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Salt-Solubilization and Ion-Pair Recognition by a Quinoline-Substituted Crown Ether

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A novel quinoline-substituted crown ether has been synthesized as a receptor for ion pairs and its binding behavior was investigated in various solvents. The binding of ion pairs in $[D_6]$DMSO and in mixed $[D_6]$DMSO/CD_3CN/$CDCl_3$ solvents was studied and the results revealed positive cooperativity effects. As a novel solubilizing agent, the crown ether can extract halide salts into organic media, especially chloride salts. ESI MS provided evidence for the formation of salt-receptor complexes. A recycling experiment showed that the receptor can solubilize salts and can be recovered. This process can be performed as a cycle. This study validates the idea that a straightforward combination of a common anion receptor and a well-studied cation complexation moiety enables the formation of ion-pair receptors and solubilizers of salts in organic solvents.

Introduction

Crown ethers were first described by C. J. Pedersen in the late 1960s[1] and have been widely applied in cation-sensing,[2] ditopic receptors,[3] catenane/rotaxane construction,[4] salt extraction,[5] supramolecular catalysis,[6] and phase-transfer catalysis.[7] The concept of ion pairs was early on discussed by Winstein et al. in the context of substitution reactions. They studied the acetolysis of 3-anisyl-2-butyl arylsulfonates and some other compounds.[8] In supramolecular chemistry, ion-pair recognition, emerging from simultaneous anion and cation coordination, has become an important field[9] and its investigation helps, for example, to understand catalysis mechanisms and to design catalysts. Some elegant studies in the field were described by, among others, Reinhoudt,[10] Beer,[9c,11] Smith,[3,12] Barboiu,[13] and Sessler[9a,9b,14] and their co-workers. Due to the conformational features of calix[4]diquinones, Beer and collaborators have investigated cooperative and ion-pair recognition by a series of calix[4]diquinone receptors.[11c] Smith and co-workers focused on the ion-pair binding properties of macrobicyclic receptors and also used them in selective solid–liquid extraction.[12b,12d] Recently, Sessler and collaborators described the recognition behavior of ion pairs of KF and CsF by a calix[4]pyrrole as well as their respective co-crystal structures.[14b]

Salt extraction and solubilization has developed with the investigation of ion-pair recognition and stabilization and is an inadequately explored area that permits ionic reactions to occur in aprotic media.[1] In 1996, Reinhoudt et al. reported a bifunctional calix[4]arene that was capable of binding anions and cations simultaneously and solubilized sodium halides into chloroform.[10c] In 1999, White and Tasker et al. studied a series of ditopic ligands for the simultaneous extraction of cations and anions.[15] Smith et al. ingeniously designed and investigated ion-pair binding and solubilization of KCl salts into dimethyl sulfoxide (DMSO).[12b] Until now, our research has focused on the binding of only anions. In this context, 2-amido-8-aminoquinolines were utilized as backbones for anion-sensing[16] and foldamer-construction.[17] We have systematically studied various types of such derivatives to tune the anion affinity of this class of receptors.[18]

Herein, we report the synthesis of a novel receptor based on quinoline and crown ether and discuss its binding behavior towards halide anions in solution. As a ditopic receptor, it binds ion pairs in various solvents and shows cooperative effects. In addition, the crown ether can efficiently solubilize inorganic halide salts into organic media, as a phase-transfer carrier, and can be subsequently regenerated.

Results and Discussion

Preparation of Receptor 4

Initially, methyl 4-isobutoxyl-8-nitroquinoline-2-carboxylate (**1**) was reduced to the corresponding amine and subsequently reacted with phenyl isocyanate to afford methyl 4-isobutoxy-8-(phenylureido)quinoline-2-carboxylate (**2**), the saponification of which was achieved in methanol/tetrahydrofuran (THF) solution with KOH to provide the quinoline carboxylic acid **3** in high yield. Receptor **4**

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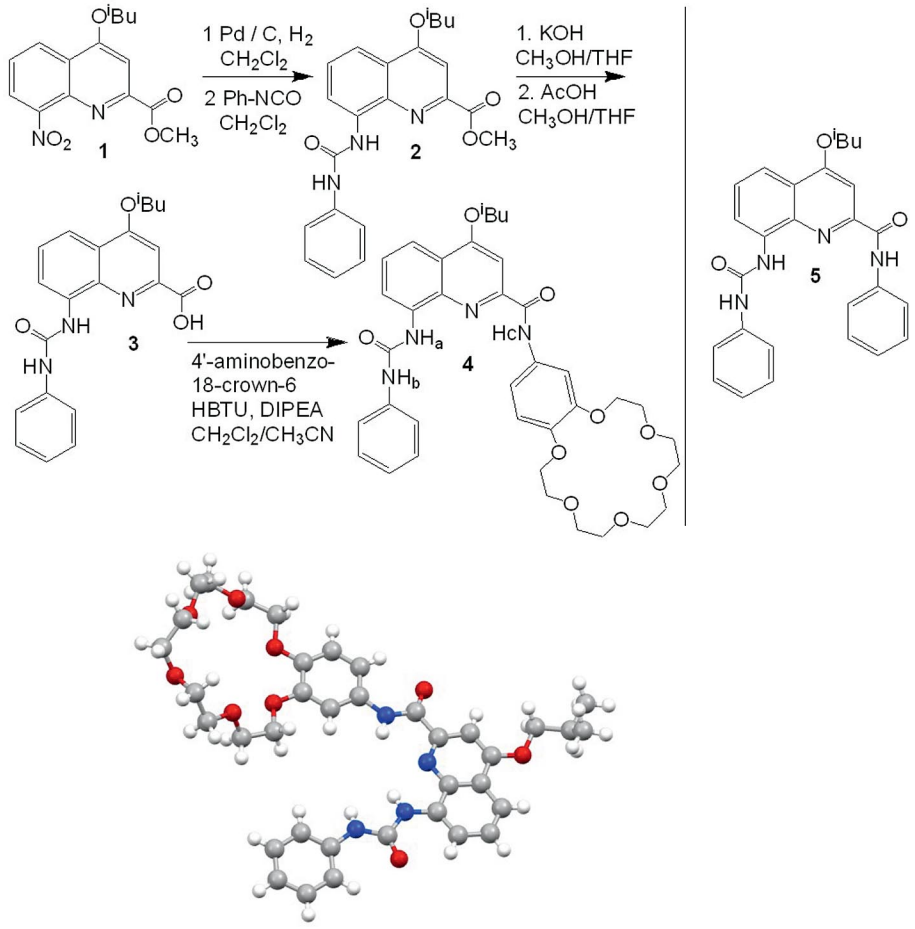


Figure 1. Synthesis of receptor **4** and its structure in the crystal obtained from DMSO (gray, C; white, H; blue, N; red, O); the chemical structure of control **5** is also included.

was obtained from acid **3** by reaction with freshly reduced 4′-aminobenzo-18-crown-6 in the presence of HBTU [*O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyl-uroniumhexafluorophosphate] and DIPEA (*N*,*N*′-diisopropylethylamine) in dichloromethane/acetonitrile. The obtained compounds were fully characterized by ^{1}H NMR, ^{13}C NMR, IR, mass spectra, melting points and elemental analyses. Two different crops of single crystals of receptor **4** were obtained from CH_3CN/CH_2Cl_2 and from DMSO and were analyzed by X-ray single-crystal diffraction.

The molecular structures obtained from both single-crystal studies proved to be very similar. Only one of the structures will be briefly discussed. The molecular structure of **4** from DMSO in the crystal is shown in Figure 1; it reveals the presence of the quinoline-based anion binding site as well as the crown ether cation recognition unit. As anticipated, the two acidic hydrogen atoms of the amide and urea groups are oriented to the front of the quinoline nitrogen atom with a distance of 2.275 and 2.269 Å, respectively, which fixes the geometry at this unit and facilitates anion binding. The 18-crown-6 has been well-studied as an excellent binding site for cations, especially for potassium ions. The presence of both an anion binding site and a cation binding site should ensure the possibility of binding ion pairs in solution.

Binding of Halide Anions in $CDCl_3$ Solution

Initially, the binding behavior of receptor **4** towards tetrabutylammonium (Bu_4N^+) halide salts was examined by ^{1}H NMR analysis in $CDCl_3$ (Figure 2). This was used as a control experiment that focused on binding of the anion at the quinoline unit. With the successive addition of Bu_4NBr salts, the three acidic hydrogen atoms of receptor **4** in $CDCl_3$ shifted downfield 0.35, 0.67 and 0.34 ppm, respectively, which indicated that there were interactions between receptor **4** and bromide anions.

In $CDCl_3$ at 298 K a 1:1 binding stoichiometry was shown by Job's method for receptor **4** and halide anions. The Job plots of receptor **4** and bromide anions are shown in Figure 3 (bottom).

Subsequently, titration experiments of receptor **4** and Bu_4N^+ halide salts were carried out in $CDCl_3$ at 298 K. Standard methods of nonlinear regression[19] treatment of titration data enabled the binding constants to be calculated

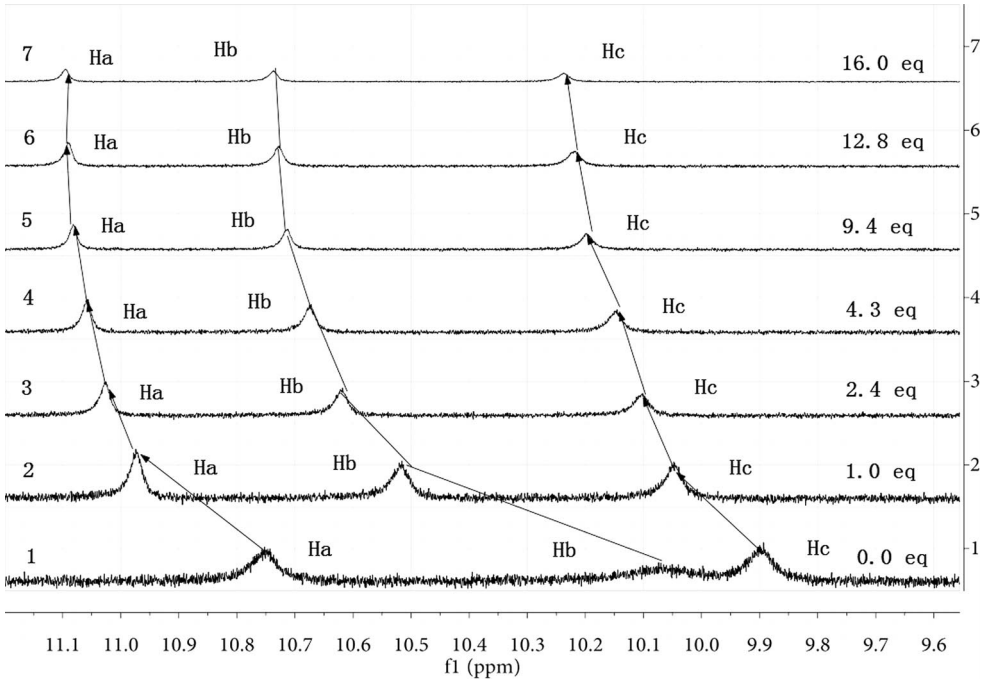


Figure 2. Partial ^{1}H NMR spectra ($CDCl_3$, 300 MHz, 298 K) of receptor **4** after successive addition of Bu_4NBr (for assignment of the protons see Figure 1).

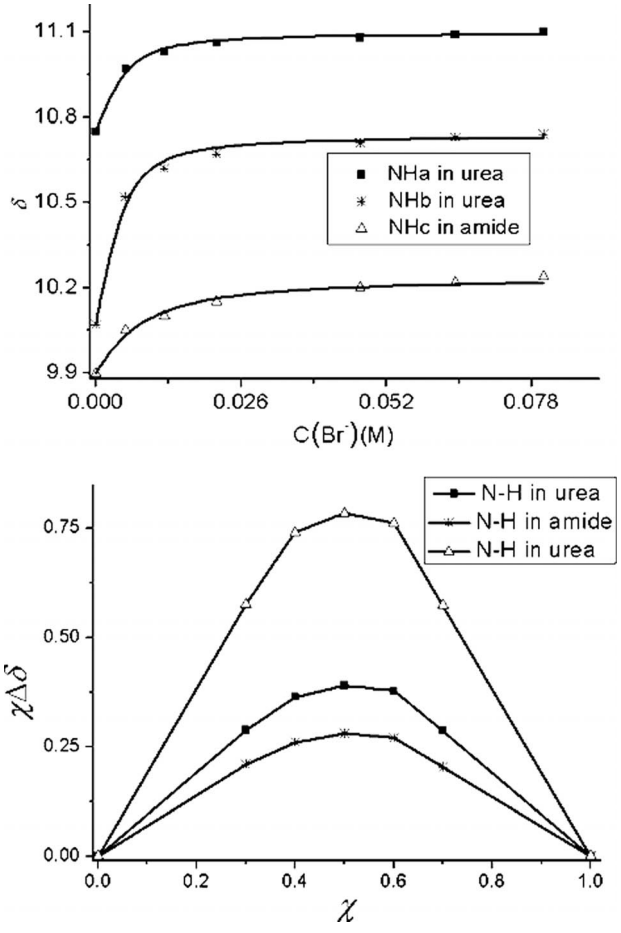


Figure 3. Titration curves of receptor **4** (0.005 M) towards bromide anions (top) and corresponding Job plots in $CDCl_3$ at 298 K (bottom, χ denotes mol fraction of receptor **4**).

as shown in Table 1. As a control, receptor **5**, which was reported previously by our group,[18b] was also studied. For comparison, the binding constants for receptors **4** and **5** towards halide anions are listed in Table 1.

Table 1. Binding constants (K, M^{-1}) of receptor **4** and control **5** with Bu_4N^+ halides in $CDCl_3$ at 298 K. The binding constants were determined by ^{1}H NMR titration experiments in $CDCl_3$ and fitted according to a 1:1 binding ratio based on Job plots. Errors are estimated to be less than 15%.

	Cl^-	Br^-	I^-
4	1008	525	236
5[18b]	7700	1100	_[a]

[a] Not reported.

The affinities of receptor **4** towards halide anions decrease in the order: $Cl^- > Br^- > I^-$. This tendency would be expected to arise from the different basicities of halide anions and the size of the receptor binding pocket. For a given receptor, the more basic the anion is (i.e., the less acidic the conjugate acid), the higher the binding affinity.[20,21] In addition, the approximate diameter of the hydrogen cavity for receptor **4** ranges from 2.968 to 3.956 Å (see the Supporting Information). The extent of the match decreases with increasing anion diameter. Receptor **4** shows lower binding affinities for specific anions compared with analogue **5**. Presumably, the hydrogen atoms of the amide group in **4** are less acidic due to the presence of extra alkyloxy groups at the phenyl group as well as due to the entropy loss and the steric hindrance effect of the crown ether substituent. Nevertheless, **4** is still a reasonable receptor for anions in solution.

Binding of Halide Anions and Ion Pairs in [D_6]DMSO and in Mixed Solvent Solutions

The binding behavior of receptor **4** towards ion-pairs was probed in [D_6]DMSO by means of ^{1}H NMR spectroscopy. Initially, the 1:1 binding stoichiometry between receptor **4** and halide anions was established from Job plots with metal cations being either present or absent (see the Supporting Information). Titration experiments were also conducted in [D_6]DMSO in the presence and absence of potassium cations, in the form of $KBPh_4$ (potassium tetraphenylborate), at 298 K, as shown in Figure 4. The obtained data were fitted by using standard methods of nonlinear regression[19] to afford binding constants between receptor **4** and chloride and bromide as 212 and 45 M^{-1} with tetrabutylammonium and 397 and 51 M^{-1} with potassium cations, respectively. According to Beer and co-workers' report, cooperativity factors were defined as $K_{ion\ pair}/K_{anion,\ free}$.[11c] The cooperativity factors for receptor **4** and chloride and bromide anions were calculated as 1.87 and 1.13, respectively.

Receptor **4** shows the tendency of decreasing binding affinities towards $Cl^- > Br^- > I^-$. In addition, a slight enhancement in chloride and bromide recognition was observed in the presence of potassium cations. This has two effects on the anion binding properties: (1) once the 18-crown-6 cavity binds a potassium cation, cation–dipole forces induce the N-H in the amide group to become more acidic; (2) the potassium cation introduces a positive charge resulting in an electrostatic attraction of the anion. Although the cooperativity effect is weak, we have to consider that the data are measured in DMSO, a highly competitive polar aprotic solvent.

To gain more insight into the cooperativity effect, we probed the ion-pair binding properties of receptor **4** in less competitive solvents. For solubility reasons, the mixed solvent system CD_3CN, $CDCl_3$ and [D_6]DMSO (v/v/v, 8:1:1) was chosen. The titration experiments between receptor **4** and halide anions were carried out in this less polar solvent and the obtained data were fitted by using standard methods of nonlinear regression, as shown in Figure 5. The

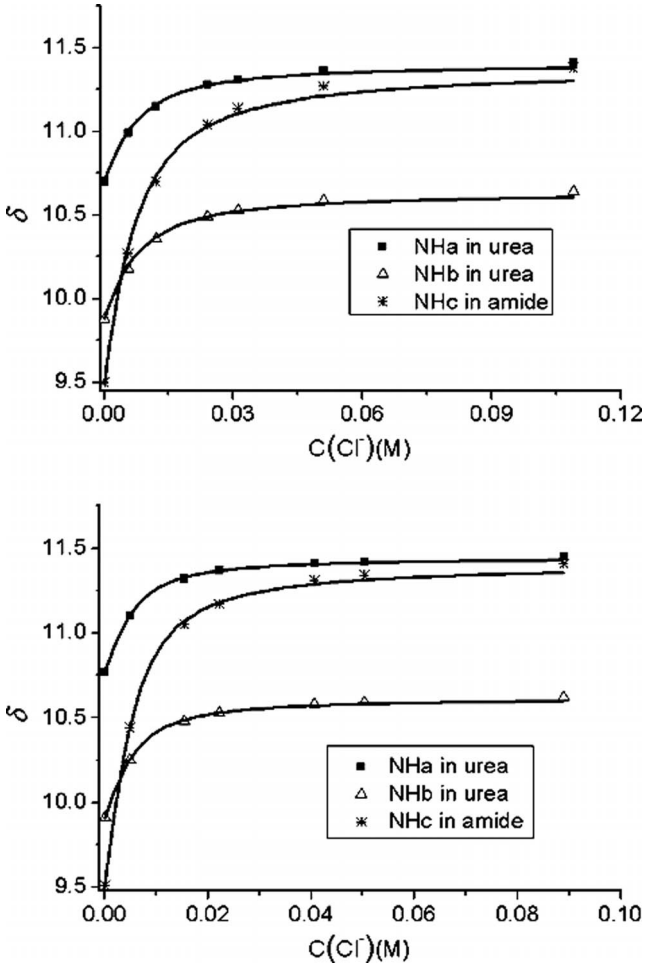


Figure 4. Titration curves of receptor **4** in the absence (top) and presence (bottom) of potassium cations (as $KBPh_4$, 1.0 equiv.) towards chloride anions in [D_6]DMSO at 298 K.

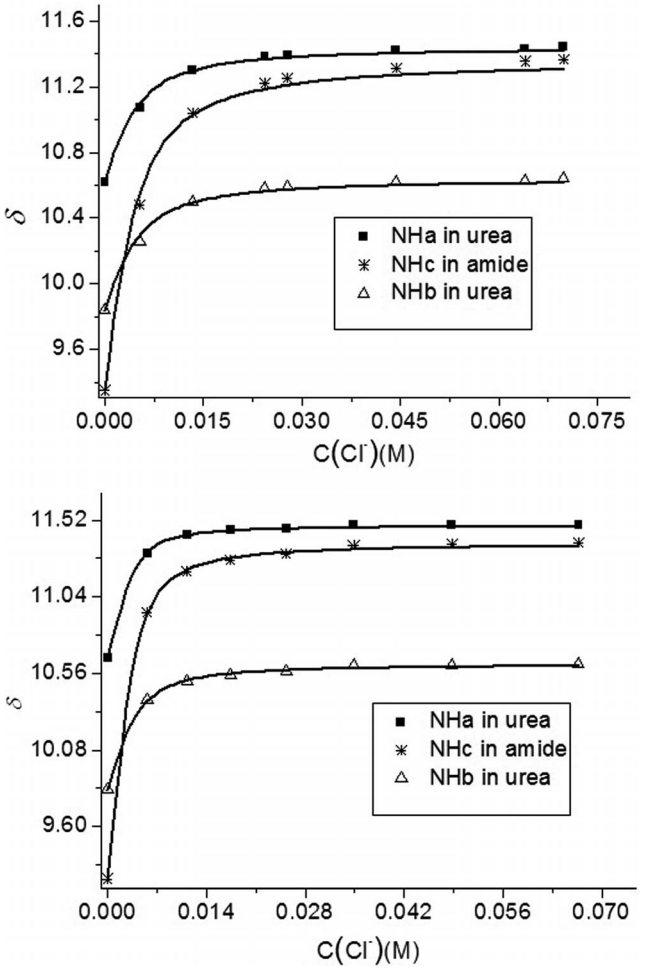


Figure 5. Titration curves of receptor **4** in the absence (top) and presence (bottom) of $KBPh_4$ towards chloride anions in mixed solvent of $CD_3CN/CDCl_3$/[D_6]DMSO (v/v/v, 8:1:1).

binding constants of receptor **4** towards chloride and bromide anions were measured as 470 and 106 M^{-1} in the absence of potassium cations and 1556 and 253 M^{-1} in the presence of potassium cations, respectively.

For comparison, the binding constants in [D_6]DMSO and in mixed solvent are listed in Table 2.

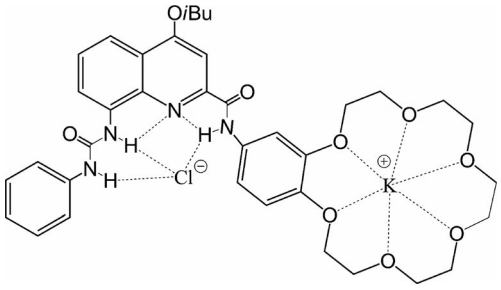
Table 2. Binding constants (K, M^{-1}) of receptor **4** with halide anions (as Bu_4N^+ salts) in the absence and presence of $KBPh_4$ (1.0 equiv.) in [D_6]DMSO and in mixed solvent (v/v/v 8:1:1, $CD_3CN/CDCl_3$/[D_6]DMSO) at 298 K. Cooperativity factors describe the ratio $K_{ion\ pair}/K_{anion}$. The binding constants were determined by ^1H NMR titration experiments and fitted according to a 1:1 binding ratio. Errors are estimated to be less than 15%. No chemical shift changes were observed upon addition of Bu_4N^+ iodide in either case.

Guest	Solvent/host	K [M^{-1}]	Cooperativity factor
	[D_6]DMSO		
Cl^-	free **4**	212	1.87
	4 + K^+	397	
Br^-	free **4**	45	1.13
	4 + K^+	51	
	$CD_3CN/CDCl_3$/[D_6]DMSO		
Cl^-	free **4**	470	3.31
	4 + K^+	1556	
Br^-	free **4**	106	2.39
	4 + K^+	253	

Upon examination of the data shown in Table 2, a number of conclusions can be drawn. As expected, because the solvents are less competitive, all of the binding constants become higher in the absence as well as in the presence of potassium cations. Furthermore, receptor **4** was found to bind the halide anions in the mixed solvent with the same trend ($Cl^- > Br^- > I^-$) as found in [D_6]DMSO. The cooperativity factors for Cl^-/Br^- of 1.87/1.13 in [D_6]-DMSO increased to 3.31/2.39 in mixed solvents. The less competitive solvent mixture not only facilitates hydrogen bonding between the receptor and anions but also supports other interactions, such as induced acidity and electrostatics due to the presence of potassium cations. The changes of binding affinities of receptor **4** towards potassium cations are expected to be another factor that facilitates anion binding. Consequently, the cooperativity factors rise.

Predicted Binding Mode

Based on the above results, a possible binding mode is shown in Scheme 1. Considering the low cooperativity factors, the binding mode is classified as separated heteroditopic ion pair recognition.[9c,11c] The low cooperativity factors are ascribable to the rigidity of the spacer phenyl group between the anion binding site and the cation complexation site.



Scheme 1. Possible binding mode of receptor **4** with ion-pair K^+/Cl^-.

Solubilizing of Salts in Chloroform

Some inorganic salts have been used in catalysis and have critical effects on organic reactions occurring in aprotic phases. For instance, sodium or potassium hypochlorite were employed in enantioselective epoxidation of α,β-unsaturated ketones.[22] However, most inorganic salts possess a low solubility in organic phases. Because receptor **4** has binding sites for both cations and anions, it is possible to be applied for the solubilization of inorganic salts, such as KCl, NaCl or NH_4Cl into organic solvents. A ^1H NMR spectroscopy study showed that receptor **4** is capable of solubilizing the mentioned salts into chloroform. The changes of chemical shifts corresponding to N-H groups and to the crown ether are depicted in Figure 6.

The samples for ^1H NMR spectroscopy were prepared by mixing receptor **4** and an excess of solid salts (KCl, NaCl or NH_4Cl) followed by stirring for 12 h in the NMR test tubes. As a representative example, receptor **4** interacting with KCl in $CDCl_3$ is discussed below in detail. In the presence of KCl, the peaks corresponding to the N-H groups of the urea and the N–H of the amide of receptor **4** clearly shifted downfield with $\Delta\delta$ = 1.31, 0.81 and 2.54 ppm, respectively (Figure 6, top B). This is similar to what was observed for binding of Bu_4NCl in $CDCl_3$. Moreover, changes of the ^1H NMR chemical shifts in the crown ether region of receptor **4** were also observed. In the absence of KCl, the crown ether is flexible and shows overlapping multiplets in the 3.60–4.05 ppm region of the ^1H NMR spectrum (Figure 6, bottom A). In the presence of KCl salts, the corresponding peaks became less overlapping and expand to 3.35–4.10 ppm. This indicates a rigidification of the crown ether due to complexation with cations (Figure 6, bottom B).[23] The significant changes in the spectra were attributed to the interaction of receptor **4** with KCl. These results support the idea that receptor **4** is capable of solubilizing KCl into organic media, such as chloroform.

We also examined receptor **4** for its ability to extract other inorganic salts into chloroform at room temperature. The changes in chemical shifts of NH protons upon addition of various salts are summarized in Figure 7.

Upon examination of above data, we can summarize some conclusions:

(1) the significant downfield shifts in ^1H NMR spectra of receptor **4** upon addition of alkali and ammonium chlor-

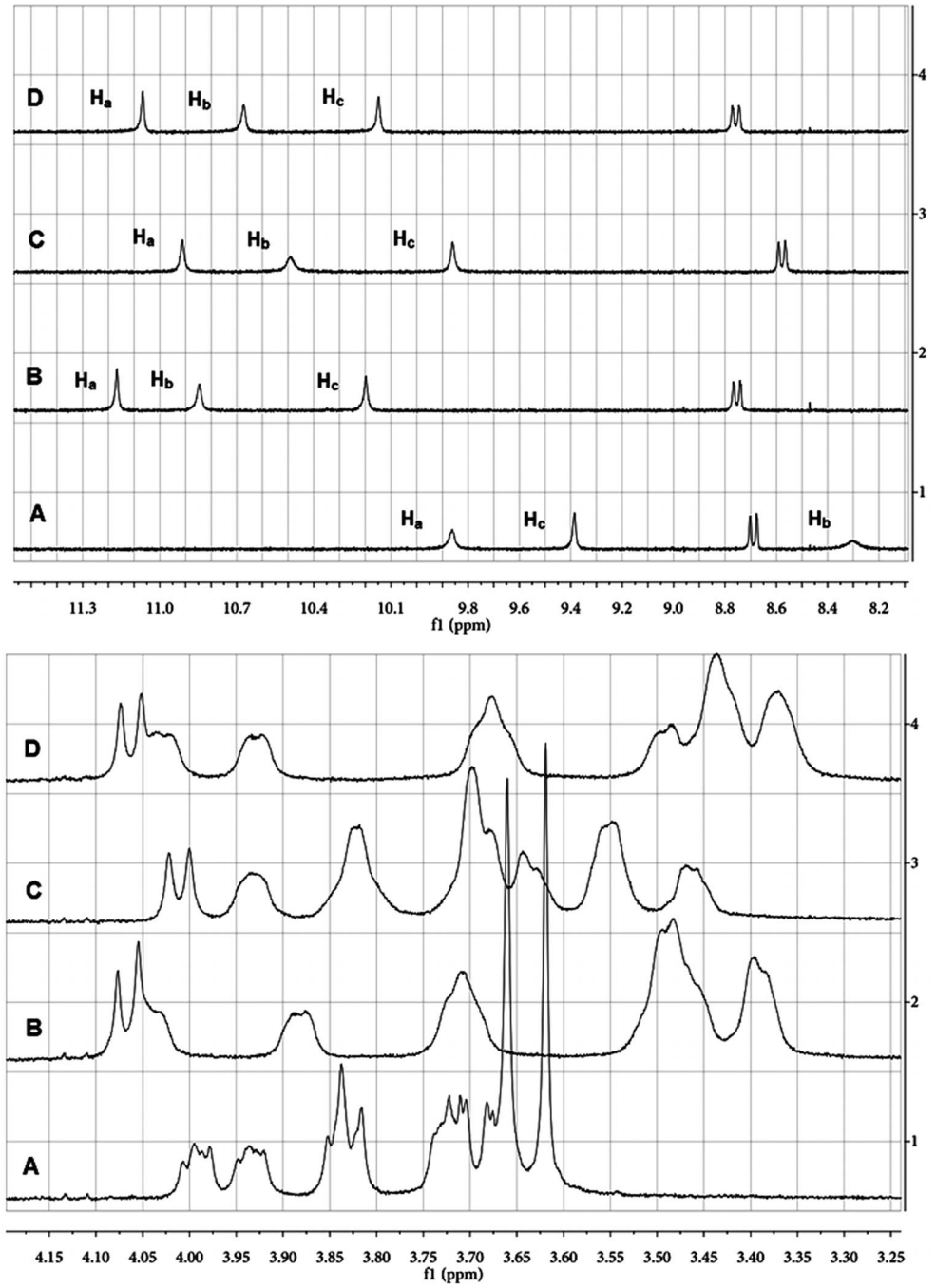


Figure 6. Region of NH signals (top) and the crown ether region (bottom) in the ^{1}H NMR spectra of (A) only **4**; (B) **4** in the presence of KCl; (C) **4** in the presence of NaCl; (D) **4** in the presence of NH_4Cl in $CDCl_3$ at 298 K.

ide salts suggest a strong interaction between receptor **4** and chloride salts, regardless of the nature of the cations. The slight downfield shifts in the ^{1}H NMR spectra of **4** towards fluoride and bromide salts suggest only weak interactions with receptor **4**. Interestingly, the anion fragments are the dominating control factor for the interactions. Receptor **4** can act as an excellent solubilizer for chloride salts irrespective of which cation is present as a counterion. Nevertheless, receptor **4** exhibits only weak binding ability towards bromide salts. This is consistent with the binding order: $Cl^- > Br^- > I^-$. Comparison of the proton $\Delta\delta$ of each set of protons of receptor **4** in the presence of soluble Bu_4NCl and of various insoluble chloride salts indicates that almost a stoichiometric amount of chloride salts is solubilized into chloroform by receptor **4**.[10c] However, the crown ether ring is crucial for this property. The corresponding NH signals of the analogous compound **5**[18b] without the crown ether shows only negligible downfield shifts upon addition of KCl

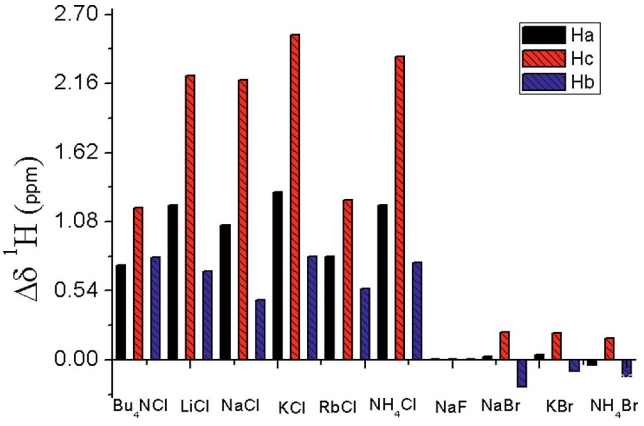


Figure 7. ^{1}H NMR chemical shift changes of receptor **4** in the presence of various salts in $CDCl_3$ at 298 K, $\Delta\delta = \delta$(in the presence of salts) – δ(free receptor).

(Figure 8, B), whereas a mixture of compound **5** and 18-crown-6 in 1:1 ratio is able to solubilize KCl into $CDCl_3$ at room temperature (Figure 8, C);

(2) The benzo-18-crown-6 fragment is well-known to act as a good potassium cation binding site. Consequently, the addition of potassium salts leads to the strongest binding for a given anion. For example, rubidium cations are somewhat larger and do not fit well into the crown ether ring, which causes minor chemical shift changes.

(3) The presence of counter cations as guests increases the selectivity of receptor **4** towards anions. As discussed above, the size of the hydrogen-bond donor cavity of receptor **4** is better suited for chloride anions than for bromide anions. In solution of either [D_6]DMSO or mixed solvents, receptor **4** showed comparable binding affinities towards chloride and bromide tetrabutylammonium salts. However, receptor **4** revealed negligible binding affinities toward metal bromide salts compared with metal chloride salts, even for the potassium bromide.

Solubilizing of Salts into DMSO

Receptor **4** can also be used to extract chloride salts into DMSO. The results are illustrated in Figure 9 (top). In addition, "titration" experiments of receptor **4** towards KCl were carried out in [D_6]DMSO at room temperature (Figure 9, bottom). As shown, the ^{1}H NMR signals corresponding to the respective NH groups of receptor **4** shift downfield dramatically with the addition of KCl in [D_6]-DMSO. However, the binding constant between receptor **4** and KCl salts could not be obtained due to low solubility of the potassium salt. The cases for NaCl and NH_4Cl are similar. The "titration" experiments are detailed in the Supporting Information.

Mass Spectrometric Investigations

The formation of salt complexes of receptor **4** with KCl was also confirmed by ESI mass spectrometry. After solid–liquid extraction, the mixtures were filtered, concentrated, dried in vacuo, and measured in chloroform by ESI MS. In the positive ESI mass spectra region of the **4**-KCl complex,

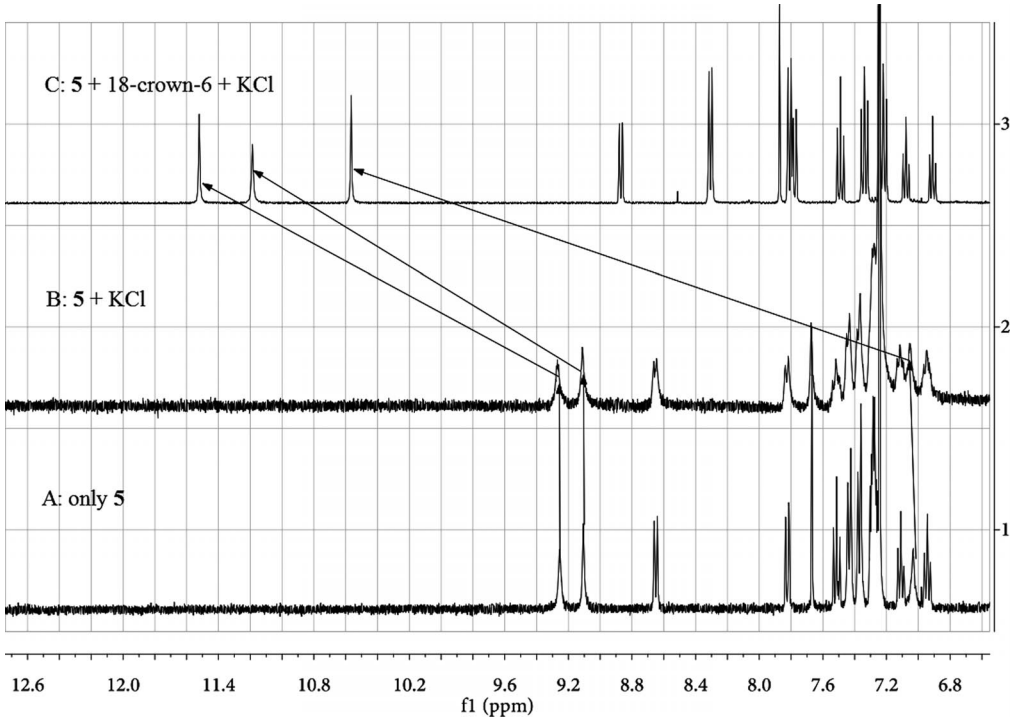


Figure 8. Partial ^{1}H NMR regions of (A) control **5**, (B) **5** in the presence of KCl, and (C) **5** with 18-crown-6 in the presence of KCl in $CDCl_3$ at 298 K.

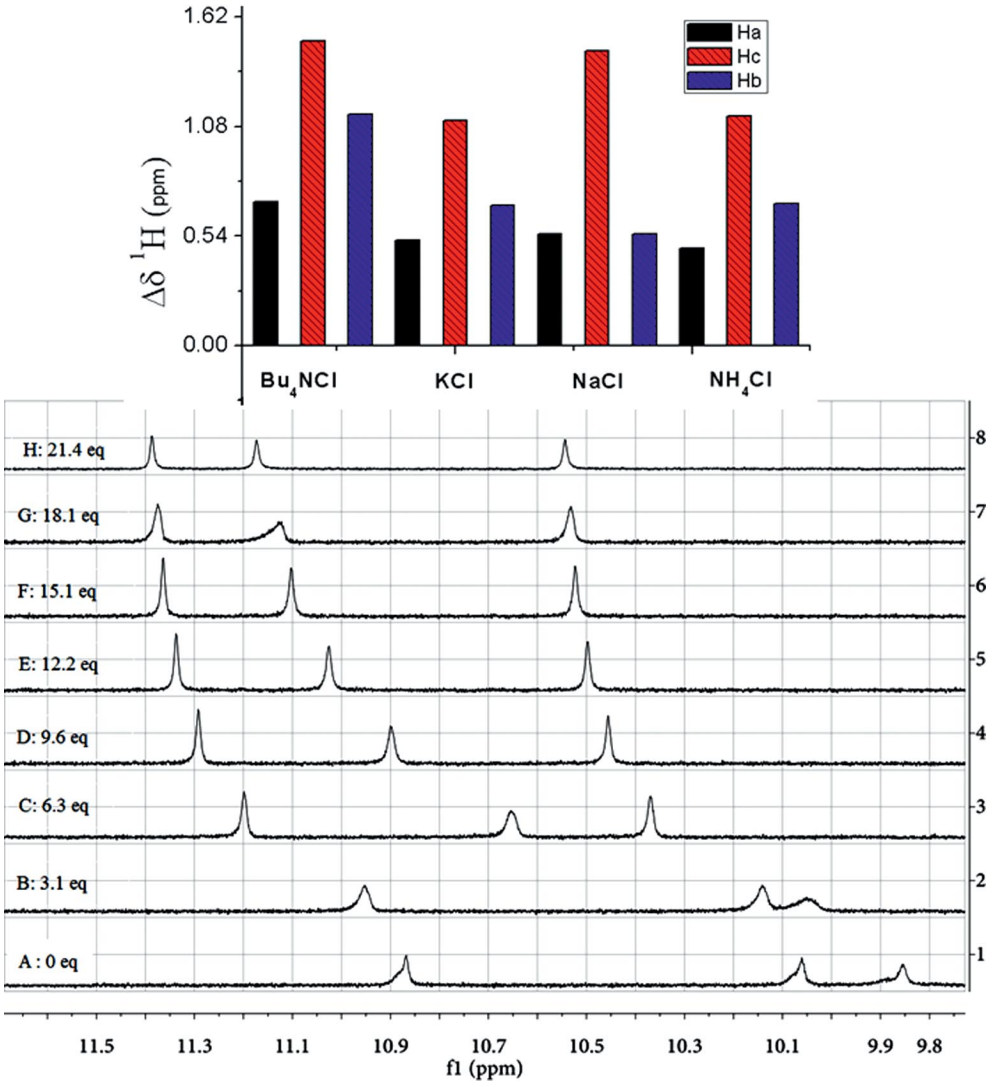


Figure 9. ^{1}H NMR chemical shift changes of receptor **4** in the presence of various chloride salts in [D$_6$]DMSO [$\Delta\delta = \delta$(in the presence of salts) – δ(free receptor)] (top), and partial ^{1}H NMR regions of receptor **4** with successive addition of KCl in [D$_6$]DMSO (bottom).

two peaks of *m*/*z* 727.279 (100.00%) and 1489.529 (80.00%) are observed, corresponding to [**4**+K]$^+$ and [2 **4** + Cl + 2 K]$^+$, respectively. In addition, the peak of *m*/*z* 723.282 (100.00%) appeared in the negative ESI mode, corresponding to [**4** + Cl]$^-$ (see parts A, B of MS data in Figure 10, for full MS see the Supporting Information). Similar results were obtained for NaCl and NH_4Cl (see the Supporting Information). These results provided additional evidence for the binding of salts to receptor **4** in $CDCl_3$.

Receptor Recycling Study

Finally, the feasibility of using the receptor for repeated KCl extraction was studied by monitoring the extraction–release cycle of KCl (solid–$CHCl_3$–water–solid; Scheme 2). Based on ^{1}H NMR analysis, KCl was easily extracted into chloroform by receptor **4** and released into the aqueous phase by water-washing. Thereby, the receptor remains in the organic phase, which can be used for the dissolution of salts again. Initially, a solution of receptor **4** (0.01 M) in $CDCl_3$ (0.80 mL) was measured by ^{1}H NMR analysis at 298 K, and the peaks of receptor **4** in $CDCl_3$ solution corresponding to H_a, H_b and H_c were found at 10.01, 9.48 and 8.55 ppm, respectively (see the Supporting Information). Subsequently an excess of solid KCl was added into the NMR tubes and the mixture was stirred for 12 h. After the treatment, NMR peaks of receptor **4** corresponding to H_a, H_b and H_c shifted downfield to 11.12, 10.14 and 10.75 ppm, respectively. Finally, the sample was washed with water, dried with $MgSO_4$ and solvent was removed in vacuo. The ^{1}H NMR spectrum of receptor **4** recovered from organic phase in $CDCl_3$ (0.8 mL) showed shifting to 9.99, 9.44 and 8.62 ppm, respectively, which were almost identical to the original positions. The KCl was isolated from the aqueous phase. The process could also be followed by monitoring the crown ether protons (see the Supporting Information).

Similar extraction experiments could be performed by using a 1:1 mixture of 18-crown-6 and receptor **5**. However,

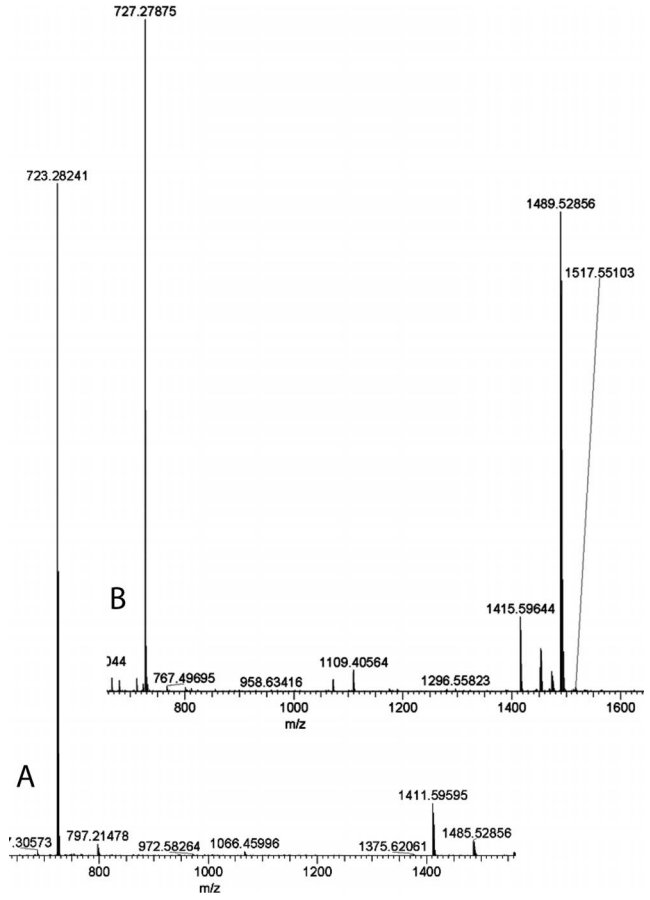
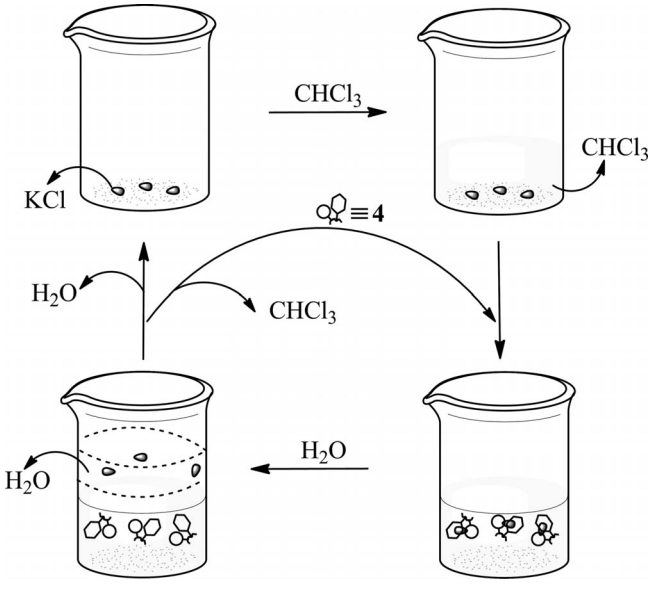


Figure 10. Part of the positive region (B) and negative region (A) of ESI mass spectra of **4**-KCl.

in this case, the differing solubilities of the two components caused problems on a longer term. After several cycles, the differing solubilities of 18-crown-6 and receptor **5** affect the ratio between anion-binding sites and cation-binding sites, which decreases their solubilization ability.



Scheme 2. Extraction–release solid–$CHCl_3$–water–solid cycle.

Conclusions

A novel ditopic receptor based on quinoline and crown ether has been prepared and its ion-pair binding and solubilizing properties were investigated. As a receptor, **4** can bind anions as well as ion-pairs and shows positive cooperativity effects when binding ion-pairs in solution. Furthermore, due to the presence of a binding site for anions and a binding site for cations, **4**, as a ditopic receptor, can extract inorganic salts into organic phases, such as chloroform and DMSO, and can be recycled. It has potential applications in separation science and catalysis. In addition, this study supports the idea that construction of ion-pair receptors and solubilizers of salts in organic phase can be achieved by means of a combination of a normal anion receptor and a cation-binding site.

Experimental Section

Synthesis of Receptor

4′-Aminobenzo-18-crown-6: A mixture of 4′-nitrobenzo-18-crown-6 (178 mg, 0.5 mmol, 1 equiv.) dissolved in CH_2Cl_2 (20 mL) and 10% Pd/C (30 mg) was stirred at room temperature under an atmosphere of hydrogen (20 bar) overnight. The solution was filtered through Celite and the filtrate was evaporated to dryness. The residue was used without characterization in the coupling reaction with **3**.

Methyl 4-Isobutoxy-8-(phenylureido)quinoline-2-carboxylate (2): A mixture of **1**[17c] (304 mg, 1 mmol, 1 equiv.) dissolved in CH_2Cl_2 (20 mL) and 10% Pd/C (30 mg) was stirred overnight at room temperature under an atmosphere of hydrogen (20 bar). The solution was filtered through Celite and the filtrate was evaporated to dryness. The residue was used directly in the next step.

A solution of methyl 8-amino-4-isobutoxyquinoline-2-carboxylate (1 mmol, 1 equiv.) and phenyl isocyanate (0.33 mL, 3 mmol, 3 equiv.) in dichloromethane (30 mL) was stirred overnight. The solvent was then removed in vacuo and the residue was purified by recrystallization (dichloromethane/MeOH) to allow isolation of a light-yellow solid, yield 169 mg (43%); m.p. 198–200 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 9.54 (s, 1 H), 8.68 (d, J = 12.0 Hz, 1 H), 7.80 (d, J = 6.0 Hz, 1 H), 7.57 (m, 2 H), 7.52 (d, J = 12.0 Hz, 2 H), 7.48 (s, 1 H), 7.35 (t, J = 6.0 Hz, 2 H), 7.11 (t, J = 6.0 Hz, 1 H), 4.04 (m, 5 H), 2.31 (m, 1 H), 1.16 (d, J = 6.0 Hz, 6 H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 166.03, 163.02, 152.58, 145.90, 138.55, 136.35, 129.11, 128.74, 123.40, 122.15, 120.18, 116.00, 113.77, 100.99, 75.13, 53.00, 28.21, 19.25 ppm. IR (KBr): $\tilde{\nu}$ = 3441, 3345, 2959, 1706, 1603, 1525, 1442, 1417, 1388, 1358, 1315, 1277, 1232, 1193, 1069, 1017, 994, 852, 817, 787, 754, 690 cm^{-1}. MS (CI): m/z (%) = 301.2 (100.00) $[C_{16}H_{17}N_2O_4]^+$, 394.2 (64.82) $[M + H]^+$, 275.2 (62.85) $[C_{15}H_{19}N_2O_3]^+$. $C_{22}H_{23}N_3O_4 \cdot H_2O$: calcd. C 64.22, H 6.12, N 10.21; found C 64.17, H 5.89, N 9.76.

4-Isobutoxy-8-(phenylureido)quinoline-2-carboxylic Acid (3): Methyl ester **2** (787 mg, 1.0 equiv.) was dissolved in a mixture of THF (100 mL) and methanol (50 mL). KOH (2.5 equiv.) was added, and

the solution was stirred at room temperature overnight. The solution was neutralized by using an excess of AcOH, then the solvents were evaporated and the residue was dissolved in dichloromethane and washed with water, dried ($MgSO_4$) and evaporated to give a yellow solid, which was characterized by ^1H NMR and MS and used without further purification, yield 668 mg (88%). ^1H NMR (400 MHz, $CDCl_3$): δ = 10.94 (s, 1 H), 9.54 (s, 1 H), 8.65 (d, J = 8.0 Hz, 1 H), 7.91 (dd, J = 12.0 Hz, 1 H), 7.80 (s, 1 H), 7.67 (t, J = 8.0 Hz, 1 H), 7.25 (m, 2 H), 7.24–7.21 (m, 2 H), 6.98 (m, 1 H), 4.22 (d, J = 8.0 Hz, 2 H), 2.34 (m, 1 H), 1.17 (d, J = 8.0 Hz, 6 H) ppm. MS (ESI, +): m/z (%) = 380.16144 (100) $[M + H]^+$. MS (ESI, –): m/z (%) = 259.11346 (100) $[C_{14}H_{15}N_2O_3]^-$, 378.15274 (50) $[M – H]^-$.

4-Isobutoxy-8-(phenylureido)quinoline-2-carboxylic Acid (6,7,9,10,12,13,15,16,18,19-decahydro-5,8,11,14,17,20-hexaoxabenzocyclooctadecen-2-yl)amide (4): Diisopropylethylamine (DIPEA; 0.75 mmol) and HBTU (0.75 mmol) were added successively to an anhydrous CH_2Cl_2 (20 mL) and CH_3CN (40 mL) solution of a mixture of quinoline acid **3** (189 mg, 0.5 mmol, 1.0 equiv.) and freshly hydrogenatively reduced 4′-aminobenzo-18-crown-6 (0.5 mmol, 1.0 equiv.). The reaction was monitored by TLC. After stirring for 6 h under nitrogen at room temperature, the reaction mixture was washed with saturated aqueous NH_4Cl. The organic extract was dried with Na_2SO_4 and filtered. Solvent was evaporated to dryness and the residue was purified on silica gel (dichloromethane/methanol, 30:1, then 10:1, v/v) to allow isolation of the **4** as a light-yellow solid, yield 189 mg (55%); m.p. 225–227 °C. ^1H NMR (600 MHz, $CDCl_3$): δ = 9.70 (s, 1 H), 9.20 (s, 1 H), 8.57 (d, J = 7.5 Hz, 1 H), 8.17 (s, 1 H), 7.73 (d, J = 8.2 Hz, 1 H), 7.61 (s, 1 H), 7.42 (t, J = 7.9 Hz, 1 H), 7.36 (d, J = 7.7 Hz, 2 H), 7.21 (s, 1 H), 7.16 (t, J = 7.5 Hz, 2 H), 6.91 (t, J = 7.2 Hz, 1 H), 6.78 (d, J = 8.4 Hz, 1 H), 6.50 (d, J = 8.1 Hz, 1 H), 3.96 (s, 2 H), 3.90 (s, 2 H), 3.83 (d, J = 3.3 Hz, 2 H), 3.78 (d, J = 6.0 Hz, 2 H), 3.72 (s, 4 H), 3.69–3.65 (m, 6 H), 3.63 (s, 4 H), 2.15 (m, 1 H), 1.01 (d, J = 6.6 Hz, 6 H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 174.15, 173.72, 164.18, 159.86, 159.62, 156.88, 149.21, 148.77, 146.18, 141.64, 139.82, 138.53, 134.44, 132.86, 131.23, 128.35, 125.51, 125.46, 124.89, 119.13, 109.55, 85.82, 81.52, 81.48, 81.42, 81.38, 81.31, 80.34, 80.18, 80.01, 79.52, 38.81, 29.86 ppm. IR (KBr): $\tilde{\nu}$ = 3532, 3262, 3127, 3070, 2875, 2292, 2108, 1990, 1957, 1693, 1600, 1524, 1600, 1524, 1443, 1392, 1355, 1262, 1202, 1113, 1062, 950, 887, 858, 809, 755, 694 cm^{-1}. MS (ESI, +): m/z (%) = 711.29730 (100) $[M + Na]^+$. MS (ESI, –): m/z (%) = 723.26831 (100) $[M + H_2O + OH]^-$. $C_{37}H_{44}N_4O_9$ (688.78): calcd. C 64.52, H 6.44, N 8.13; found C 64.14, H 6.30, N 7.92.

X-ray quality crystals were obtained from DMSO: $C_{37}H_{44}N_4O_9{\cdot}2(C_2H_6OS)$; Mr = 845.02; crystal size $0.24 \times 0.09 \times 0.04$ mm^3; triclinic; space group $P\bar{1}$; a = 11.9166(16) Å, b = 13.5384(18) Å, c = 13.9031(19) Å; α = 83.641(3)°, β = 73.138(3)°, γ = 82.993(3)°; V = 2123.8(5) $Å^3$; Z = 2; $\rho_{calcd.}$ = 1.321 $g\,cm^{-3}$; μ = 0.19 mm^{-1}; $F(000)$ = 900.0; 26044 collected reflections θ_{max} = 26.570° of which 8807 were independent (R_{int} = 0.069); T_{max} = 0.993; T_{min} = 0.956; T = 100 K; full-matrix least-square on F^2 with 7 restraint and 551 parameters; GOF = 1.050; $R1$ = 0.0552[$I > 2\sigma(I)$]; $\omega R2$ (all data) = 0.1254; peak/hole = 0.57/–0.38 e $Å^{-3}$.

CCDC-929585 (**4** from DMSO) and -932302 (**4** from CH_2Cl_2/CH_3CN) contain the supplementary crystallographic data for this paper. These data are available free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Solid-Liquid Extraction:[24] Receptor **4** is soluble in appropriate deuterated solvents ($CDCl_3$ or [D_6]DMSO). Insoluble guests (such as KCl, NaCl, NH_4Cl etc.) were added in excess as powders, and the NMR tubes were stirred for 12 h at room temperature. After standing 1 h, the NMR spectra were acquired.

Supporting Information (see footnote on the first page of this article): ^1H and ^{13}C NMR spectra, titration curves, Job plots, MS, and XRD data.

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[1] C. J. Pedersen, *Science* **1988**, *241*, 536–540.
[2] C. J. Pedersen, *J. Am. Chem. Soc.* **1967**, *89*, 7017–7036.
[3] R. Shukla, T. Kida, B. D. Smith, *Org. Lett.* **2000**, *2*, 3099–3102.
[4] a) A. Coskun, M. Hmadeh, G. Barin, F. Gandara, Q. Li, E. Choi, N. L. Strutt, D. B. Cordes, A. M. Slawin, J. F. Stoddart, J. P. Sauvage, O. M. Yaghi, *Angew. Chem.* **2012**, *124*, 2202; *Angew. Chem. Int. Ed.* **2012**, *51*, 2160–2163; b) L. Fang, S. Basu, C. H. Sue, A. C. Fahrenbach, J. F. Stoddart, *J. Am. Chem. Soc.* **2011**, *133*, 396–399; c) Y. Liu, Z.-J. Zhang, *Synlett* **2012**, 1733–1750; d) Z. J. Zhang, H. Y. Zhang, H. Wang, Y. Liu, *Angew. Chem.* **2011**, *123*, 11026; *Angew. Chem. Int. Ed.* **2011**, *50*, 10834–10838.
[5] P. D. Beer, P. K. Hopkins, J. D. McKinney, *Chem. Commun.* **1999**, 1253–1254.
[6] T. Tozawa, S. Tokita, Y. Kubo, *Tetrahedron Lett.* **2002**, *43*, 3455–3457.
[7] a) D. J. Cram, G. D. Y. Sogah, *J. Chem. Soc., Chem. Commun.* **1981**, 625–628; b) T. A. Chupakhina, V. O. Kur'yanov, V. Y. Chirva, R. Y. Grigorash, S. A. Kotlyar, G. L. Kamalov, *Russ. J. Bioorg. Chem.* **2004**, *30*, 301–303; c) S. H. Korzeniowski, L. Blum, G. W. Gokel, *Tetrahedron Lett.* **1977**, *18*, 1871–1874.
[8] S. Winstein, E. Clippinger, A. H. Fainberg, R. Heck, G. C. Robinson, *J. Am. Chem. Soc.* **1956**, *78*, 328–335.
[9] a) S. K. Kim, J. L. Sessler, *Chem. Soc. Rev.* **2010**, *39*, 3784–3809; b) G. J. Kirkovits, J. A. Shriver, P. A. Gale, J. L. Sessler, *J. Inclusion Phenom. Macrocyclic Chem.* **2001**, *41*, 69–75; c) A. J. McConnell, P. D. Beer, *Angew. Chem.* **2012**, *124*, 5138; *Angew. Chem. Int. Ed.* **2012**, *51*, 5052–5061.
[10] a) D. M. Rudkevich, W. Verboom, D. N. Reinhoudt, *J. Org. Chem.* **1994**, *59*, 3683–3686; b) D. M. Rudkevich, J. D. Mercer-Chalmers, W. Verboom, R. Ungaro, F. de Jong, D. N. Reinhoudt, *J. Am. Chem. Soc.* **1995**, *117*, 6124–6125; c) J. Scheerder, J. P. M. van Duynhoven, J. F. J. Engbersen, D. N. Reinhoudt, *Angew. Chem.* **1996**, *108*, 1172; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1090–1093.
[11] a) P. D. Beer, M. G. B. Drew, R. J. Knubley, M. I. Ogden, *J. Chem. Soc., Dalton Trans.* **1995**, 3117; b) M. D. Lankshear, A. R. Cowley, P. D. Beer, *Chem. Commun.* **2006**, 612–614; c) M. D. Lankshear, I. M. Dudley, K. M. Chan, A. R. Cowley, S. M. Santos, V. Felix, P. D. Beer, *Chem. Eur. J.* **2008**, *14*, 2248–2263; d) S. C. Picot, B. R. Mullaney, P. D. Beer, *Chem. Eur. J.* **2012**, *18*, 6230–6237.
[12] a) J. M. Mahoney, R. A. Marshall, A. M. Beatty, B. D. Smith, S. Camiolo, P. A. Gale, *J. Supramol. Chem.* **2001**, *1*, 289–292; b) M. J. Deetz, M. Shang, B. D. Smith, *J. Am. Chem. Soc.* **2000**, *122*, 6201–6207; c) J. M. Mahoney, J. P. Davis, A. M. Beatty, B. D. Smith, *J. Org. Chem.* **2003**, *68*, 9819–9820; d) J. M. Mahoney, A. M. Beatty, B. D. Smith, *Inorg. Chem.* **2004**, *43*, 7617–7621.
[13] a) M. Barboiu, G. Vaughan, A. van der Lee, *Org. Lett.* **2003**, *5*, 3073–3076; b) C. Arnal-Herault, M. Barboiu, E. Petit, M. Michau, A. van der Lee, *New J. Chem.* **2005**, *29*, 1535.
[14] a) J. L. Sessler, E. A. Bruker, *Tetrahedron Lett.* **1995**, *36*, 1175–1176; b) S. K. Kim, V. M. Lynch, N. J. Young, B. P. Hay, C. H. Lee, J. S. Kim, B. A. Moyer, J. L. Sessler, *J. Am. Chem. Soc.* **2012**, *134*, 20837–20843.

[15] D. J. White, N. Laing, H. Miller, S. Parsons, P. A. Tasker, S. Coles, *Chem. Commun.* **1999**, 2077–2078.
[16] H.-Y. Hu, C.-F. Chen, *Tetrahedron Lett.* **2006**, *47*, 175–179.
[17] a) N. Delsuc, L. Poniman, J.-M. Léger, I. Huc, *Tetrahedron* **2012**, *68*, 4464–4469; b) H. Jiang, C. Dolain, J. M. Leger, H. Gornitzka, I. Huc, *J. Am. Chem. Soc.* **2004**, *126*, 1034–1035; c) H. Jiang, J.-M. Léger, C. Dolain, P. Guionneau, I. Huc, *Tetrahedron* **2003**, *59*, 8365–8374; d) G. Guichard, I. Huc, *Chem. Commun.* **2011**, *47*, 5933–5941.
[18] a) M. Albrecht, Triyanti, M. de Groot, M. Bahr, E. Weinhold, *Synlett* **2005**, 2095–2097; b) M. Albrecht, Triyanti, S. Schiffers, O. Osetska, G. Raabe, T. Wieland, L. Russo, K. Rissanen, *Eur. J. Org. Chem.* **2007**, 2850–2858; c) Z.-H. Sun, M. Albrecht, R. Fröhlich, *Eur. J. Org. Chem.* **2013**, 3254–3262.
[19] K. A. Connors, *Binding Constants: The measurement of Molecular Complex Stability*, Wiley, New York, **1987**.
[20] T. Steiner, *Angew. Chem.* **2002**, *114*, 50; *Angew. Chem. Int. Ed.* **2002**, *41*, 48–76.
[21] M. Boiocchi, L. Del Boca, D. E. Gomez, L. Fabbrizzi, M. Licchelli, E. Monzani, *J. Am. Chem. Soc.* **2004**, *126*, 16507–16514.
[22] a) B. Lygo, P. G. Wainwright, *Tetrahedron Lett.* **1998**, *39*, 1599–1602; b) E. J. Corey, F.-Y. Zhang, *Org. Lett.* **1999**, *1*, 1287–1290; c) T. Ooi, D. Ohara, M. Tamura, K. Maruoka, *J. Am. Chem. Soc.* **2004**, *126*, 6844–6845.
[23] D. Makuc, J. R. Hiscock, M. E. Light, P. A. Gale, J. Plavec, *Beilstein J. Org. Chem.* **2011**, *7*, 1205–1214.
[24] M. J. Deetz, M. Shang, B. D. Smith, *J. Am. Chem. Soc.* **2000**, *122*, 6201–6207.

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