed between the urea NH connected to adamantane and the adamantane CH at the position 2, than with the *endo*- and the *exo*-H atoms. The finding indicates prevalence of the complex geometry B-**3**·$2H_2PO_4^-$ (Scheme 9). However, the NH connected to the naphthalene is also in a NOE interaction with the *exo*-H atoms of the adamantane. The latter interaction suggests that **3**·$2H_2PO_4^-$ exists also in the conformations A-**3**·$2H_2PO_4^-$ or D-**3**·$2H_2PO_4^-$. That is, the complexed species probably represent a dynamic system wherein different conformers are engaged in fast dynamic exchange. However, in the aromatic region of the spectrum, a NOE interaction was observed between the NH and the naphthalene CH at the position 3 (and not at the position 1), suggesting that there is no free rotation of the naphthalene moiety in the complex **3**·$2H_2PO_4^-$. In the NOESY spectrum of **2**·$H_2PO_4^-$ no interaction was observed between the aromatic or the NH signals with the aliphatic CH atoms that would indicate prevalence of any complex conformations.

3. Conclusion

New alkylenebisurea derivatives **1**–**5** were synthesized and their binding with anions, F^-, Cl^-, Br^-, AcO^-, HSO_4^-, NO_3^- and $H_2PO_4^-$ was investigated. In CH_3CN or DMSO solutions, urea receptors **1**–**5** form complexes with all anions studied. The strongest binding is observed with $H_2PO_4^-$ and F^-. Introducing an additional urea binding site generally increases anion binding ability of the adamantane-urea receptors, that is, the stability of the complexes significantly depends on the number of possible H-bonding interactions between the host and the receptor. The finding may be due to the statistical reason because of dynamic exchange of the complex conformations. However, the data strongly indicates that the stability of the complexes depends on the geometry and preorganization of the hosts. The strongest binding and the best selectivity can be attained with constrained receptors with some molecular mobility. The most flexible receptor, on the other hand, formed less stable 1:1 complexes due to probable intramolecular urea interactions. Rigid adamantane receptors showed stronger binding of $H_2PO_4^-$, compared to the flexible alkyl derivatives. On the contrary, the binding of OAc^- was hindered by molecular rigidity. The most stable complexes were formed with $H_2PO_4^-$ and receptor **4**, characterized by stoichiometry 1:2 and the association constant among the highest reported for urea-anion complexes. Besides geometry, the solvent plays a pivotal role in the complexation. Change in solvent polarity and H-bond donating ability induces changes in complex stoichiometries and selectivity of an anion receptor. Thermodynamics of the complexation of **4** with $H_2PO_4^-$ and OAc^- in CH_3CN was examined by isothermal calorimetry. The enthalpic contribution to the overall complex stability was found to be the predominant one. The changes in entropy for the formation of 1:1 complexes were positive, whereas for the formation of 1:2 complex of $H_2PO_4^-$ with receptor **4** the calculated $\Delta_r S^\circ$ had negative value. The binding results from this study provide some data, that is useful in the rational design of the future molecular receptors for anions currently underway in our laboratory.

4. Experimental

4.1. General

^1H and ^{13}C NMR spectra were recorded on a Bruker Spectrometer at 300 or 600 MHz. All NMR spectra were measured in $CDCl_3$ using tetramethylsilane as a reference. High-resolution mass spectra (HRMS) were measured on an Applied Biosystems 4800 Plus MALDI TOF/TOF instrument. Melting points were obtained using an Original Kofler apparatus and are uncorrected. IR spectra were recorded on Perkin–Elmer M-297 and ABB Bomem M-102 spectrophotometers. Solvents were purified by distillation. Adamantane diacids[29] were prepared in the laboratory according to known procedure. β-Naphthyl amine and naphthalene-2-carboxylic acid were obtained from the usual commercial sources.

*4.1.1. 1,1′-(Propane-1,3-diyl)-bis[3-(naphthalen-2-yl)urea] (**1**).* A round-bottom flask (50 mL) equipped with a condenser and N_2 inlet was charged with naphthalene-2-carboxylic acid (200 mg, 1.16 mmol). Under a stream of N_2 the acid was suspended in anhydrous toluene (10 mL). To the suspension triethylamine (180 μL, 1.28 mmol) was added, and the suspension was stirred at rt for 45 min, and than, diphenylphosphoryl azide DPPA (290 μL, 1.34 mmol) was added. The reaction mixture was heated at 40 °C for 1 h, and after that 4 h at reflux. To the mixture, a solution of 1,3-propane diamine (50 μL, 0.58 mmol) in 1 mL of dry toluene was added, and refluxing was continued for 16 h. The solvent was removed on a rotational evaporator and the residue treated with methanol. The white precipitate was filtered off, washed with water and methanol, and dried in vacuum (100 mbar) at 60 °C for

1h to afford 175 mg (73%) of pure product **1**. Colorless crystals, mp 273–275 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ/ppm 8.73 (br s, 2H, NH), 8.04 (d, 2H, J=1.4 Hz), 7.68–7.81 (m, 6H), 7.37–7.50 (m, 4H), 7.31 (dt, 2H, J=7.5 Hz, J=0.9 Hz), 6.30 (t, 2H, J=5.7 Hz, NH), 3.15–3.26 (m, 4H), 1.59–1.71 (m, 2H); ^{13}C (DMSO-d_6, 75 MHz) δ/ppm 155.41 (s, 2C), 138.22 (s, 2C), 133.79 (s, 2C), 128.68 (s, 2C), 128.14 (d, 2C), 127.34 (d, 2C), 126.71 (d, 2C), 126.13 (d, 2C), 123.46 (d, 2C), 119.50 (d, 2C), 112.54 (d, 2C), 36.60 (t, 2C), 30.72 (t, 1C); IR (KBr) ν_{max}/cm^{-1} 1231 (m), 1279 (m), 1561 (s), 1623 (s), 2870 (w), 2939 (w), 3299 (m), 3338 (m); HRMS (MALDI): MH$^+$ found 413.1980. $C_{25}H_{25}N_4O_2$ requires 413.1972.

4.2. General procedure for the preparation of ureas 2–5

A round-bottom flask (50 mL) equipped with a condenser and N_2 inlet was charged with carboxylic acid (1 mmol). Under a stream of N_2 the acid was suspended in anhydrous toluene (10 mL). To the suspension, triethylamine (2 mmol, 1 mmol for **5**) was added, and the suspension was stirred at rt for 45 min, and then, diphenylphosphoryl azide DPPA (2.1 mmol, 1.1 mmol for **5**) was added. The reaction mixture was heated at 40 °C for 1 h, and after that 4 h at reflux. To the mixture, a solution of β-naphthylamine (2 mmol, 1 mmol for **5**) in 1 mL of dry toluene was added, and refluxing was continued for 16 h. The solvent was removed on a rotational evaporator and the residue treated with methanol. Product in the form of precipitate was filtered off, washed with water and methanol, and dried in vacuum (10 mbar) at 40 °C for 1 h.

*4.2.1. 1,1′-(Pentane-1,5-diyl)-bis[3-(naphthalen-2-yl)urea] (**2**).* Obtained from pimelic acid (200 mg, 0.79 mmol), triethylamine (245 μL, 1.74 mmol), DPPA (395 μL, 1.82 mmol), and 2-aminonaphthalene (250 mg, 1.74 mmol), in 15 mL of dry toluene. Colorless crystals (82%, 450 mg), mp 264–265 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ/ppm 8.63 (br s, 2H, NH), 8.03 (d, 2H, J=1.6 Hz), 7.68–7.80 (m, 6H), 7.36–7.48 (m, 4H), 7.30 (dt, 2H, J=7.5, 1.0 Hz), 6.25 (t, 2H, J=5.6 Hz, NH), 3.13 (dd, 4H, J=12.3 Hz), 1.44–1.57 (m, 4H), 1.32–1.42 (m, 2H); ^{13}C (DMSO-d_6, 75 MHz) δ/ppm 155.29 (s, 2C), 138.26 (s, 2C), 133.84 (s, 2C), 128.67 (s, 2C), 128.20 (d, 2C), 127.37 (d, 2C), 126.75 (d, 2C), 126.17 (d, 2C), 123.47 (d, 2C), 119.48 (d, 2C), 112.43 (d, 2C), 39.08 (t, 2C), 29.56 (t, 1C) 23.86 (t, 1C); IR (KBr) ν_{max}/cm^{-1} 1252 (m), 1561 (s), 1625 (s), 2861 (w), 2934 (w), 3334 (m); HRMS (MALDI): MH$^+$ found 441.2296. $C_{27}H_{29}N_4O_2$ requires 441.2285.

*4.2.2. 1,1′-(Adamantane-1,3-diyl)-bis[3-(naphthalen-2-yl)urea] (**3**).* Obtained from 1,3-adamantane dicarboxylic acid (200 mg, 0.89 mmol), triethylamine (275 μL, 1.96 mmol), DPPA (440 μL, 2.05 mmol), and 2-aminonaphthalene (281 mg, 1.96 mmol), in 15 mL of dry toluene. Colorless crystals (36%, 160 mg), mp 259–260 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ/ppm 8.46 (br s, 2H, NH), 8.04 (br s, 2H), 7.68–7.80 (m, 6H), 7.26–7.44 (m, 6H), 6.10 (br s, 2H, NH), 2.28 (br s, 2H), 2.20 (br s, 2H), 1.97 (d, 4H, J=11.3 Hz), 1.90 (d, 4H, J=11.3 Hz), 1.59 (br s, 2H); ^{13}C NMR (DMSO-d_6, 150 MHz) δ/ppm 154.31 (s, 2C), 138.27 (s, 2C), 134.03 (s, 2C), 128.83 (s, 2C), 128.43 (d, 2C), 127.55 (d, 2C), 126.93 (d, 2C), 126.42 (d, 2C), 123.69 (d, 2C), 119.53 (d, 2C), 112.50 (d, 2C), 51.68 (t, 1C), 46.06 (s, 2C), 40.94 (t, 4C), 35.23 (t, 1C), 29.59 (d, 2C); IR (KBr) ν_{max}/cm^{-1} 1222 (m), 1351 (m), 1557 (s), 1681 (s), 2912 (m), 3299 (m), 3613 (s); HRMS (MALDI): MH$^+$ found 505.2562. $C_{32}H_{33}N_4O_2$ requires 505.2598.

*4.2.3. 1,1′-[(Adamantane-1,3-diyl)dimethylene]-bis[3-(naphthalen-2-yl)urea] (**4**).* Obtained from 1,3-adamantane diacetic acid (200 mg, 0.79 mmol), triethylamine (245 μL, 1.74 mmol), DPPA (395 μL, 1.82 mmol), and 2-aminonaphthalene (250 mg, 1.74 mmol), in 15 mL of dry toluene. Colorless crystals (45%, 190 mg), mp 237–238 °C; ^{1}H NMR (DMSO-d_6, 600 MHz) δ/ppm 8.63 (br s, 2H, NH), 8.03 (d, 2H, J=2.0 Hz), 7.77 (d, 4H, J=8.9 Hz), 7.72 (d, 2H, J=8.0 Hz), 7.39–7.43 (m, 4H), 7.30 (dt, 2H, J=8.0, 1.1 Hz), 6.25 (t, 2H, J=6.0 Hz, NH), 2.90 (d, 4H, J=6.0 Hz), 2.06 (br s, 2H), 1.59 (br s, 2H), 1.47 (d, 4H, J=11.7 Hz), 1.40 (d, 4H, J=11.7 Hz), 1.25 (br s, 2H); ^{13}C (DMSO-d_6, 150 MHz) δ/ppm 155.52 (s, 2C), 138.27 (s, 2C), 133.88 (s, 2C), 128.68 (s, 2C), 128.28 (d, 2C), 127.41 (d, 2C), 126.77 (d, 2C), 126.22 (d, 2C), 123.49 (d, 2C), 119.38 (d, 2C), 112.27 (d, 2C), 50.52 (t, 2C), 42.49 (s, 2C), 39.39 (t, 4C), 36.09 (t, 1C), 34.14 (t, 1C), 27.85 (d, 2C); IR (KBr) ν_{max}/cm^{-1} 1243 (m), 1557 (s), 1645 (s), 2902 (m), 3309 (w), 3340 (m); HRMS (MALDI): MH$^+$ found 533.2904. $C_{34}H_{37}N_4O_2$ requires 533.2911.

*4.2.4. 1-(Adamantane-1-yl)-3-(naphthalen-2-yl)methylurea (**5**).* Obtained from adamantane-1-acetic acid (200 mg, 1.03 mmol), triethylamine (160 μL, 1.13 mmol), DPPA (260 mg, 1.18 mmol), and 2-aminonaphthalene (147 mg, 1.03 mmol), in 15 mL of dry toluene. Colorless crystals (43%, 143 mg), mp 217–219 °C; ^{1}H NMR (DMSO-d_6, 600 MHz) δ/ppm 8.57 (br s, 1H, NH), 8.01 (d, 1H, J=1.8 Hz), 7.77 (d, 2H, J=8.6 Hz), 7.72 (d, 2H, J=8.2 Hz), 7.38–7.43 (m, 2H), 7.30 (dt, 1H, J=7.6, 1.0 Hz), 6.19 (t, 1H, J=6.1 Hz, NH), 2.84 (d, 2H, J=6.1 Hz), 1.96 (br s, 3H), 1.69 (d, 3H, J=12.1 Hz), 1.61 (d, 3H, J=12.1 Hz), 1.46–1.50 (m, 6H); ^{13}C NMR (DMSO-d_6, 150 MHz) δ/ppm 155.43 (s, 1C), 138.24 (s, 1C), 133.82 (s, 1C), 128.61 (s, 1C), 128.19 (d, 1C), 127.33 (d, 1C), 126.69 (d, 1C), 126.13 (d, 1C), 123.39 (d, 1C), 119.31 (d, 1C), 112.20 (d, 1C), 50.71 (t, 1C), 39.74 (t, 3C), 36.56 (t, 3C), 33.46 (s, 1C), 27.67 (d, 3C); IR (KBr) ν_{max}/cm^{-1} 1241 (m), 1559 (s), 1647 (s), 2899 (m), 3305 (w), 3350 (w); HRMS (MALDI): MH$^+$ found 335.2115. $C_{22}H_{27}N_2O$ requires 335.2118.

4.3. UV–vis titrations

The anion receptor was dissolved in CH_3CN or DMSO in the concentration range 10^{-4}–10^{-5} M, corresponding to a absorbance maximum in the range 0.5–1.5. A solution of the receptor was placed in a quartz cuvette (1 mL) and small volumes (5–20 μL) of the following solutions of anion were added: Bu_4NF (1 M in THF, containing <wt 5% H_2O, diluted with CH_3CN or DMSO to 1×10^{-3} M), Bu_4NCl, Bu_4NBr, Bu_4NOAc, Bu_4NHSO_4, Bu_4NNO_3 or $Bu_4NH_2PO_4$ (from 1×10^{-2} to 1×10^{-5} M in CH_3CN or DMSO). After each addition, UV–vis spectra were recorded. The titrations were performed at rt (20 °C). The data were analyzed by SPECFIT program to reveal the stability constants of the complexes.

4.4. Fluorescence titrations

The anion receptor was dissolved in CH_3CN or DMSO in the concentration range 10^{-5}–10^{-6} M, corresponding to an absorbance maximum in the range 0.08–0.1. The solution of the receptor was placed in a quartz cuvette (2 mL) and small volumes (10 μL) of the solutions of anion are added: Bu_4NF (1 M in THF, containing <wt 5% H_2O, diluted with DMSO to 1×10^{-3} M), or $Bu_4NH_2PO_4$ (from 1×10^{-2} to 1×10^{-5} M in DMSO). After each addition, fluorescence spectra were recorded, using the excitation wavelength at 295 nm, or emission at 370 nm. The titrations were performed at rt (20 °C).

4.5. Calorimetry

Microcalorimetric measurements were performed by an isothermal titration microcalorimeter Microcal VP-ITC at 25.0 °C. Origin 7.0 software, supplied by the manufacturer, was used for the data acquisition and manipulation. The calorimeter was calibrated electrically and its reliability was checked by carrying out the complexation of barium(II) by 18-crown-6 in aqueous medium at 25 °C. The results obtained (log K=3.76, Δ_rH=31.9 kJ mol^{-1}) were in good agreement with the literature values (log K=3.77, Δ_rH=31.4 kJ mol^{-1}).[30]

During titrations, the enthalpy changes were recorded upon stepwise addition of the CH_3CN solution of Bu_4NOAc or $Bu_4NH_2PO_4$ (V=10 or 15 μL) into solution of **4** ($c \approx 1.6\times10^{-3}$ M, V_0=1.4182 cm^3). Blank experiments were carried out in order to obtain heats of dilution of salt solutions, which were subtracted from the heats measured in the complexation experiments. The dependence of successive enthalpy changes on the volume of the added titrant was processed by non-linear least-square fitting procedure using OriginPro 7.5 program. All measurements were done in triplicate.

4.6. NMR titrations

In an NMR tube was placed 0.5 mL of the DMSO-d_6 solution of **3**, **4** or **1**. The concentration of the **3**, **4** or **1** in the NMR experiment was typically 0.05 M. To the solution in the tube was added a solution of Bu_4NF (1 M in THF, containing <wt 5% H_2O) or Bu_4NCl, Bu_4NBr, Bu_4NHSO_4, $Bu_4NH_2PO_4$, Bu_4NOAc, Bu_4NNO_3 (~0.5 M in DMSO-d_6). The concentrations of the salt ranged from 0.01 to 0.1 M, reaching the maximal ratio of anion:receptor=4:1. After each addition, NMR spectra were recorded. The association constants were determined by fitting the dependence of the chemical shift of the NH signal ($\Delta\delta$) to the anion concentration, using EQNMR program.[21]

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Supplementary data

UV–vis binding data (Job plots, UV–vis titrations), NMR titrations data, ^1H and ^{13}C NMR spectra of compounds **1**–**5**. Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2011.03.096.

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