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Recognition of Anions and Neutral Guests by Dicationic Pyridine-2,6-dicarboxamide Receptors

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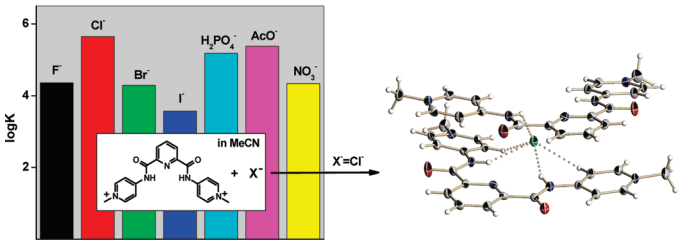

Dicationic N-methylated at pyridyl or quinolyl moieties derivatives of three isomers of *N*,*N*′-bis(pyridyl)-pyridine-2,6-dicarboxamide (*o*-, *m*-, and *p*-**1**) and of *N*,*N*′-bis(3-quinolyl)pyridine-2,6-dicarboxamide (**4**) strongly bind anions in MeCN (log *K* in the range 3.5−6.5) with pronounced selectivity for Cl^- and also bind neutral urea and amide guests with log *K* in the range 1.1−2.8. Crystal structures of the triflate salts of *m*-**1**, *p*-**1**, and **4** show that amide NH and pyridinium *o*-CH groups are directed inside the receptor cleft with their four protons forming a circle of radius ca. 2.35 Å optimal for inclusion of Cl^-. The binding of anions to these protons is evident from the crystal structure of a mixed triflate/chloride salt of *p*-**1**, calculated (DFT/B3LYP 6-31G**) structures of 1:1 complexes of all receptors with Cl^-, and results of ^{1}H NMR titrations. In the crystal structure of *o*-**1** pyridinium N-Me^+ groups are directed inside the receptor cleft impeding the anion complexation, but calculations demonstrate that simple rotation of pyridinium rings in opposite directions by ca. 30° creates a cavity to which the Cl^- ion can fit forming 4 hydrogen bonds to amide NH and aliphatic CH groups of N-Me^+. The results of ^{1}H NMR titrations confirm this type of binding in solution. Anions quench the intense fluorescence of **4**, which allows their fluorescent sensing in the μM range. A new methodology for determination of anion binding constants to strongly acidic receptors by inhibitory effects of anions on the receptor deprotonation by an external base has been developed. High affinity and selectivity of anion complexation by dicationic pyridine-2,6-dicarboxamides is attributed to the rigid preorganized structure of receptors, the high acidity of NH and CH groups, and the electrostatic charge effect.

Introduction

The design of new receptors for anions continues to be an active area of research.[1] Among the most popular building blocks for such receptors are substituted diamides of isophthalic and pyridine-2,6-dicarboxylic acids,[1−6] which are also employed for recognition of neutral guests like ureas or sulfoxides.[7,8] Several approaches for improving their binding properties by preorganizing and increasing acidity of amide NH donor groups were proposed including internal Lewis acid coordination of the amide oxygens with boronate groups,[9] internal hydrogen bonding of the amide oxygens

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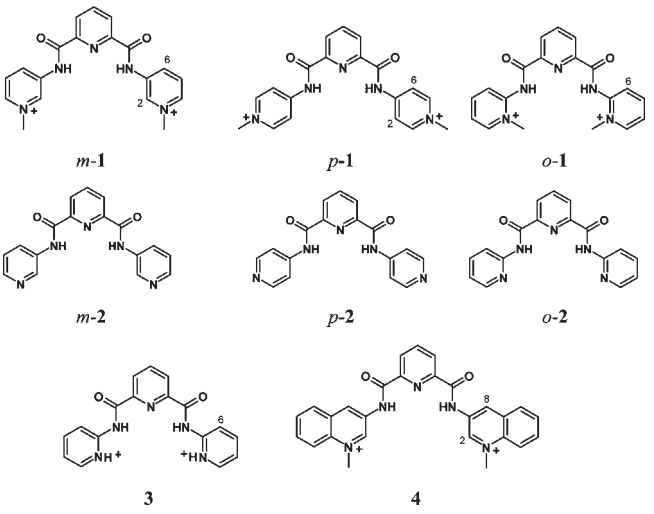
SCHEME 1. Pyridine-2,6-dicarboxamide Receptors Employed in This Study



to properly positioned hydroxyl groups,[10] changing amide to thioamide derivatives,[11] and incorporation of strong electron accepting substituents.[12] In this paper we explore to what extent the affinity and selectivity of pyridine-2,6-dicarboxamide receptors can be modified by incorporation of positive charges into their structures. To this end the dicationic receptors *o*-**1**, *m*-**1**, and *p*-**1** have been prepared by methylation of the respective neutral bisamides *o*-**2**, *m*-**2**, and *p*-**2** (Scheme 1). We chose this way of modification expecting that besides providing an extra electrostatic attraction the quaternization of aminopyridine moieties of **2** will acidify CH and NH bonds of the receptors making them better proton donors for hydrogen bonding of both anions and neutral guests. In addition, when carrying out the same reaction with appropriate alkylating reagents, these cationic dicarboxamide fragments could be incorporated easily into more sophisticated polyfunctional or macrocyclic receptors. Two additional structurally related to **1** receptors **3** and **4** were prepared. Diprotonated receptor **3** was chosen as a sterically unconstrained analogue for *o*-**1**, which in addition could provide a bidentate anion complexation through amide and pyridinium NH donors. The quinoline derivative **4** was prepared as a fluorescent analogue of **1** to explore a possibility of optical sensing of anions by receptors of this type. This compound has been reported previously as a selective G-quadruplex ligand, but its structure was not determined and its interactions with anions were not studied.[13]

Receptors combining *N*-alkylpyridinium and amide groups were first prepared and employed for binding of carboxylates by Jeong and Cho,[14] who also demonstrated the involvement of both amide NH and pyridinium CH groups in the hydrogen bonding of the anion. The importance of interactions with CH groups became particularly clear after demonstration that bidentate binding of anions to only one ureido NH donor and a pyridinium CH proton donor in tricationic tripodal tris(urea) receptors can compete with chelation of anions by two NH donors of a single ureido group present in the same receptor molecule.[15] Functionally related cationic 3-amino-1-alkylpyridinium receptors were prepared and employed for studies of conformational aspects of anion complexation.[16] Monocationic and tricationic *N*-alkylpyridinium receptors containing sulfonamide or pyrrole moieties were found to provide highly efficient anion complexation via simultaneous binding to NH and pyridinium CH proton donors.[17] Monocationic carboxamide-1-alkylpyridinium receptors were used for anion-templated pseudorotaxane formation.[18] Another type of cationic receptor, which bind anions through $CH\cdots X^-$ interactions, constitute imidazolium derivatives.[19,20]

A dicationic bisamide receptor derived from isophthalic acid and two 3-aminopyridine molecules quaternized by methylanthracene groups, which is a close analogue to *m*-**1**, has been recently reported.[21] The receptor showed a modest affinity to AcO^- and F^- (log *K* between 3 and 4 in MeCN) and did not bind other halide anions. A possible reason for the low affinity of this receptor is the unfavorable conformation of the isophthalamide fragment, which often leads to much weaker anion binding by these derivatives as compared to better preorganized pyridine-2,6-dicarboxamides.[3,4]

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For most of the *N*-alkylpyridinium systems discussed above no comparison was made between cationic and parent neutral receptors, but the binding data show that cationic receptors generally offer higher affinity and selectivity than would be expected for respective neutral molecules. In several instances the peak selectivity for Cl^- was reported.[16−18] The charge effect on anion binding by polyamide receptors was studied recently by converting neutral monocyclic and bicyclic receptors into dications by quaternization of two bridging amino groups and appeared to be a complex phenomenon.[22] With monocyclic receptors cationic derivatives clearly showed stronger affinity than their neutral counterparts, but with bicyclic receptors the effect was less significant and conformational changes were more important than additional electrostatic attraction of anions. One of the purposes of this paper is to obtain more insight into the nature of the charge effect in anion recognition by hydrogen-bonding receptors.

Binding of several representative neutral urea and amide guests in addition to anions was tested in order to see the effect of acidification of amide groups free of additional electrostatic effect. It should be noted that recognition of neutral guests is a more difficult task and a search for more powerful receptors for such guests is of considerable interest.

Results and Discussion

Structures of Receptors and Complexes. Compounds **2** were prepared by reacting 2,6-pyridinedicarbonyl dichloride with respective isomers of aminopyridine and were converted to iodides of **1** by prolonged treatment with MeI under reflux. The respective triflates were obtained by treatment with silver triflate in MeCN. Compound **3** was prepared as methanesulfonate by reacting *o*-**2** with 2 equiv of methanesulfonic acid in MeCN and compound **4** was prepared in the same way as *m*-**1** with 3-aminoquinoline instead of 3-aminopyridine.

Crystal structures were obtained for the triflates of *p*-**1**, *o*-**1**, and **4**, bromide of *m*-**1**, chloride of *o*-**1**, mixed chloride-triflate of *p*-**1**, and methansulfonate of **3** (see Table S1 in the Supporting Information for crystallographic data for all compounds). Parameters for selected hydrogen bonding interactions related to receptor−anion binding within the crystal structures of these compounds are collected in Table 1.

Figure 1A shows a perspective view of the molecular structure of *p*-**1** triflate illustrating anion−receptor interactions found in the crystal structure. The receptor possesses a rather high degree of planarity: the dihedral angles between *N*-methylated pyridinium rings and the central pyridine ring are 2.43° and 18.88°. One of the triflate anions is positioned with one oxygen atom (O6) turned toward the plane of the central pyridine ring and set at the distance of 1.271 Å from it. It can be seen that the NH bonds of both amide groups are oriented toward this oxygen atom forming two N−H···O hydrogen bonds (Table 1). An additional bonding occurs through C−H···O interactions with the aromatic CH groups in the ortho-position of the aminopyridine fragment (Table 1). It can be expected that a similar binding mode for this and other tetrahedral anions such as dihydrogenphosphate might occur also in solution.

Crystallization of a 1:1 mixture of *p*-**1** triflate with Me_4NCl from MeCN produced a compound having the composition $(p\text{-}\mathbf{1})_3(Cl)_2(CF_3SO_3)_4$. In the crystal structure the receptor dications are stacked along axis *c* with intercalating chloride anions (Figure S1, Supporting Information). Only chloride anions form close contacts with the amide NH groups within the receptor cleft, while the triflate anions show only contacts with CH groups at the periphery of the receptor. This indicates that the chloride ions are capable of replacing the triflate ions from the binding site of this receptor. Figure 2A shows the binding interactions of the chloride ion stacked between two receptor dications.

The Cl^- ion forms two N−H···Cl^- hydrogen bonds and two weaker C−H··· Cl^- bonds with the aromatic CH groups in the ortho-position of the aminopyridyl fragment (Table 1) with the receptor dication at the lower part of the complex. Additionally, the chloride ion forms a hydrogen bond with one NH group of the second, more distant dication at the upper part of the complex (Table 1). In the reported structure of a related chloride complex with neutral receptor *N*,*N*′-bis(3-nitrophenyl)isophthalamide[23] the anion bonding to amide groups has a similar geometry (N−H, 0.88 Å; H···Cl, 2.38 and 2.46 Å; N···Cl, 3.237 and 3.324 Å; N−H···Cl, 163 and 166°), but the C−H···Cl^- contacts are approximately 0.3 Å longer (2.97 and 2.84 Å) than in the present case and are very close to the sum of the corresponding van der Waals radii (3.00 Å).

The hydrogen bonding of chloride with the second dication certainly disturbs the fitting of anion into the receptor cleft and this effect will be absent in solution. To obtain a better approximation to the binding mode in solution the structure of the 1:1 complex obtained by removal of the upper dication was optimized by DFT/B3LYP 6-31G(**) calculation. This produced the structure shown in Figure 2B, where chloride is accommodated in the receptor cleft symmetrically between amide groups with Cl···H distances 2.18 Å, N···Cl distances 3.17 Å, and Cl···H−N angles 158.9° and is hydrogen bonded to aromatic CH groups with Cl···H distances 2.33 and 2.35 Å, C···Cl distances 3.29 and 3.30 Å, and Cl···H−C angles 145.3° and 144.8°. All Cl···H distances in the calculated structure are shorter by 0.2−0.3 Å than those in the crystal structure and the anion lies practically in the plane of the central pyridine ring. At the same time the conformation of the receptor remains essentially unchanged; in particular, the deeper insertion of chloride into the receptor cleft does not require a significant widening of the cleft as follows from comparison of distances between amide nitrogen atoms (4.706 Å in the crystal structure and 4.77 Å in the calculated complex structure) and between carbon atoms bound to anion aminopyridinium CH groups (6.344 Å in the crystal structure and 6.46 Å in the calculated complex structure). A comparison of calculated and experimental structures needs a cautionary note, however. The conformation of the receptor in the triflate salt does not necessarily coincide with the conformation of free dication in

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TABLE 1. Selected Hydrogen Bonding Interactions within the Crystal Structures of Salts of Dicationic Pyridine-2,6-dicarboxamide Receptors

compd	H-bond	D−H [Å]	H···A [Å]	D···A [Å]	∠DHA [deg]	symmetry code
(*p*-**1**)Tf_2	N2−H···O6	0.86	2.26	3.052(2)	154	$+x,+y,+z$
	N4−H···O6	0.86	2.36	3.127(3)	150	$+x,+y,+z$
	C8−H···O6	0.95	2.54	3.337(3)	141	$+x,+y,+z$
	C14−H···O6	0.95	2.65	3.371(3)	133	$+x,+y,+z$
(*o*-**1**)Tf_2	N4−H···O8	0.86	2.20	2.948(3)	146	$+x,+y,+z$
	C19−H···O8	0.98	2.49	3.342(4)	146	$+x,+y,+z$
	N2−H···O38	0.86	2.43	2.996(3)	124	$+x,-y+{}^1/_2,+z-{}^1/_2$
	C18−H···O38	0.98	2.58	3.307(3)	131	$+x,-y+{}^1/_2,+z-{}^1/_2$
	C19−H···O38	0.98	2.56	3.089(4)	114	$+x,-y+{}^1/_2,+z-{}^1/_2$
	N32−H···O4	0.86	2.47	2.919(3)	113	$+x,-y+{}^1/_2,+z+{}^1/_2$
	C48−H···O4	0.98	2.41	3.138(4)	131	$+x,-y+{}^1/_2,+z+{}^1/_2$
	N34−H···O33	0.86	2.13	2.878(3)	145	$+x,+y,+z$
	C49−H···O33	0.98	2.44	3.247(4)	140	$+x,+y,+z$
	C48−H···O33	0.98	2.49	3.225(3)	131	$+x,+y,+z$
(*p*-**1**)$_3Cl_2Tf_4$	N2−H···Cl1	0.86	2.43	3.248(3)	159	$-x+1,+y,-z+{}^1/_2$
	N4−H···Cl1	0.86	2.42	3.194(4)	150	$-x+1,+y,-z+{}^1/_2$
	C8−H···Cl1	0.95	2.58	3.342(3)	137	$-x+1,+y,-z+{}^1/_2$
	C14−H···Cl1	0.95	2.69	3.420(4)	134	$-x+1,+y,-z+{}^1/_2$
	N32−H···Cl1	0.86	2.66	3.307(3)	133	$-x+2,+y,-z+{}^1/_2$
(*o*-**1**)Cl_2	C10−H···Cl1	0.98	2.79	3.682(3)	152	$+x,-y,+z-{}^1/_2$
	C9−H···Cl1	0.95	2.63	3.505(3)	153	$+x,-y,+z-{}^1/_2$
	C7−H···Cl1	0.95	2.73	3.614(3)	154	$-x+{}^1/_2,-y+{}^1/_2,-z+1$
	N2−H···Cl1	0.86	2.68	3.221(3)	123	$+x,+y,+z$
	C10−H···Cl1	0.98	2.79	3.570(3)	137	$+x,+y,+z$
(*m*-**1**)$(H_2O)_3Br_2$	N2−H···O_w	0.86	2.03	2.838(5)	157	$+x,+y+1,+z$
	N4−H··· O_w	0.86	2.12	2.967(4)	167	$+x,+y+1,+z$
	C8−H··· O_w	0.95	2.55	3.251(5)	151	$+x,+y+1,+z$
	C14−H···O_w	0.95	2.39	3.211(5)	144	$+x,+y+1,+z$
(**3**)$(CH_3SO_3)_2$	N2−H···O4	0.86	2.07	2.895(2)	160	$+x+1,+y,+z$
	N4−H···O4	0.86	2.04	2.833(2)	153	$+x+1,+y,+z$
	N5−H···O4	0.86	2.27	2.939(2)	135	$+x+1,+y,+z$
	C8−H···O4	0.95	2.53	3.254(3)	133	$+x+1,+y,+z$
	N5−H···O6	0.86	2.22	2.901(2)	136	$+x,+y,+z$
	C8−H···O7	0.95	2.68	3.179(2)	113	$+x,+y,+z$
	N3−H···O1	0.86	2.06	2.692(2)	130	$+x,+y,+z$
(**4**)$(Tf)_2$	N2−H···O7	0.86	2.59	3.361(5)	150	$-x+1,-y+1,-z+1$
	N4−H···O7	0.86	2.46	3.177(4)	141	$-x+1,-y+1,-z+1$
	C18−H···O7	0.95	2.59	3.356(4)	138	$-x+1,-y+1,-z+1$
	C18−H···O6	0.95	2.55	3.334(4)	140	$-x+1,-y+1,-z+1$
	C27−H···O6	0.98	2.39	3.256(5)	148	$-x+1,-y+1,-z+1$
	C8−H···O8	0.95	2.54	2.918(5)	104	$-x+1,-y+1,-z+1$
	C8−H···O5	0.95	2.45	3.328(4)	153	$-x+1,-y+1,-z+1$
	C27−H···O3	0.98	2.58	3.050(5)	109	$-x+1,-y+1,-z+1$
	C26−H···O4	0.98	2.33	3.279(4)	164	$-x+1,-y+1,-z+1$

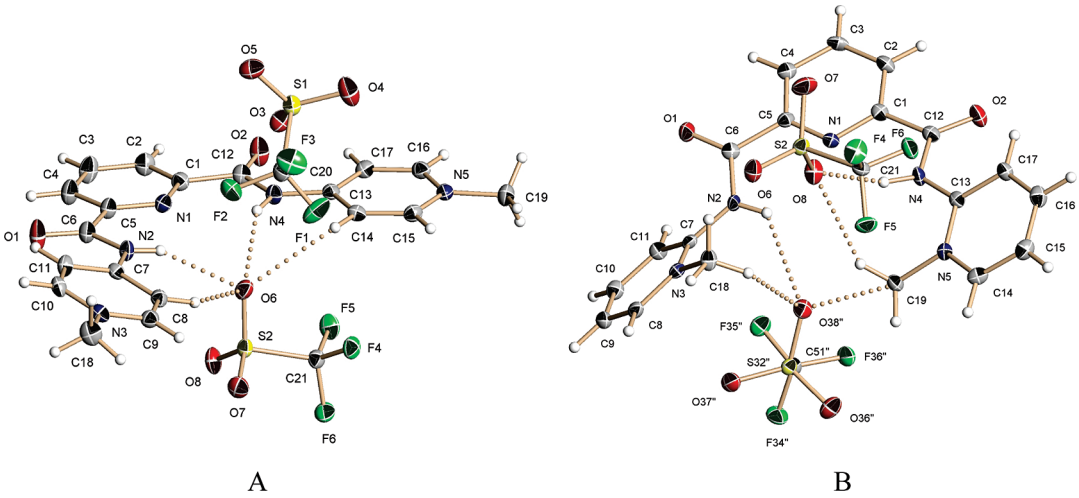


FIGURE 1. Perspective views of the molecular structures of *p*-**1** triflate (A) and *o*-**1** triflate (B). Ellipsoids are shown at the 50% probability level.

solution and the complexation-induced conformational change may be more significant. Also the "shortening" of Cl···H distances in the calculated structure does not necessarily mean stronger hydrogen bonding: a similar

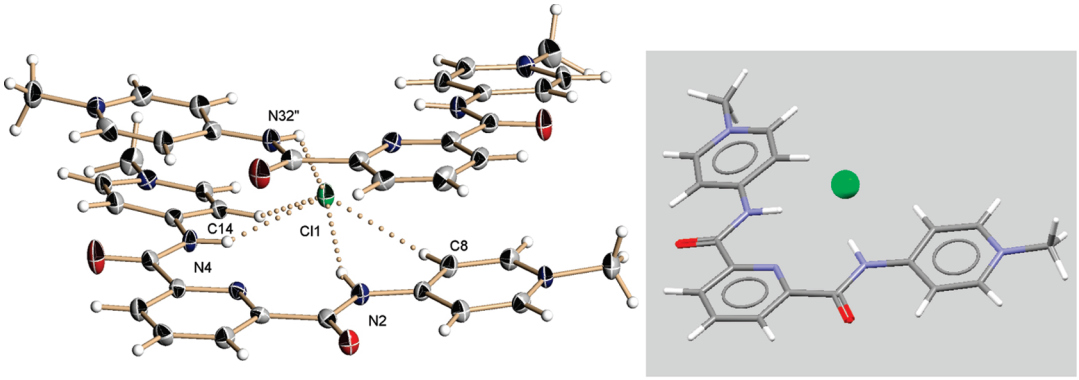


FIGURE 2. (A) Perspective view of a fragment of the crystal structure of $(p\text{-}\mathbf{1})_3(Cl)_2(CF_3SO_3)_4$. Ellipsoids are shown at the 50% probability level. (B) The calculated (DFT/B3LYP 6-31G**) structure of the 1:1 complex of *p*-**1** with Cl^-.

effect can be seen in comparison of calculated[24] and experimental[25] Cl···H distances for hydrogen bonds between Cl^- and $CHCl_3$ or CH_2Cl_2 (calculated values 2.07 and 2.22 Å and experimental values 2.39 and 2.53 Å for $CHCl_3$ and CH_2Cl_2, respectively).

A perspective view of the crystal structure of *o*-**1** triflate is shown in Figure 1B. The N-Me^+ groups are directed inside the cleft and significantly disturb the planarity of the receptor: aminopyridinium rings are turned by 20.95° and 26.31° with respect to the plane of the central pyridine ring. The N−H bonds of amide groups do not converge over a single donor atom of the anion but each amide group forms an N−H···O hydrogen bond with one of the triflate anions located at opposite sides of the plane of the central pyridine ring. Interestingly, protons of aliphatic N-Me^+ groups form even shorter C−H···O hydrogen bonds with the triflate oxygen than those formed between aromatic CH groups and the triflate anion in the structure of *p*-**1** triflate (Table 1). Attempts to crystallize the chloride complex of *o*-**1** from a 1:1 mixture of *o*-**1** triflate with Me_4NCl from MeCN were unsuccessful, and crystals suitable for X-ray diffraction analysis could be obtained only from water with an excess of chloride. In the crystal structure of *o*-**1** chloride the receptor has a similar conformation as in the triflate salt, and also in this case the chloride anions are positioned symmetrically at opposite sides of the receptor dication. Each chloride anion forms one N−H···Cl^- and four C−H···Cl^- contacts (Table 1) with aromatic and aliphatic CH groups of aminopyridinium rings of three neighboring receptor dications (Figure 3A). It seems from these results that even a small chloride anion cannot enter the bisamide binding site of this more sterically encumbered isomer of **1**. In fact *o*-**1** forms one of the most stable chloride complexes among all studied in these work receptors (vide infra). Probably in the solid state the anion is stabilized better by interactions with CH groups of several neighboring receptor dications than it would be stabilized by interactions possible in the inclusion complex with the single receptor dication, which nevertheless can be formed in solution.

Since the crystal structure of the chloride salt did not reflect a possible structure of the chloride complex in solution, theoretical calculations at the DFT/B3LYP 6-31G** level of theory were carried out, starting from the crystal structure of the receptor dication and one Cl^- anion. The resulting structure is shown in Figure 3B. The only significant change in the receptor conformation consists of a rotation by ca. 30° of aminopyridinium rings with respect to the plane of the central pyridine at opposite directions so that the distance between carbons of methyl groups increases from 3.798 Å to 6.691 Å, sufficient to accommodate Cl^-. The anion is hydrogen bonded to both NH groups with Cl···H distances of 2.17 Å and Cl···H−N angles of 152.00° and 151.72° as well as to protons of N-Me^+ groups with Cl···H distances of 2.41 Å and Cl···H−C angles of 142.56° and 143.34°, which are within the limits of parameters (Cl···H distances from 2.12 to 2.66 Å, Cl···H−C angles from 144° to 180°) calculated for $XCH_3\cdots Cl^-$ hydrogen bonds.

Crystals suitable for single-crystal X-ray diffraction of *m*-**1** could be obtained only in the presence of bromide counterions from water. The crystals were strongly hydrated with the consequence that the receptor cleft was occupied by a water molecule, while the bromide anions were located at the periphery (Figure 4A). Similar to the triflate and chloride binding described above, the water molecule is bound through two N−H···O and two C−H···O interactions (see Table 1). The calculated structure of the *m*-**1**/chloride complex is shown in Figure 4B. It resembles very closely that of the *p*-**1**/chloride complex. The anion is bound by four hydrogen bonds, two N−H···Cl^- interactions (H···Cl, 2.44 and 2.41 Å; N···Cl, 3.39 and 3.36 Å; N−H···Cl, 152.49° and 152.28°) and two C−H···Cl^- interactions with the aromatic CH groups located in the ortho-position (H···Cl, 2.21 and 2.20 Å; C···Cl, 3.24 and 3.21 Å; C−H···Cl, 154.72° and 154.16°). When comparing the receptor geometries of the experimental solid state and the calculated structures, it can be seen that the principal conformational changes upon complexation with Cl^- are rotations of lateral pyridinium rings, which form dihedral angles of 32.27° and 12.37° in the solid state, but less than 2° in the complex.

Fragments of the crystal structures of compounds **3**·methanesulfonate and **4**·triflate are shown in Figure 5, parts A and B. In comparison to all isomers of **1** described above, these receptors are almost planar as can be seen from the angles formed between the plane of the central pyridine

(24) Pedzisa, L.; Hay, B. P. *J. Org. Chem.* **2009**, *74*, 2554–2560.
(25) Steiner, T. *Acta Crystallogr.* **1998**, *B54*, 456–463.

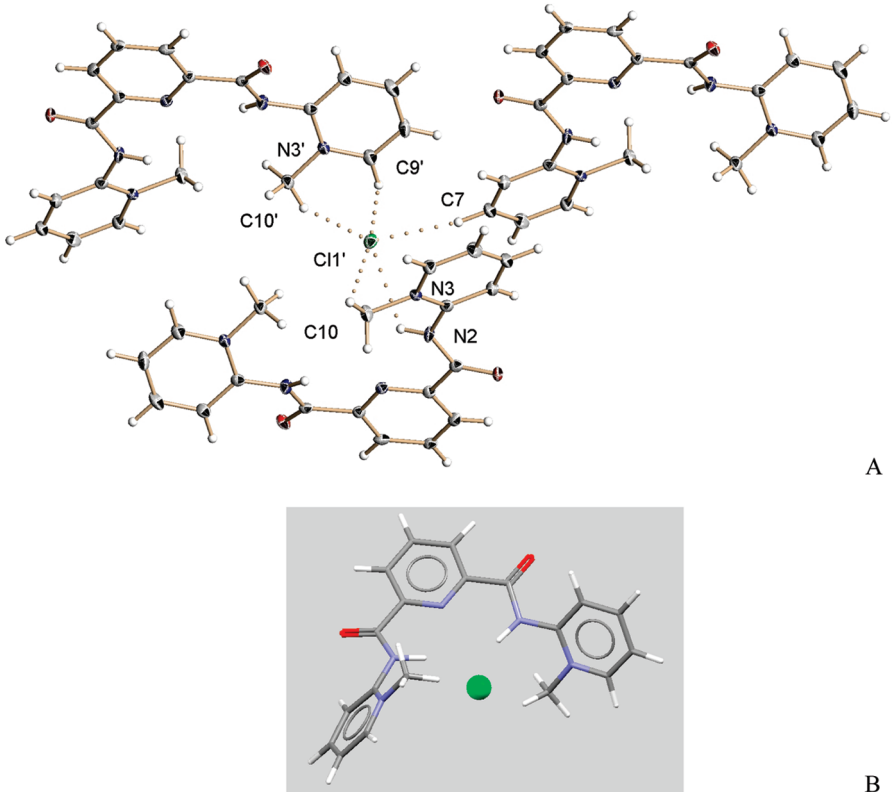


FIGURE 3. (A) Fragment of the crystal structure of *o*-**1** chloride, showing the N−H···Cl^- and C−H···Cl^- contacts with the chloride anion. Ellipsoids are shown at the 50% probability level. (B) The calculated (DFT/B3LYP 6-31G**) structure of the 1:1 complex of *o*-**1** with Cl^-.

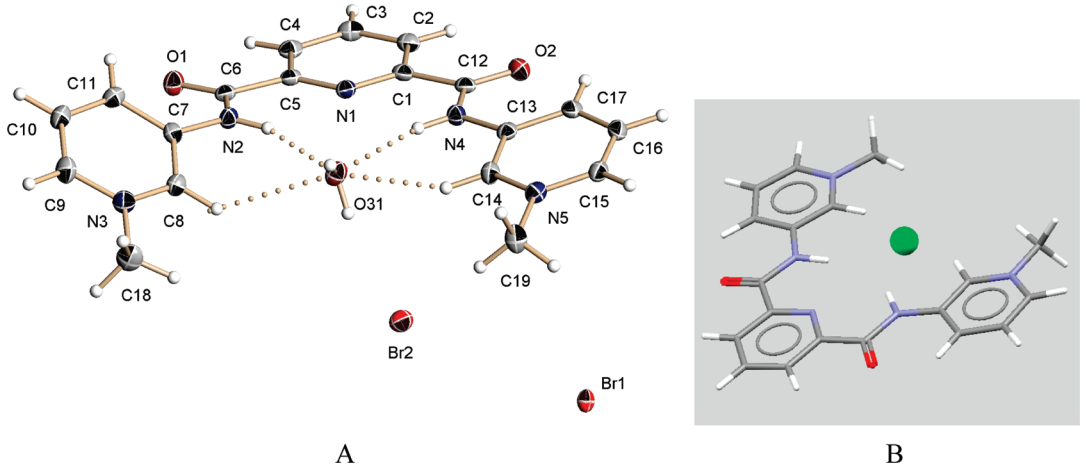


FIGURE 4. (A) Perspective view of a fragment of the crystal structure of *m*-**1** bromide (two additional water molecules were omitted for clarity). Ellipsoids are shown at the 50% probability level. (B) Calculated (DFT/B3LYP 6-31G**) structure of the 1:1 *m*-**1**:chloride complex.

ring and the planes of the lateral rings (6° and 9° for **3**; 10° and 12° for **4**). In **3**·methanesulfonate one of the pyridinium NH^+ groups is directed into the cleft, forming a bifurcate N−H···O hydrogen bond with two methanesulfonate anions (Table 1). The second NH^+ group is located outside the cleft and forms an intramolecular hydrogen bond with the carbonyl group of the amide function (Table 1). In compound **4** one triflate anion is bound to the receptor through N−H···O and C−H···O interactions (Table 1), but directed to different oxygen atoms of the anion, while the second triflate ion shows C−H···O interactions (Table 1, Figure 5B). Unfortunately, with receptors **3** and **4** crystals containing chloride could not be obtained. The calculated structure of the 1:1 chloride complex of **4** (Figure S2, Supporting Information) resembles very much the structure of the *m*-**1**/chloride complex.

All the structures presented above involve NH···X^-···HC chelation of anions previously described for some amino and ureido pyridinium receptors.[15] In addition, the structure of *o*-**1**/chloride (Figure 3A) involves CH···X^-···HC chelation with one aromatic and one aliphatic CH groups.

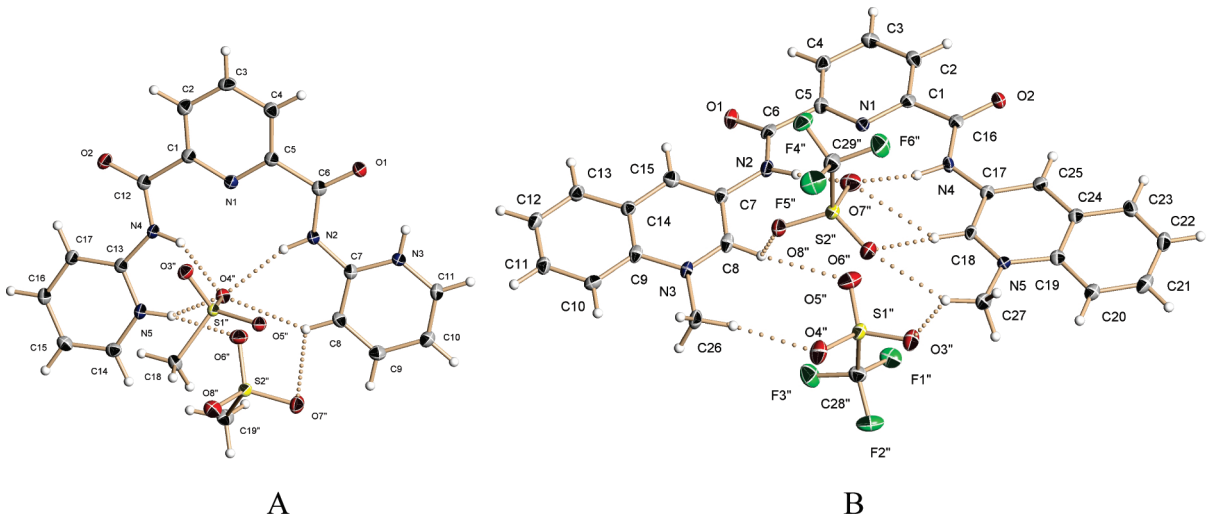


FIGURE 5. Perspective views of fragments of the crystal structure of **3**·methanesulfonate (A) and **4**·triflate (B). Ellipsoids are shown at the 50% probability level.

The results for the solid-state structures described herein confirm that in all receptors the amide NH groups are turned inside the cleft as is typical for other pyridine-2,6-dicarboxamides.[3] In all cases the amide groups are practically coplanar with the central pyridine ring with the largest deviation observed for *o*-**1** triflate where amide groups are turned by 10° in opposite directions with respect to the central ring. In contrast, the amide groups in anion complexes of isophthalamide receptors are out of the plane of the central arene ring.[2,23] It seems therefore that anion complexation with pyridine-2,6-dicarboxamides should occur in the plane of the central pyridine ring, but in the structure of chloride complex with *p*-**1** the anion is positioned out of the plane although the amide NH groups still are in the plane. This occurs, however, due to a secondary interaction of the anion with another receptor molecule in the solid state. In theoretically calculated structures of isolated chloride 1:1 complexes with all three isomers of **1** and with **4** the anion indeed lies practically in the plane of the central pyridine ring with maximum deviation of 0.37 Å for *p*-**1** and receptors adopt favorable for NH···X$^-$···HC chelation planar conformation. Obviously the binding will be more efficient if the aminopyridine rings will be coplanar with the central ring already in the triflate salt. The degree of coplanarity may be characterized by the sum of dihedral angles between both aminopyridine rings and the central ring, which decreases in the order *o*-**1** > *m*-**1** > *p*-**1** ≈ **4** > **3** representing the order of increased receptor preorganization.

On the other hand the size of the cleft must be of primary importance for the binding selectivity. Due to the symmetry of the receptors the degree of complementarity between the cleft and a spherical anion can be analyzed by using a simple geometrical approach. The protons of NH and *o*-CH donor groups form approximately the vertices of an isosceles trapezoid around which it is possible to circumscribe a circle of radius *R*, as shown schematically for *p*-**1** in Figure 6.

For the optimum fit of a spherical anion X$^-$ the H···X$^-$ distance must be equal to *R*. This is actually a cavity radius

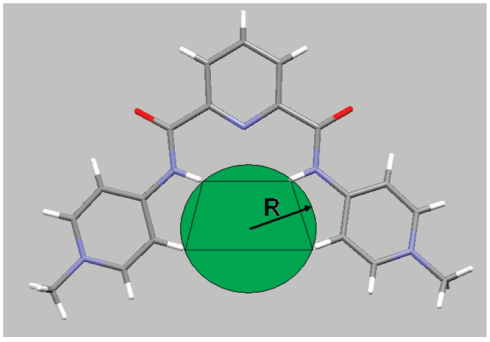


FIGURE 6. Schematic view of anion fitting to the receptor cleft of *p*-**1**.

defined by Hay et al.[26] for the analysis of size selectivity of anion binding by urea hosts. The H···X$^-$ distance is larger for CH donors than for NH donors, but for strong CH donors the difference is less than 0.2 Å (e.g., for $>N_{sp2}-H\cdots Cl^-$ the average distance is 2.22 Å and for $Cl_3C-H\cdots Cl^-$ it is 2.39 Å).[25] The calculated values of *R* for triflate salts are 2.30 ± 0.07 Å (*p*-**1**), 2.4 ± 0.2 Å (*m*-**1**), 2.34 ± 0.09 Å (**4**), 2.0 ± 0.1 Å (**3**) and the mean H···X$^-$ distances for $>N_{sp2}-H\cdots X^-$ are 1.64, 2.221, 2.39, and 2.69 Å for X = F, Cl, Br, and I, respectively.[25] For the optimum fit to both NH and CH donors the *R* value should match a distance increased by approximately 0.1 Å, which will correspond to the average between distances of NH···X$^-$ and CH···X$^-$ bonds. From comparison of these numbers one concludes that *p*-**1** and **4** show the best fit to Cl$^-$ and probably will display peak selectivity for this anion while **3** will accommodate better F$^-$ and *m*-**1** has a cavity size intermediate between the distances for Cl$^-$ and Br$^-$. The optimum cavity radius calculated for binding of Cl$^-$ to two urea molecules, providing the same number of 4 hydrogen bonds, is 2.363 Å,[26] remarkably close to *R* values for *p*-**1** and **4**. Large uncertainty in *R* for *m*-**1** reflects most significant deviations of positions of hydrogen atoms from the shape of an isosceles trapezoid and this receptor probably will be less selective being able to accommodate anions of different sizes. Of course, this analysis ignores the conformational changes

(26) Hay, B. P.; Firman, T. K.; Moyer, B. A. *J. Am. Chem. Soc.* **2005**, *127*, 1810–1819.

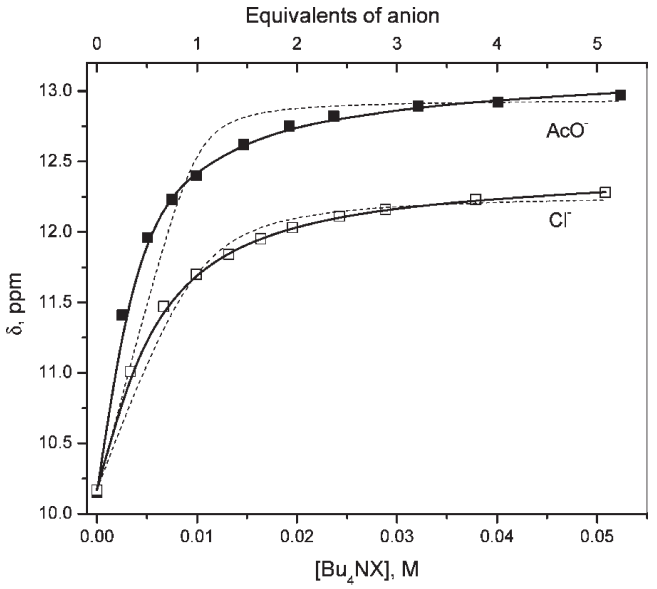


FIGURE 7. ^{1}H NMR titrations of *m*-**2** with acetate (solid squares) and chloride (open squares). Solid lines are the fitting curves to the model involving both 1:1 and 2:1 receptor/anion complexes generated by Hyperquad; dashed lines are the fitting curves to the model involving only 1:1 complexes.

induced by anion binding to receptors, but as follows from comparisons of conformations of receptors in crystal structures of triflates and in calculated 1:1 chloride complexes the major changes are rotations of pyridinium rings, which affect very little the interatomic distances (with exclusion of the case of *o*-**1**) around the binding site.

Anion Complexation Studies. The binding of anions (chloride and acetate) to parent neutral receptors **2** was studied for comparative purposes by ^{1}H NMR titrations in MeCN-d_3. Addition of anions to *m*-**2** or *p*-**2** induced large downfield shifts of signals of amide protons, smaller also downfield shifts of 2-CH and 6-CH protons (see Scheme 1 for the numbering scheme), and small upfield shifts of other protons (Figure S3, Supporting Information). These results are consistent with involvement of aminopyridine CH groups in hydrogen binding of anions and show that the binding can occur with the receptor in two conformations with either 2-CH or 6-CH protons turned inside the cleft (see below).

The titration plots illustrated in Figure 7 for amide protons of *m*-**2** clearly show significant deviations from a simple 1:1 binding model, the fitting to which is shown by dashed lines. The best fit was obtained by using the Hyperquad 2003 program for a model involving formation of both 1:1 and 2:1 (receptor/anion) complexes with association constants given in Table 2.[27] Job plots (Figure S4, Supporting Information) show maxima at a 0.6 mole fraction of the receptor in agreement with simultaneous formation of 1:1 and 2:1 complexes. Titration plots for *p*-**2** shown in Figure S5 (Supporting Information) agree with 1:1 binding with Cl^-, but require inclusion of both 1:1 and 2:1 complexes with AcO^-. No binding with Cl^- and very weak binding with AcO^- were observed with *o*-**2** apparently because of strong interaction of amide protons with nitrogen atoms of three pyridine groups.

(27) Hyperquad does not have an option for fitting the NMR titrations data, but the fitting can be performed by using the option for absorbance titration data provided the product of the chemical shift by total receptor concentration is used as a variable.

TABLE 2. Association Constants (log *K*) of Receptors 2 with Anions and Neutral guests in MeCN[a]

guest	*m*-**2**	*p*-**2**	*o*-**2**
Cl^-	1.8(1); 4.23(7)[b]	2.85(3)	–[c]
AcO^-	2.6(2); 4.7(1)[b]	3.48(6); 6.5(2)[b]	0.7(2)
ethyleneurea	< 0.3	–[c]	0.6(1)

[a]Values in parentheses are standard errors in the last significant digit. [b]log β_{21} for the 2:1 (receptor/anion) complex. [c]No interaction.

TABLE 3. Association Constants (log *K*) of receptors 1, 3, and 4 with Anions and Neutral Guests in MeCN and pK_a Values of Receptors in Water[a]

guest	*m*-**1**	*p*-**1**	*o*-**1**	**3**	**4**
F^-	5.28(8)	4.36(7)			5.15(5)
Cl^-	5.27(9)	5.65(6)	5.85(9)	4.3(1)[b]	6.45(6)
Br^-	5.24(7)	4.29(7)	5.40(8)	3.27(9)[b]	4.09(9)
I^-	3.80(7)	3.57(9)	3.80(8)	–[c]	4.22(9)
$H_2PO_4^-$	4.20(6)	5.18(9)			4.3(1)[d]
AcO^-	4.40(7)	5.38(8)			5.51(5)
NO_3^-	4.11(9)	4.34(5)	4.40(6)		3.76(8)
urea	2.52(8)	2.77(7)	2.48(7)		
	0.86(7)[b]	0.98(4)[b]	0.91(5)[b]		
ethyleneurea	2.16(5)	2.43(5)	2.37(5)		
	0.88(3)[b]	1.34(5)[b]	1.09(4)[b]		
pyrrolidone	1.10(9)	1.42(6)	–[c]		
	−0.03(5)[b]	0.66(6)[b]			
pK_{a1}[e]	9.20(2)	8.76(1)	4.47(2)		9.17(6)
pK_{a2}[e]	11.66(3)	11.3(2)	6.58(2)		11.5(1)

[a]Values in parentheses are standard errors in the last significant digit. Association constants were obtained for *m*-**1** and *p*-**1** by spectrophotometric titrations, for *o*-**1** by competition experiments with deprotonaiton by pyridine, for **3** by NMR titrations in the presence of added methanesulfonic acid, and for **4** by fluorescence titrations. [b]^{1}H NMR titration. [c]No interaction. [d]log β_{12} = 10.2(2) for the 1:2 (receptor/anion) complex. [e]In water.

A neutral guest ethyleneurea interacts with measurable stability constant only with *o*-**2**, which possesses complementary pyridine nitrogen atoms for hydrogen bonding to guest NH groups.[7] Stronger binding of anions to *p*-**2** than to *m*-**2** probably can be attributed to weaker repulsion of anions from more distant nitrogen lone pairs in the para isomer. For all isomers the binding of more basic acetate is stronger than that of chloride.

The methylation of pyridines brings about a very strong acidification of amide groups. Spectrophotometric titrations of isomers of **1** and **4** in water (Figure S6, Supporting Information) allowed us to determine first and second pK_a values of receptors given in Table 3. Typical pK_a values of amides are about 15 and so the methylation increases the acidity of NH-donor groups up to 10 orders of magnitude.

Additions of anions to cationic receptors under conditions of NMR experiments induced precipitation often already below 1:1 molar ratio. Therefore the binding constants were determined by spectrophotometric titrations of much more diluted solutions and NMR results were used for a qualitative analysis of the binding process. A typical spectrophotometric titration experiment is illustrated in Figure 8 for interactions of *m*-**1** and *p*-**1** with Cl^-. Similar red shifts of the absorption band around 300 nm were observed with all anions and neutral guests with larger shifts for more basic anions.

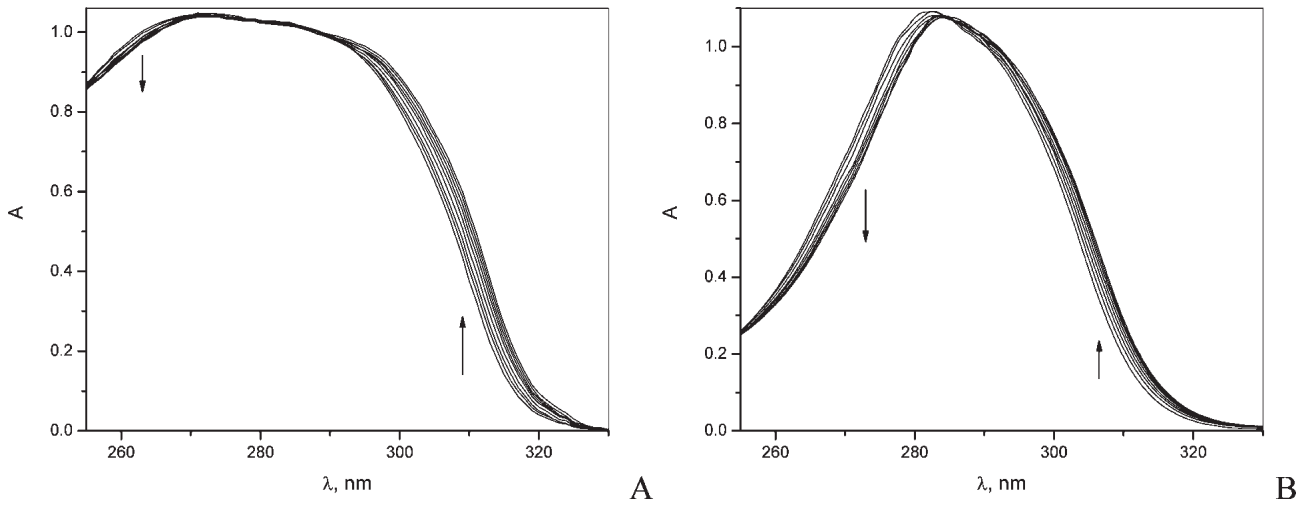


FIGURE 8. Spectrophotometric titrations of 0.04 mM *m*-**1** (A) and 0.02 mM *p*-**1** (B) in MeCN by Me_4NCl. The arrows show the direction of spectral changes.

Titration plots for *m*-**1** are shown in Figure 9. Similar plots were observed for *p*-**1** and in all cases a satisfactory fit to a 1:1 complexation model was obtained with the binding constants given in Table 3. Job plots confirming the 1:1 stoichiometry were obtained for Cl^- and AcO^- with all receptors (Figure S7, Supporting Information, illustrates the plots for *m*-**1**). Interactions with F^- and AcO^- induced deprotonation of both receptors evidenced by the appearance of a new intense absorption band at 350 nm although NMR titrations clearly showed formation of hydrogen-bonded complexes. This is a typical behavior related to the smaller degree of deprotonation observed at higher receptor concentrations.[28] Titrations with acetate were performed in the presence of 0.5 mM AcOH, which was sufficient to suppress deprotonation and the observed binding constant was corrected for homoconjugation between AcO^- and AcOH ($K = 9.7 \times 10^3\ M^{-1}$).[28] In the case of fluoride the homoconjugation constant is very large and titration with an excess of HF is impossible. Instead we used for titration a buffer mixture of Bu_4NF and HF (generated in situ by adding $MeSO_3H$) at a molar ratio 2.5:1 in which only the hydrogen bonding was observed.

The acidity of *o*-**1** in water is similar to that of AcOH (Table 3) and its deprotonation by acetate cannot be suppressed by acetic acid. Moreover, even titrations with low basic anions like Cl^- or Br^- induced some deprotonation of the receptor apparently due to a sort of salt effect. With these anions the deprotonation can be suppressed by adding a strong acid, but we found that titrations in the presence of, e.g., $MeSO_3H$ induced very small spectral changes and estimated equilibrium constants were rather inaccurate. At the same time deprotonation induces a very large spectral change and therefore the anion binding can be conveniently studied by the inhibitory effect of anions on deprotonation of the receptor by an external base. The best results were obtained with pyridine as a base, which has an appropriate basicity and does not interfere with the absorption of the deprotonated receptor. Figure 10 shows the course of titration of *o*-**1** by pyridine accompanied by the appearance of an intense band at 354 nm that belongs to the deprotonated receptor. The equation for the absorbance at a fixed wavelength as a function of added pyridine concentration takes the form of eq 1, where A is the absorbance, ε is the molar absorptivity of the deprotonated form, [R] and [Py] are the total concentrations of *o*-**1** and pyridine, and K is the deprotonation constant for the reaction $RH_2^{2+} + Py = RH^+ + PyH^+$.

$$A = 0.5\varepsilon\{K([R]+[Py])/(K-1)\}\{1-(1-4(K-1)[R][Py]/K([R]+[Py])^2)^{0.5}\} \quad (1)$$

The inset in Figure 10 shows the fitting of the absorbace at 354 nm to eq 1 from which $K = 0.15 \pm 0.02$. Since $\log K = pK_a(PyH^+) - pK_a(RH_2^{2+})$ one may calculate the pK_a value of *o*-**1** in MeCN from the known pK_a 12.3 of PyH^+ in the same solvent.[29] This gives $pK_a = 13.1$, which means that *o*-**1** in MeCN is a stronger acid than AcOH ($pK_a = 22.3$).

When titration is performed in the presence of added guest G (anion, urea, etc.) it binds to the receptor in dicationic form and protects it from deprotonation. This is manifested in a decrease in the observed deprotonation constant according to the equation $K_{obs} = K/(1 + K_{assoc}[G])$. From this one obtains eq 2 for the association constant of the receptor with the guest.[30]

$$K_{assoc} = (K/K_{obs} - 1)/[G] \quad (2)$$

The deprotonaiton plots in the presence of added guests are shown in Figure 11 in semilogarithmic coordinates. Obviously added guests inhibit the deprotonation as expected. Association constants calculated from these results are given in Table 3. It is worth noting that receptor deprotonation can be observed often, e.g., with thioureas, and it is always accompanied by much more significant spectral changes than those observed upon hydrogen bonding of anions. In such cases

(28) Pérez-Casas, C.; Yatsimirsky, A. K. *J. Org. Chem.* **2008**, *73*, 2275–2284.

(29) Izutsu, K. *Acid-Base Dissociation Constants in Dipolar Aprotic Solvents*; Blackwell Scientific Publications: Oxford, UK, 1990.

(30) In equ 2 [G] is the equilibrium concentration. For all anions besides Cl^- the condition $[G]_T \gg [o\text{-}\mathbf{1}]_T$ was valid and therefore $[G] \approx [G]_T$. For Cl^- the profile in Figure 11 was fitted to the scheme involving deprotonation and association equilibria with a known value of K by Hyperquad.

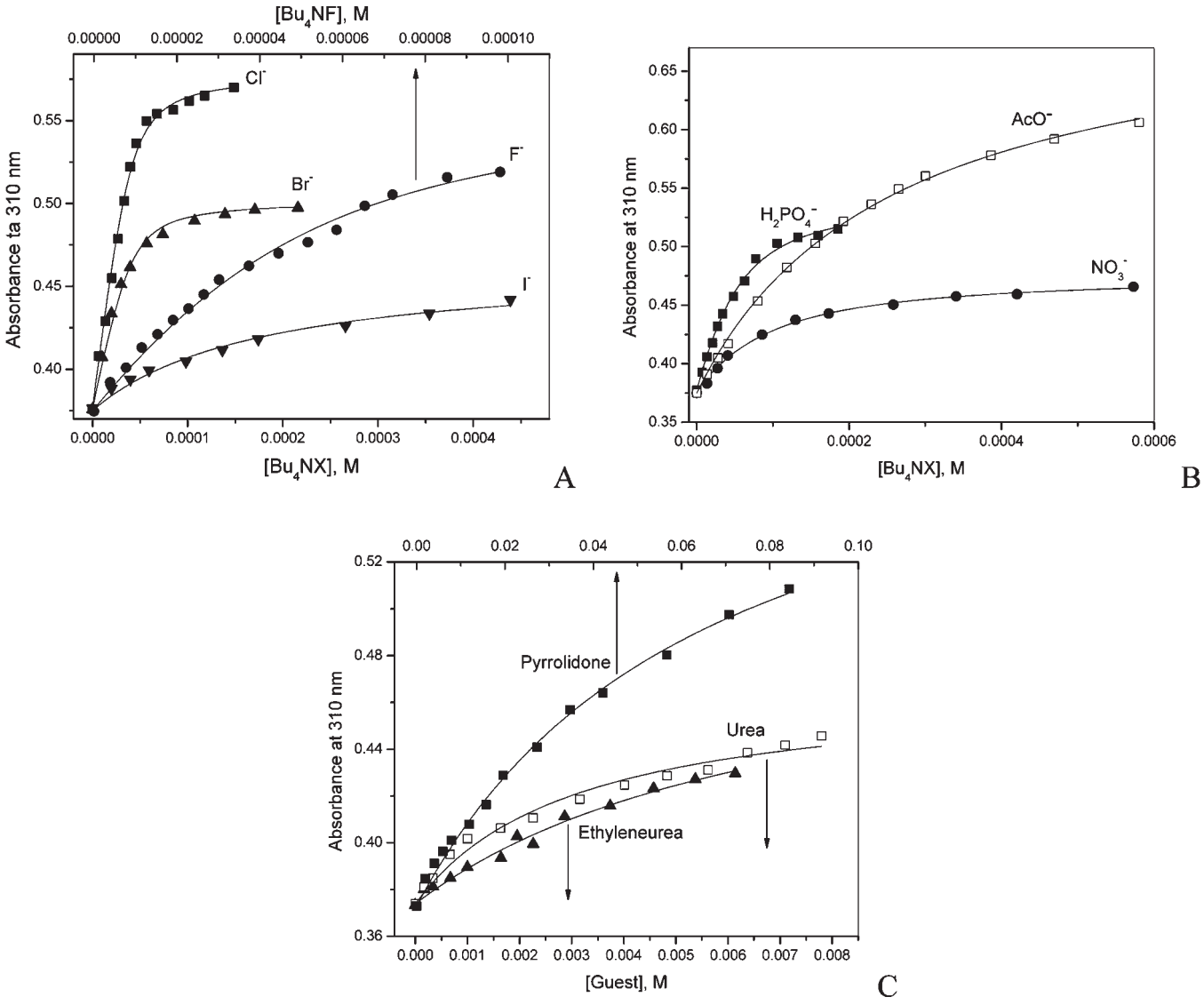


FIGURE 9. Spectrophotometric titration plots for 0.04 mM *m*-**1** in MeCN: (A) halide anions, (B) oxoanions, and (C) neutral guests. The solid curves are the fitting profiles to the 1:1 binding isotherm.

the above procedure can be conveniently employed for more precise measurements of the anion binding constants.

In the case of also highly acidic diprotonated receptor **3** this procedure does not work because the receptor looses first pyridinium protons. Spectral changes observed in the presence of an excess of $MeSO_3H$ added to suppress the deprotonation were too small and therefore the only way to estimate the association constants was the ^1H NMR titration in the presence of a small excess of added strong acid. Fortunately this receptor did not precipitate until an excess of anion was added. Associaiton constants for **3** with halide anions are given in Table 3.

The aminoquinolinium derivative **4** is strongly fluorescent with the emission maximum at 400 nm. The quenching of *N*-alkylquinolinium cations by halide anions is employed as a method of determination of chloride in biological samples.[31] Recently a new tricationic tris(6-methoxy-1-methylquinolinium) receptor designed as a fluorescent anion sensor in MeCN has been reported.[32] The sensing was based on quenching of the receptor by anions, which involved both static and dynamic contributions. The dynamic quenching was rather insensitive to the type of anion with Stern−Volmer constants around 10^3 M^{-1} and the static quenching was incomplete with Cl^- and NO_3^-, i.e. the receptor−anion complexes still possessed some reduced fluorescence. Effects of anions on the fluorescence of receptor **4** are shown in Figure 12. The profiles are of the type expected for incomplete static quenching for all anions besides NO_3^-, which enhances the fluorescence. The excitation spectra (not shown) underwent small red shifts in the presence of anions similar to those observed in absorption spectra of *m*- and *p*-**1** (Figure 8). Such behavior agrees with the static quenching model, which implies formation of an anion−receptor ground state complex with reduced fluorescence intesity. On this assumption the fitting of

(31) Verkman, A. S.; Sellers, M. C.; Chao, A. C.; Leung, T.; Ketcham, R. *Anal. Biochem.* **1989**, *178*, 366–361.

(32) Amendola, V.; Fabbrizzi, L.; Monzani, E. *Chem.—Eur. J.* **2004**, *10*, 76–82.

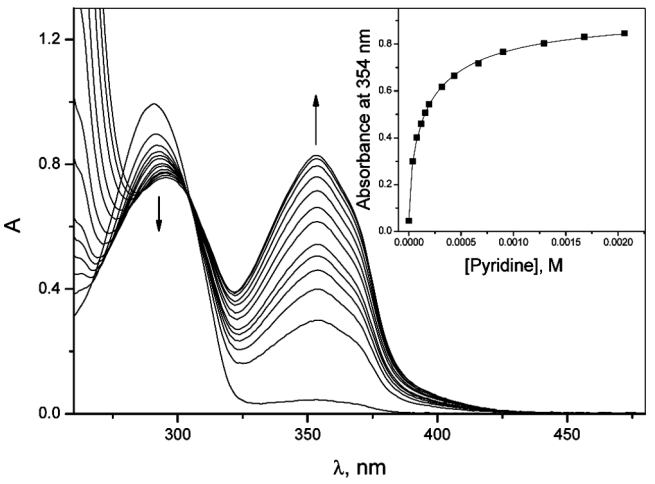


FIGURE 10. Spectral course of deprotonation of *o*-**1** (40 μM in MeCN) by pyridine.

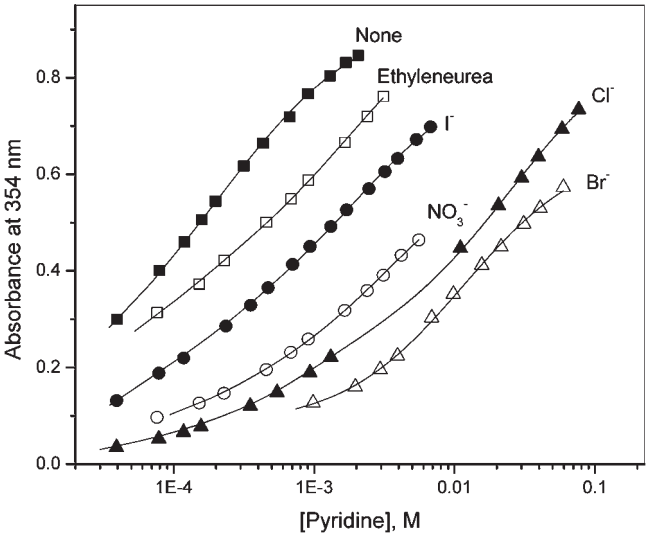


FIGURE 11. Deprotonation of 0.04 mM *o*-**1** by pyridine in the presence of added guests: 3 mM ethyleneurea, 1 mM Bu_4NI, 2 mM Bu_4NNO_3, 1 mM Bu_4NBr, and 0.08 mM Bu_4NCl.

profiles in Figure 12 to the usual binding isotherm for 1:1 complexation allowed us to calculate the association constants given in Table 3. In case of $H_2PO_4^-$ the titration profile indicates the consequtive binding of one and two anions.

The NMR titrations not disturbed by precipitation were possible with neutral guests. They induced downfield shifts of NH signals by ca. 1 ppm (at saturation) and did not affect signals of aromatic protons. The binding constants calculated from NMR titrations were approximately 10 times smaller than those determined by spectrophotometric titrations (see Table 3). The difference can be attributed to much higher concentrations of cationic receptors employed in NMR titrations (5−10 mM) than in spectrophotometric titrations (0.02−0.04 mM), which results in significant competition of counterions with guest molecules in the former case (see below).

Figure 13 shows changes in ^{1}H NMR spectra of *m*-**1** induced by additions of 1 equiv of different anions (signals

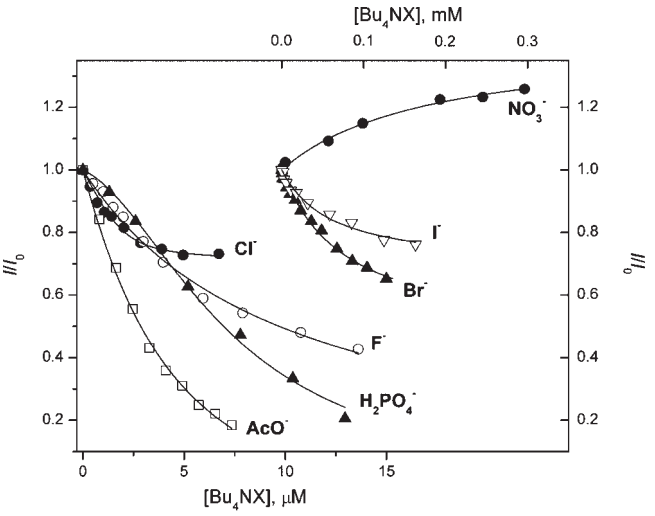


FIGURE 12. Fluorimetric titration plots for 2×10^{-6} M **4** in MeCN. Solid lines are the fitting curves to a 1:1 binding isotherm for all anions except $H_2PO_4^-$.

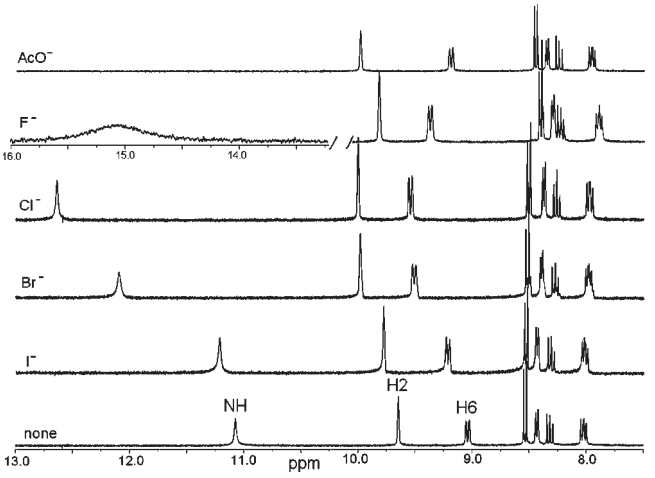


FIGURE 13. ^{1}H NMR spectra of *m*-**1** alone and in the presence of 1 equiv of anions.

were assigned on the basis of a HMBC spectrum of *m*-**1** in CD_3CN, Figure S24, Supporting Information.). Respective data for *p*-**1** and *o*-**1** are shown in Figures S8 and S9 (Supporting Information). As in the case of neutral receptors **2** anions induce large downfield shifts of signals of amide protons, smaller also downfield shifts of 2-CH and 6-CH protons (for the numbering of protons see Scheme 1), and upfield shifts of other protons. In the presence of AcO^- the signal of the NH group disappears, but this is not due to deprotonation of the receptor because signals of 2-CH and 6-CH protons undergo downfield shifts indicating the hydrogen bonding. Deprotonation induced by addition of Bu_4NOH also caused the disappearance of the NH signal, but induced significant upfield shifts of the signals of 2-CH and 6-CH protons by 0.4 and 0.6 ppm, respectively. Interestingly, F^- induces a much stronger shift of the NH signal than any other anion, but smaller shifts of CH signals than Cl^- and even Br^-. Also smaller shifts of CH signals are observed with AcO^-. These observations are in line with the predicted best fit of Cl^- to the receptor cleft.

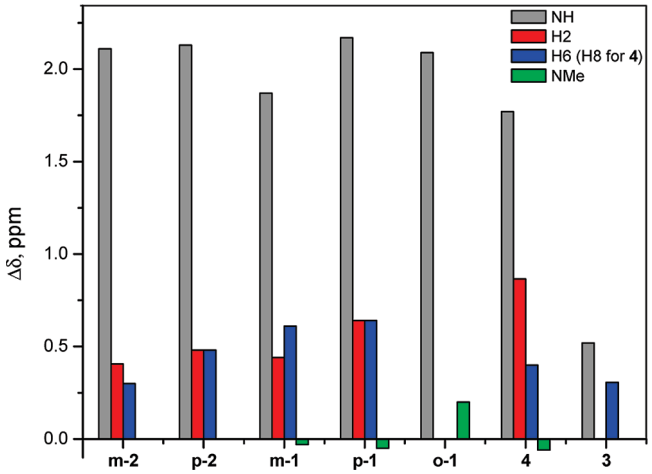
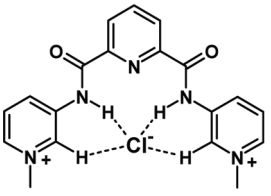


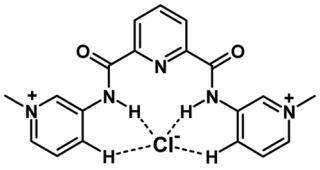
FIGURE 14. Shifts in positions of ^{1}H NMR signals of receptors induced by complexation with Cl^-.

The complexation-induced shifts of the signals of protons involved in anion binding with Cl^- are shown for all receptors in Figure 14. The largest downfield shifts are observed for the signals of amide NH protons. They are similar for neutral receptors **2** and for much more acidic cationic receptors **1** and **4**, but surprisingly the shift is much smaller for the diprotonated receptor **3**. It may be possible that with **3** the anion is bound to one or both pyridinium NH^+ groups, but this cannot be proved because this group does give a detectable signal in the NMR spectrum.

Downfield shifts of the signals of protons of pyridinium CH groups relative to those of NH groups are larger for cationic receptors reflecting more significant involvement of $CH\cdots Cl^-$ interactions. Signals of protons of both 2-CH and 6-CH (8-CH for **4**) groups are shifted approximately equally indicating formation of two isomeric complexes schematically shown as **5a** and **5b** for *m*-**1**. In case of *p*-**1** these protons are equivalent and their equivalence is conserved in the presence of chloride. This means that complexes of types **5a** and **5b** are in a fast equilibrium with each other. In the case of receptor **3** the signal of 6-CH is shifted to approximately the same extent as the signal of the amide NH group, but for *o*-**1** the signal of 6-CH remains unchanged.



5a



5b

The signal of protons of the N-Me^+ group undergoes upfield shifts in *m*-**1**, *p*-**1**, and **4** resulting from the inductive effect of the negative charge of the anion, but it undergoes a downfield shift in *o*-**1** indicating the hydrogen bonding of chloride to teh N-Me^+ group is in agreement with structural and calculation results discussed above.

Inspection of results collected in Tables 2 and 3 indicates that cationic receptors **1** bind anions 10^2-10^4 times stronger than neutral receptors **2**. An obvious contribution to this stronger binding is the electrostatic attraction of anions to dicationic receptors. It is rather difficult, however, to estimate this contribution quantitatively.

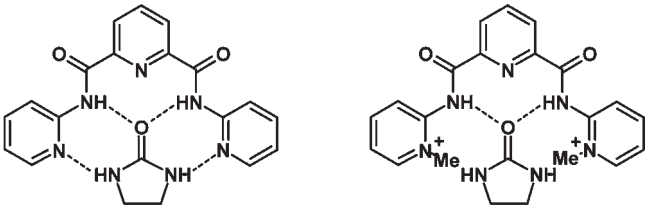
One aspect of this problem is that cationic receptors may form ion pairs with counterions, which compete with guest anions compensating for the expected affinity gain due to electrostatic attraction. Binding constants for methansulfonate and triflate anions to *o*-**1** measured by competition with Py-induced deprotonation (see above) equal $(2.8 \pm 0.5) \times 10^3$ and $(4.2 \pm 0.7) \times 10^3$ M^{-1} respectively. Similar, but less accurate values were found for other isomers of **1** by spectrophotometric titrations. With such constants the ion pairing with counterions is negligible under conditions of UV−vis and fluorimetric titrations, but in 5−10 mM receptor solutions employed for NMR titrations between 80% and 90% of the receptor exist as ion pairs. This should cause a 10-fold decrease in the experimentally observed binding constant for a given guest in comparison with conditions when the receptor exists as a free dication. This effect agrees well with the difference in binding constants for neutral guests found by spectrophotometry and by NMR mentioned above. It also should be noted that binding constants given in Table 3 for the receptor **3** may be underestimated since in this case the measurements were possible only by NMR titrations.

The direct electrostatic contribution to the anion binding probably is not large because of strong delocalization of the positive charge of the receptor. Valuable information on electrostatic interactions in systems of this type was obtained by studying the ion pairing of mono- and dicationic pyridinium-substituted indolizines with Cl^- and PF_6^- by conductometry in MeCN.[33] The logarithms of association constants were in the range 2.2−2.8 showing little dependence on charge of indolizine (+1 or +2) and on anion size. This is consistent with significant nonelectrostatic contribution to the association. For the association of Cl^- with Me_4N^+ in MeCN log K = 1.75, but for association with $Me_2NH_2^+$ or $EtNH_3^+$ log K increases to 4,[34] indicating a strong contribution of hydrogen bonding. The stronger binding of anions to indolizines as compared to a tetraalkylammonium ion can be attributed in view of this to the presence of aromatic CH groups in pyridinium rings, which can provide some hydrogen bonding contribution. Interestingly, interactions of anions with tetraamide macrocyclic receptors containing two quaternized amine functionalities induced downfield shifts of the ^{1}H NMR signals of methylenes adjacent to N^+ atoms indicating a hydrogen bonding contribution in addition to the charge effect.[22a] The stabilization effect of two positive charges in this system varied between 1 and 2 orders of magnitude, but was absent for the smallest F^- anion probably because it could not make contacts simultaneously with both amide and ammonium functionalities.

Further evidence in favor of the primary significance of nonelectrostatic contributions comes from the fact that although all receptors have the same total charge +2 and

(33) Carter, P. W.; Di Magnot, S. C.; Porter, J. D.; Streitwieser, A. *J. Phys. Chem.* **1993**, *97*, 1085–1096.
(34) Janz, G. J.; Tomkins, R. P. T. *Nonaqueous Electrolytes Handbook*; Academic Press: New York, 1972; Vol. 1.

SCHEME 2. Binding Modes of Ethyleneurea to *o*-1 and *o*-2



all anions −1, the increase in binding constants in comparison with neutral receptors is very much variable. There is also a possible contribution from the anion−π interaction with the electron-deficient pyridinium parts although an inspection of crystal structures of receptor salts does not show an evidence for this. Finally, a large increase in binding constants is observed also with neutral guest molecules: the K values for ethyleneurea increase by factors of ∼70 for *m*-**1**, $>10^2$ for *p*-**1** and 60 for *o*-**1**. This effect can be attributed entirely to increased acidity of amide NH groups. In the case of the ortho isomer methylation of pyridine nitrogens actually eliminates two additional binding sites for NH groups of ethyleneurea (Scheme 2). So, the improvment reached by acidification of amide groups is larger than that provided by additional hydrogen bonding. All receptors **1** bind unsubstituted urea with similar strength and even have measurable affinity to the amide guest pyrrolidone (Table 3).

It follows form the above discussion that the major stabilizing contribution of positive charges in receptors **1** is due to increased acidity of NH and CH donors. The affinity of these receptors as well as that of **3** and **4** to anions is remarkably high for simple acyclic compounds. For comparison, the logarithms of binding constants for a similar set of anions in MeCN reported for a tricationic tripodal tris(ureidopyridinium) receptor are in the range from 3.4 to 4.6,[15] for a family of structurally similar tris(aminopyridinium) receptors from 3.5 to 5.0,[16b] and for a tris(9*H*-β-carbolin-2-ium) receptor from 4.4 to 7.[17b] All these receptors have a larger positive charge +3, bind anions through 6 instead of 4 hydrogen bonds to proton donors of approximately the same acidity as in the case of receptors **1**, **3**, and **4**, and nevertheless show similar affinities to anions. Most probably the advantage of pyridine-2,6-dicarboxamide receptors is their more rigid preorganized structure, while the binding to the receptors mentioned above takes place through the induced fit mechanism.

Bis(imidazolium) derivatives represent another family of dicationic hydrogen-bonding receptors for which association constants with anions in MeCN were reported. These receptors have the same total charge +2 as **1**, **3**, and **4**, but form only two strong hydrogen bonds with anions involving C-2 protons of imidazolium rings and are expected therefore to have lower affinities. Indeed, bis(imidazolium) calix[4]arene receptors bind chloride and acetate anions in MeCN with log K values ranging from 2.3 to 3.6, which is the affinity typical for neutral receptors **2** (see Table 2).[20] Similar affinities were reported for a *m*-xylene-bridged bis(imidazolium) receptor[35] and for an acyclic bis(imidazolium) ferrocene derivative, in the latter case with log K increasing to the range 3.5−4.5 upon macrocyclization, which provides additional contacts with aromatic CH donors.[36]

General trends in binding constants for anions collected in Table 3 agree well with predictions made above on the basis of structural data: receptors *p*-**1** and **4** demonstrate pronounced peak selectivity to Cl^-, *m*-**1** practically lacks any selectivity toward halide anions besides weaker binding of obviously too large I^-, the highest affinity to Cl^- is observed for the most preorganized receptor **4**. The binding to the less preorganized receptor *o*-**1** is fairly strong, however. This can be attributed to the largest acidity of amide groups of this receptor. Results for **3** are rather incomplete and therefore inconclusive. It shows the expected decrease in binding constants, on the basis of its cavity size, on going from Cl^- to Br^- and to I^-, but the binding constant for F^- could not be measured because of extensive deprotonation of the receptor by this basic anion. Interestingly, the binding to neutral receptors **2** is stronger for AcO^- than for Cl^- in accordance with basicity rather than cavity size determined selectivity. Probably due to the lower acidity of aromatic CH groups in receptors **2** the anion binding occurs principally to amide groups with less significant cavity size restriction. In general, the selectivity of anion complexation by simple hydrogen bonding receptors is usually determined by anion basicity while size or shape selectivity can be achieved by using rigid macrocyclic receptors.[37] Results for receptors **1**, **3**, and **4** demonstrate that significant size selectivity can be achieved also with sufficiently rigid simple cleft receptors.

In sense of possible future applications the most promising is using the fluorescence quinolinium derivatives exemplified here with receptor **4**. The most unusual feature of this receptor is that it is efficiently quenched by phosphate, which has zero quenching efficiency toward simple quinolinium compounds.[31] This observation prompted us to test the quenching of **4** by some biological phosphates in water and in preliminary experiments we did observe strong quenching by nucleotides. This opens perspectives for using quinolinium derivatives like **4** for fluorescence sensing of these important metabolites.

Conclusion

Dicationic pyridine-2,6-dicarboxamide receptors containing N-methylated pyridinium or quinolinium groups attached to amide nitrogens have greatly increased affinities to anions and neutral guests (ureas, amides) as compared to their neutral counterparts. The principal reason for this is strong acidification of both NH (amide) and CH (aromatic or aliphatic for the ortho isomer) proton donors induced by quaternization of lateral pyridine or quinoline moieties. The acidification of amide groups was characterized quantitatively by determination of pK_a values of receptors in water. Analysis of crystal structures of triflate salts of the receptors allowed us to predict the complexation selectivity toward chloride anion, which was observed experimentally. Crystal structures of chloride salts of receptors did not show,

(35) In, S.; Cho, S. J.; Lee, K. H.; Kang, J. *Org. Lett.* **2005**, *7*, 3993–3996.

(36) Niu, H.-T.; Yin, Z.; Su, D.; Niu, D.; Ao, Y.; He, J.; Cheng, J.-P. *Tetrahedron* **2008**, *64*, 6300–6306.

(37) Schneider, H.-J.; Yatsimirsky, A. K. *Chem. Soc. Rev.* **2008**, *37*, 263–277.

however, an adequate representation of expected solution structures of receptor−anion complexes because of involvement of chloride anion into numerous binding interactions with neighboring receptor dications. Possible structures of solution complexes with Cl^- were simulated by DFT calculations, which together with results of ^1H NMR titrations confirmed the expected mode of anion binding, in particular, through hydrogen bonding with aliphatic CH donors of N-Me^+ groups in the sterically encumbered ortho isomer of **1**.

Experimental Section

Materials. The reagents were obtained from commercial suppliers and used as received without further purification. Solvents were purified and dried with use of standard procedures.

2,2′-[Pyridine-2,6-diylbis(carbonylimino)]bis(1-methylpyridinium) trifluoromethylsulfonate ((*o*-1)(CF_3SO_3)$_2$). The neutral dicarboxamide *o*-**2** (0.50 g, 1.56 mmol) prepared as described in ref 38 was reacted with 20 equiv of CH_3I in DMF/acetone (1:3 v/v, 80 mL) for 1 week under reflux. The resulting pale yellow powder was filtered and washed with acetone and cold MeOH to give (*o*-**1**)I_2. The iodide salt (0.30 g, 0.49 mmol) was dissolved in 80 mL of H_2O, 2 equiv of silver triflate (0.25 g, 0.98 mmol) was added, and the mixture was stirred overnight at room temperature. The suspension was filtered off and the solvent was evaporated under reduced pressure to produce the triflate salt (0.21 g) in 65% yield. ^1H NMR (300 MHz, DMSO-d_6) δ 11.63 (s, 2H), 9.02 (s, 2H), 8.68 (t, J = 7.24 Hz, 2H), 8.60 (d, J = 7.86 Hz, 2H), 8.47 (m, 3H), 7.98 (s, 2H), 4.38 (s, 6H); ^{13}C NMR (300 MHz, DMSO-d_6) δ 162.4, 147.1, 146.6, 146.2, 141.1, 127.5, 124.5, 124.1, 118.1, 44.4; MS (FAB, m/z) 498 [M + Tf]$^+$; IR (KBr) 3355, 3099, 1719, 1521, 1282, 1255 cm^{-1}. Anal. Calcd for $C_{21}H_{19}F_6N_5O_8S_2$ (647.53): C, 38.95; H, 2.96; N, 10.82. Found: C, 39.01; H,2.83; N,10.80.

***N*,*N*′-Di(pyridin-3-yl)pyridine-2,6-dicarboxamide (*m*-2).** Mixture of 3-aminopyridine (0.92 g, 9.50 mmol) and 2,6-pyridinedicarbonyl dichloride (1.00 g, 4.75 mmol) in 50 mL of dry toluene was refluxed for 2 h. The resulting precipitate was collected by filtration and washed with acetone, then with 5% $NaHCO_3$, and then with water to give the product (1.42 g) in 94% yield. ^1H NMR (300 MHz, DMSO-d_6) δ 11.14 (s, 2H), 9.10 (s, 2H), 8.41 (m, 4H), 8.34 (m, 2H), 8.30 (m, 1H), 7.48 (m, 2H); ^{13}C NMR (300 MHz, DMSO-d_6) δ 162.1, 148.4, 145.4, 142.7, 140.3, 134.7, 128.2, 125.6, 123.7; MS(FAB, m/z) 320 [M + H]$^+$; IR (KBr) 3257, 1685, 1589, 1538 cm^{-1}. Anal. Calcd for $C_{17}H_{13}N_5O_2$ (319.317): C, 63.94; H, 4.10; N, 21.93. Found: C, 63.01; H, 4.45; N, 21.21.

3,3′-[Pyridine-2,6-diylbis(carbonylimino)]bis(1-methylpyridinium) Trifluoromethylsulfonate ((*m*-1)(CF_3SO_3)$_2$). (*m*-**1**)(CF_3SO_3)$_2$ was obtained following the same procedure as for (*o*-**1**)(CF_3SO_3)$_2$ from *m*-**2** instead of *o*-**2** with a shorter time (4 days) of the first alkylation step. ^1H NMR (300 MHz, DMSO-*d*6) δ 11.67 (s, 2H), 9.72 (s, 2H), 8.84 (t, J = 7.21 Hz, 4H), 8.56 (d, J = 8.15 Hz, 2H), 8.46 (t, J = 7.32, 1H), 8.26 (m, 2H), 4.47(s, 6H); ^{13}C NMR (300 MHz, DMSO-d_6) δ 162.4, 147.3, 141.1, 137.9, 136.4, 135.1, 127.8, 126.6, 122.8, 118.5; MS (FAB, m/z) 498 [M + Tf]$^+$; IR (KBr) 3391, 3098, 1695, 1550, 1274 cm^{-1}. Anal. Calcd for $C_{21}H_{19}F_6N_5O_8S_2$ (647.53): C, 38.95; H, 2.96; N, 10.82. Found: C, 38.36; H, 2.98; N, 10.42.

***N*,*N*′-Di(pyridin-4-yl)pyridine-2,6-dicarboxamide (*p*-2).** *p*-**2** was obtained following the same procedure as for *m*-**2** from 4-aminopyridine. ^1H NMR (300 MHz, DMSO-d_6) δ 11.25 (s, 2H), 8.59 (d, J = 5.44 Hz, 4H), 8.45 (d, J = 8.36 Hz, 2H), 8.35 (t, J = 7.39 Hz, 1H), 7.97 (d, 4H); ^{13}C NMR (300 MHz, DMSO-d_6) δ 162.2, 150.2, 147.9, 144.5, 140.0, 125.7, 114.1; MS (FAB, m/z) 320 [M + H]$^+$; IR (KBr) 3235, 1678, 1583, 1511 cm^{-1}. Anal. Calcd for $C_{17}H_{13}N_5O_2$ (319.317): C, 63.94; H, 4.10; N, 21.93. Found: C, 63.48; H, 4.58; N, 21.21.

4,4′-[Pyridine-2,6-diylbis(carbonylimino)]bis(1-methylpyridinium) Trifluoromethylsulfonate ((*p*-1)(CF_3SO_3)$_2$). (*p*-**1**)(CF_3SO_3)$_2$ was obtained following the same procedure as for (*m*-**1**)(CF_3SO_3)$_2$ from *p*-**2**. ^1H NMR (300 MHz, DMSO-d_6) δ 11.97 (s, 2H), 8.88 (d, J = 7.38 Hz, 4H), 8.58 (d, J = 8.44 Hz, 2H), 8.49 (m, 5H), 4.26 (s, 6H); ^{13}C NMR (300 MHz, DMSO-d_6) δ 163.3, 150.8, 146.2, 141.0, 127.4, 122.8, 118.5, 116.0; MS (FAB, m/z) 498 [M + Tf]$^+$; IR (KBr) 3263, 3072, 1706, 1523, 1260 cm^{-1}. Anal. Calcd for $C_{21}H_{19}F_6N_5O_8S_2$ (647.53): C, 38.95; H, 2.96; N, 10.82. Found: C, 38.97; H, 2.97; N, 10.81.

***N*,*N*′-Di(2-pyridinium methanesulfonate)pyridine-2,6-dicarboxamide ((3)(CH_3SO_3)$_2$).** A mixture of *o*-**2** (0.30 g, 0.940 mmol) and methanesulfonic acid (122 μL, 1.88 mmol) in 30 mL of MeCN was stirred at ambient temperature and the crystalline product was separated after slow evaporation of the solvent during 2 days. ^1H NMR (300 MHz, DMSO-d_6) δ 11.94 (s, 2H), 8.54 (d, J = 5.18, 2H), 8.47 (d, J = 7.92 Hz, 2H), 8.35 (t, J = 7.80 Hz, 1H), 8.30 (d, J = 8.49 Hz, 2H), 8.09 (t, J = 7.90 Hz, 2H), 7.38 (t, J = 7.38 Hz, 2H), 6.91 (s, 6H); ^{13}C NMR (300 MHz, DMSO-d_6) δ 163.0, 150.4, 148.4, 146.0, 140.6, 140.2, 126.4, 120.7, 115.8; MS (FAB, m/z) 498 [M + CH_3SO_3]$^+$; IR (KBr) 3263, 3072, 1706, 1523, 1260 cm^{-1}. Anal. Calcd for $C_{19}H_{21}N_5O_8S_2$ (511.53): C, 44.61; H, 4.14; N, 13.69. Found: C, 44.39; H,4.46; N,13.47.

***N*,*N*′-Di(3-*N*′-methylquinolinium)pyridine-2,6-dicarboxamide Trifluoromethanesulfonate ((4)(CF_3SO_3)$_2$).** A mixture of 3-aminoquinoline (1.4 g, 9.50 mol) and 2,6-pyridinedicarbonyl dichloride (1.00 g, 4.75 mmol) in 40 mL of dry toluene was stirred under refluxed for 4 h. The yellow precipitate was collected by filtration and washed with acetone and 5% $NaHCO_3$ to give *N*,*N*′-bis-(3-quilonyl)pyridine-2,6-dicarboxamide (1.80 g) in 87% yield, which was reacted with 20 equiv of CH_3I in DMF/acetone (1:1 v/v, 50 mL) for 5 days. The resulting yellow powder was filtered and washed with cold MeOH to give (**4**)I_2. The iodide salt (0.30 g, 0.42 mmol) was dissolved in 300 mL of hot MeOH, 2 equiv of silver triflate (0.22 g, 0.85 mmol) were added, and the mixture was stirred overnight at room temperature. The precipitate was filtered off and the solvent was removed under reduced pressure to produce the product (0.18 g) in 58% yield. ^1H NMR (300 MHz, DMSO-d_6) δ 11.88 (s, 2H), 10.11 (s, 2H), 9.66 (s, 2H), 8.58 (m, 6H), 8.50 (t, J = 7.59 Hz, 1H), 8.26 (t, J = 7.85 Hz, 2H), 8.10 (t, J = 7.74 Hz, 2H), 4.80 (s, 6H); ^{13}C NMR (300 MHz, DMSO-d_6) δ 162.5, 147. 5, 144.7, 141.2, 135.9, 134.5, 134.1, 132.3, 130.5, 129.9, 129.3, 126.5, 122.8, 119.3, 118.5, 49.2; MS (FAB, m/z) 598 [M + Tf]$^+$; IR (KBr) 3318, 3083, 1690, 1549, 1278 cm^{-1}. Anal. Calcd for $C_{29}H_{23}F_6N_5O_8S_2$ (747.643): C, 46.59; H, 3.10; N, 9.37. Found: C, 46.60; H, 3.10; N, 9.35.

X-ray Crystallography. Crystals of salts of isomers of **1** suitable for X-ray diffraction were grown by slow solvent evaporation from aqueous solutions. Crystals of salts of (**3**)(CH_3SO_3)$_2$ and (*p*-**1**)$_3$(Cl)$_2$(CF_3SO_3)$_4$ were grown also by slow solvent evaporation from MeCN and (**4**)(CF_3SO_3)$_2$ from MeOH.

X-ray diffraction studies were performed on a Bruker-APEX diffractometer with a CCD area detector ($\lambda_{M\sigma K\alpha}$ = 0.71073 Å, monochromator: graphite). Frames were collected at T = 100 K (via ω/ϕ-rotation at 10 s per frame (SMART).[39a] The measured intensities were reduced to F^2 and corrected for absorption with SADABS (SAINT-NT).[39b] Corrections were made for Lorentz

(38) Jain, S. L.; Bhattacharyya, M. H. L.; Slawin, A. M. Z.; Crayston, J. A.; Woollins, J. D. *Dalton Trans.* **2004**, 862–871.

(39) (a) Bruker Analytical X-ray Systems, *SMART*: Bruker Molecular Analysis Research Tool, Versions 5.057 and 5.618, 1997 and 2000. (b) Bruker Analytical X-ray Systems. *SAINT + NT*, Versions 6.01 and 6.04, 1999 and 2001. (c) Sheldrick, G. M. *SHELX86*, Program for Crystal Structure Solution; University of Göttingen: Göttingen, Germany, 1986. (d) Bruker Analytical X-ray Systems, *SHELXTL-NT*, Versions 5.10 and 6.10, 1999 and 2000

and polarization effects. Structure solution, refinement, and data output were carried out with the SHELXTL-NT program package.[39c,d] Non-hydrogen atoms were refined anisotropically. C−H hydrogen atoms were placed in geometrically calculated positions, using a riding model. O−H and N−H hydrogen atoms have been localized by difference Fourier maps and refined fixing the bond lengths to 0.84 and 0.86 Å, respectively; the isotropic temperature factors have been fixed to a value 1.5 times that of the corresponding oxygen/nitrogen atoms. Figures were created with SHELXTL-NT.[39c,d] Hydrogen-bonding interactions in the crystal lattice were calculated with the WINGX program package.[40]

Crystallographic data for the five crystal structures have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications no. CCDC 756624−756630. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44)1223−336−033; e-mail: deposit@ccdc.cam.ac.uk, www: http://www.ccdc.cam.ac.uk).

Calculation Method. Electronic structure calculations in the gas phase were performed with Jaguar (versions 7.5 and 7.6) quantum chemistry software.[41] DFT calculations were carried out with Becke's[42] three-parameter functional and the correlation function of Lee, Yang, and Parr (B3LYP).[43] The geometries of all complexes were optimized by using the standard 6-31G(**) basis set. The solvation energies were determined by using the self-consistent reaction field (SCRF) method combined with a Poisson−Boltzmann solver coded in Jaguar.[44] Calculated absolute energies and the number of imaginary frequencies for all complexes are given in Table S2 (Supporting Information).

Spectrophotometric and ^{1}H NMR Titrations. The absorption spectra were recorded after additions of aliquots of guests stock solutions in MeCN to a 10^{-5}−10^{-4} M receptor solution in a quartz cuvette placed in a compartment of a diode array spectrophotometer thermostated at 25 ± 0.1 °C with a recirculating water bath. NMR titrations were performed on a 300 MHz spectrometer with more concentrated stock solutions of guests in CH_3CN-d_3 adding aliquots of them to 5−20 mM receptor solutions directly to NMR tubes. Nonlinear least-squares fits of the experimental results to the binding isotherms for 1:1 complexation equilibria were performed by using the Microcal Origin version 7.5 program. For analysis of more complex equilibria the Hyperquad 2003 program[45] was employed.

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Supporting Information Available: Crystallographic data, spectrophotometric and ^{1}H NMR titrations, ^{1}H and ^{13}C NMR spectra for synthesized compounds, and Cartesian coordinates for calculated structures of chloride complexes. This material is available free of charge via the Internet at http://pubs.acs.org.

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