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# Recognition and Extraction of Sodium Chloride by a Squaramide-Based Ion Pair Receptor

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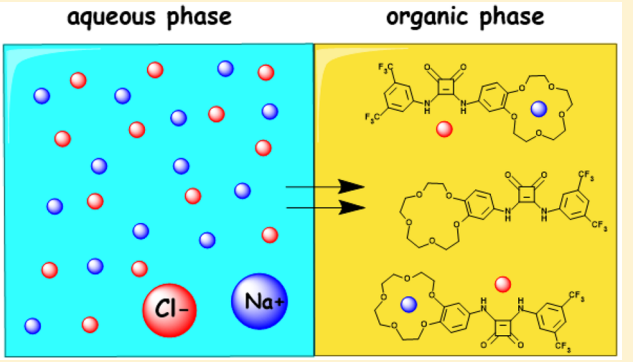
Supporting Information

**ABSTRACT:** We synthesized an ion pair receptor **1** consisting of a crown ether cation binding site and a squaramide anion binding domain and compared its binding properties to those of its analogous urea counterpart **2**. We studied their salt binding properties using spectrophotometric and spectroscopic measurements in an acetonitrile solution and in acetonitrile/water mixtures. Apart from carboxylate anions, all of the anions tested were found to associate with receptor **1** and **2** more strongly in the presence of sodium cations. A homotopic anion receptor **3**, lacking a crown ether unit, was unable to bind sodium salt more strongly than tetrabutylammonium salts. Solution and solid-state X-ray measurements revealed strong sodium chloride coordination to receptor **1**, which is able to bind this salt even in the presence of 10% water. In contrast to the urea-based ion pair receptor **2** or anion receptor **3**, ditopic receptor **1** is capable of extracting sodium chloride from aqueous media to the organic phase, as was evidenced unambiguously by $^{1}$H nuclear magnetic resonance, mass spectrometry, and atomic absorption spectroscopy analyses.




## INTRODUCTION

The design and synthesis of squaramide-based molecular receptors is an emerging field of modern supramolecular chemistry.[1] Several monotopic receptors that can bind anions have recently been proposed and found to be more efficient than their urea or thiourea analogues.[2] The squaramide moiety has an excellent hydrogen bonding capacity, and this feature has been used in the synthesis of various synthetic receptors. Some of them are so effective that they can be used to recognize anions in highly competitive aqueous media.[3] The reaction of diesters of squaric acid with excess amines generates symmetrical squaramide-based receptors.[4] In this context, by using terminal diamines and alkoxysquarate, an elegant approach to the synthesis of fluorescent poly(squaramide) that can detect anions was proposed.[5] However, the most convenient method is the successive amidation of squaric acid esters and generation of asymmetric squaramides.[6] Such an approach creates the unique opportunity to synthesize receptors in a modular fashion by combining two functional parts whose properties can be directed toward specific purposes. Within this, the combination of suitable reporters and cation binding domains possessing amino function with dialkoxysquarate derivatives is especially promising and can lead to ion pair receptors. Nevertheless, this area of supramolecular chemistry is highly unexplored, and to date, only a few papers concerning ditopic ion pair receptors consisting of squaramide units have been published.[7] Some of these receptors require multistep synthesis, are not fully explored in terms of ion pair binding, or are able to bind only anions with transition metal cations.

Recently, more attention has been paid to small molecules that can facilitate the transport of anions across lipid bilayers. Because of this ability, such compounds can be treated as potential drugs in the treatment of channelopathies.[8] In this context, squaramides have been shown to be potent transmembrane transporters with anion transport activities that are better than those of the corresponding ureas and thioureas. Very recently, it has been suggested that squaramide-based anion receptors can be used as prospective anticancer agents. It was shown experimentally for the first time that such monotopic receptors can perturb cellular chloride concentrations, promote sodium chloride influx into cytosol, disrupt autophagy, and induce apoptosis.[9] Thus, we envisioned that using squaramide-based, small drug-like molecules that can bind cations and anions simultaneously can lead to molecular receptors that are more efficient than monotopic ones and can be applied to affect sodium cation and chloride anion concentrations simultaneously under interfacial conditions. Therefore, the aim of this study was to examine the binding properties of squaramide-based ion pair receptor **1** and compare them with the salt recognition ability of urea-based ion pair receptor **2** and monotopic anion receptor **3**, which does not have a crown ether moiety.

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Table 1. Crystal Data and Structural Refinement Parameters for the Obtained Complexes of 1 with Various Salts

| | [1×NaCl][a] | [1×NaCl/$NaNO_3$] | [1×NaBr] |
|---|---|---|---|
| chemical formula | 4×**1** + 4×NaCl + 7×DMSO | **1** + 0.56×NaCl + 0.44×$NaNO_3$ | **1** + NaBr |
| | $C_{118}H_{138}Cl_4F_{24}N_8Na_4O_{35}S_7$ | $C_{26}H_{24}Cl_{0.56}F_6N_{2.44}NaO_{8.32}$ | $C_{26}H_{24}BrF_6N_2NaO_7$ |
| $M_x$ (g/mol) | 3142.54 | 660.68 | 693.37 |
| $T$ (K) | 100(2) | 110(2) | 100(2) |
| $\lambda$ (Å) | 0.71073 | 0.71073 | 0.71073 |
| crystal size | 0.113 mm × 0.246 mm × 0.371 mm | 0.115 mm × 0.123 mm × 0.390 mm | 0.098 mm × 0.284 mm × 0.464 mm |
| crystal system | triclinic | triclinic | triclinic |
| space group | $P\bar{1}$ | $P\bar{1}$ | $P\bar{1}$ |
| unit cell dimensions | $a$ = 15.8755(11) Å | $a$ = 7.6253(18) Å | $a$ = 7.6840(5) Å |
| | $b$ = 21.5070(15) Å | $b$ = 12.254(3) Å | $b$ = 12.5243(8) Å |
| | $c$ = 23.3742(16) Å | $c$ = 15.887(4) Å | $c$ = 15.4520(9) Å |
| | $\alpha$ = 65.485(2)° | $\alpha$ = 96.465(8)° | $\alpha$ = 77.0664(13)° |
| | $\beta$ = 71.362(2)° | $\beta$ = 101.607(8)° | $\beta$ = 75.7210(13)° |
| | $\gamma$ = 83.716(2)° | $\gamma$ = 102.405(8)° | $\gamma$ = 78.0090(13)° |
| $V$ (Å$^3$), $Z$ | 6878.0(8), 2 | 1401.2(6), 2 | 1386.11(15), 2 |
| $D_x$ (g/cm$^3$) | 1.517 | 1.566 | 1.661 |
| $\mu$ (mm$^{-1}$) | 0.316 | 0.205 | 1.588 |
| $F$(000) | 3244 | 676 | 700 |
| $\theta_{min}$, $\theta_{max}$ | 2.19°, 25.05° | 2.34°, 25.04° | 2.91°, 25.04° |
| index ranges | $-17 \le h \le 18$ | $-9 \le h \le 9$ | $-9 \le h \le 9$ |
| | $-22 \le k \le 25$ | $-14 \le k \le 14$ | $-14 \le k \le 14$ |
| | $0 \le l \le 27$ | $-18 \le l \le 18$ | $-18 \le l \le 18$ |
| no. of reflections collected/independent | 211398[b]/ 24338 | 23992/4911 | 33708/4894 |
| | $R_{int}$ = 0.0829[b] | $R_{int}$ = 0.1016 | $R_{int}$ = 0.0242 |
| completeness (%) | 99.9 | 99.1 | 99.9 |
| absorption correction | multiscan | multiscan | multiscan |
| $T_{max}$, $T_{min}$ | 0.965, 0.892 | 0.977, 0.924 | 0.860, 0.526 |
| refinement method | full-matrix least squares on $F^2$ | full-matrix least squares on $F^2$ | full-matrix least squares on $F^2$ |
| data/restraints/parameters | 24338/231/1991 | 4911/41/452 | 4894/6/410 |
| goodness of fit on $F^2$ | 1.114 | 1.060 | 1.066 |
| final $R$ indices | 19740 data; $I > 2\sigma(I)$ | 2931 data; $I > 2\sigma(I)$ | 4763 data; $I > 2\sigma(I)$ |
| | $R_1$ = 0.0805 | $R_1$ = 0.0961 | $R_1$ = 0.0193 |
| | $wR_2$ = 0.2110 | $wR_2$ = 0.2321 | $wR_2$ = 0.0485 |
| | all data | all data | all data |
| | $R_1$ = 0.1039 | $R_1$ = 0.1537 | $R_1$ = 0.0202 |
| | $wR_2$ = 0.2270 | $wR_2$ = 0.2663 | $wR_2$ = 0.0491 |
| extinction coefficient | 0.0005(1) | – | 0.0048(4) |
| $\rho_{max}$, $\rho_{min}$ (e Å$^{-3}$) | 0.748, −0.801 | 0.598, −0.356 | 0.347, −0.230 |

[a]Crystal twinned with partial overlap of reflections; data integration based on two domains. [b]Number of all collected reflections and $R_{int}$ value given for data up to $\theta$ = 25.41°.

## EXPERIMENTAL SECTION

All reagents and chemicals were of reagent grade quality and purchased commercially. $^1$H and $^{13}$C nuclear magnetic resonance (NMR) spectra were recorded on a Bruker 300 MHz spectrometer. $^1$H NMR chemical shifts ($\delta$) are reported in parts per million referenced to a residual solvent signal [dimethyl sulfoxide-$d_6$ (DMSO-$d_6$) or $CD_3CN$].

**Preparation of Compound S3.** To a solution of 3,4-dimethoxy-3-cyclobutane-1,2-dione (2.00 g, 14.1 mmol) in MeOH (20 mL) was added 3,5-bis(trifluoromethyl)aniline (2.40 mL, 15.5 mmol, 1.1 equiv) at room temperature. After being stirred for 3 days, the reaction mixture was filtered, and the collected solid material was washed with MeOH. The obtained light yellow solid was dried *in vacuo* to give desired product **S3** (4.54 g, 13.4 mmol, 95%): HRMS (ESI) calcd for $C_{13}H_7F_6NO_3Na$ $[M + Na]^+$ 362.0228, found 362.0225; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 11.19 (s, 1H), 8.05 (s, 2H), 7.78 (s, 1H), 4.41 (s, 3H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 187.4, 184.5, 179.9, 169.1, 140.2, 131.9, 131.4, 131.0, 130.5, 128.5, 124.9, 121.3, 119.2, 117.6, 116.1, 61.0.

**Preparation of Receptor 1.** To a degassed solution of 4-nitrobenzo-15-crown-5-ether (940 mg, 3 mmol) in 50 mL of a tetrahydrofuran (THF)/MeOH mixture (1:4) was added 25 mg of 10% Pd/C. The reaction mixture was kept under a $H_2$ atmosphere (balloon pressure) at room temperature overnight. The catalyst was removed by filtration through a pad of Celite and washed with MeOH. The filtrate was concentrated under reduced pressure to give the crude product in quantitative yield (856 mg). The amine was used in the next step without further purification.

To the solution of amine (456 mg, 1.61 mmol) in MeOH (5 mL) was added a compound **S3** (543 mg, 1.60 mmol) at room temperature. The mixture was stirred at room temperature for 2 days. The reaction mixture was filtered, and the collected solid material was washed with MeOH. The obtained white solid was dried *in vacuo* to give the desired receptor containing one molecule of methanol per molecule of receptor **1** in a 90% yield (900 mg, 1.45 mmol). The residual solvent can be removed by dissolution of the receptor in chloroform and evaporation of the solvent under reduced pressure: HRMS (ESI) calcd for $C_{26}H_{24}F_6N_2O_7Na$ $[M + Na]^+$ 613.1385, found 613.1379; $^1$H NMR (300 MHz, $CD_3CN$) $\delta$ 8.42–8.23 (bs, 2H), 7.98 (s, 2H), 7.67 (s, 1H), 7.15–7.05 (m, 1H), 6.96–6.89 (m, 1H), 6.85–6.75 (m, 1H), 4.15–4.05 (m, 4H), 3.86–3.75 (m, 4H), 3.25–3.10 (m, 8H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$


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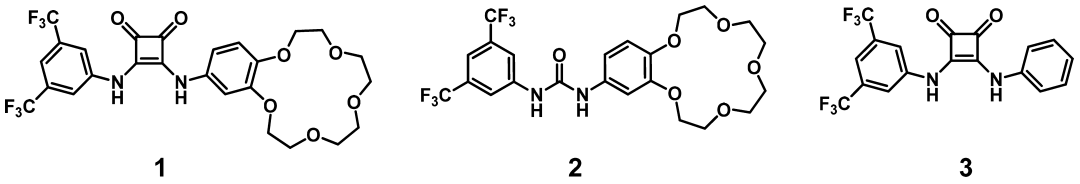
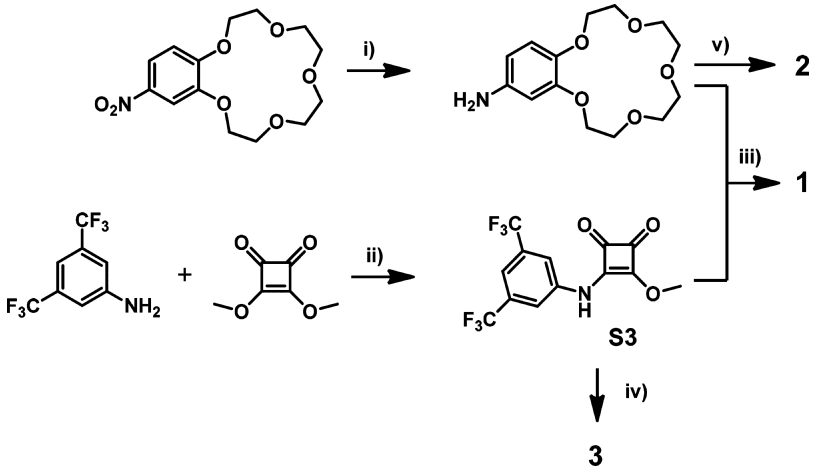


**Figure 1.** Structures of receptors **1**–**3**.

**Scheme 1. Synthesis of Receptors 1 and 2**[a]



[a]Reagents and conditions: (i) $H_2$, Pd/C, MeOH/THF, 12 h, room temperature, quantitative; (ii) methanol, 72 h, room temperature, 95%; (iii) methanol, 48 h, room temperature, 90%; (iv) aniline, methanol, 48 h, room temperature, 71%; (v) 3,5-trifluoromethylisocyanate, methylene dichloride, 12 h, room temperature, 75%.

182.8, 181.3, 166.4, 163.8, 149.1, 145.3, 140.6, 131.8, 131.3, 130.9, 130.4, 124.6, 121.0, 118.2, 115.2, 114.7, 111.1, 106.2, 70.0, 69.7, 69.5, 69.2, 68.7, 68.4. Anal. Calcd for $C_{26}H_{24}F_6N_2O_8{\cdot}H_2O$: C, 51.32; H, 4.31; N, 4.60. Found: C, 51.35; H, 4.28; N, 4.76.

**Preparation of Receptor 2.** To a solution of 4-aminobenzo-15-crown-5-ether (500 mg, 1.77 mmol) in methylene dichloride (10 mL) was added 3,5-trifluoromethylisocyanate (300 $\mu$L, 1.76 mmol) at room temperature. After being stirred for 12 h, the reaction mixture was filtered, and the collected solid material was washed with diethyl ether. The obtained white solid was dried *in vacuo* to give the desired product in a 75% yield (710 mg, 1.32 mmol): HRMS (ESI) calcd for $C_{23}H_{24}F_6N_2O_6Na$ $[M + Na]^+$ 561.1436, found 561.1440; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 9.31 (s, 1H), 8.81 (s, 1H), 8.13 (s, 2H), 7.63 (s, 1H), 7.20 (s, 1H), 6.90 (s, 2H), 4.11–3.95 (m, 4H), 3.87–3.75 (m, 4H), 3.70–3.57 (m, 8H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 152.9, 149.2, 144.7, 142.5, 133.3, 131.8, 131.4, 131.0, 130.5, 125.6, 122.0, 118.4, 115.2, 112.0, 106.6, 70.8, 70.4, 70.2, 69.5, 68.9. Anal. Calcd for $C_{23}H_{24}F_6N_2O_6$: C, 51.31; H, 4.49; N, 5.20. Found: C, 51.38; H, 4.56; N, 5.15.

**Preparation of Receptor 3.** To a solution of compound **S3** (204 mg, 0.60 mmol) in MeOH (5 mL) was added aniline (56 mg, 0.60 mmol) at room temperature. The mixture was stirred for 2 days. Then the reaction mixture was filtered, and the collected solid material was washed with MeOH. The obtained white solid was dried *in vacuo* to give the desired receptor (170 mg, 0.425 mmol, 71%): HRMS (ESI) calcd for $C_{18}H_{10}F_6N_2O_2Na$ $[M + Na]^+$ 423.0544, found 423.0535; $^1$H NMR (300 MHz, $CD_3CN$) $\delta$ 8.40–8.21 (bs, 2H), 7.96 (s, 2H), 7.66 (s, 1H), 7.44–7.32 (m, 4H), 7.21–7.10 (m, 1H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 182.5, 181.9, 166.5, 164.4, 140.5, 137.8, 131.3, 130.9, 128.9, 123.4, 120.9, 118.6, 118.4, 115.0. Anal. Calcd for $C_{26}H_{24}F_6N_2O_8$: C, 54.01; H, 2.52; N, 7.00. Found: C, 53.83; H, 2.66; N, 6.90.

**Ultraviolet–Visible (UV–vis) Titration Experiments.** The UV–vis titration was performed using a Thermo Spectronic Unicam UV500 spectrophotometer at 298 K in acetonitrile. In each case, 2500 $\mu$L of a freshly prepared $2.93 \times 10^{-5}$ M solution of the receptor was added to a cuvette. Then small aliquots of TBAX, containing a constant concentration of the receptor, were added, and a spectrum was acquired after each addition. Where applicable, the solution also contained 1 molar equivalent of cation (1 equiv of $NaClO_4$, $LiClO_4$, or $KPF_6$ with respect to the receptor). The resulting titration data were analyzed using the BindFit (version 0.5) package, available online at http://supramolecular.org.

**$^1$H NMR Titration Experiments.** The $^1$H NMR titration was performed on a Bruker 300 spectrometer at 298 K in $CD_3CN$. In each case, 500 $\mu$L of a freshly prepared 3.13 mM solution of receptor **1** was added to a 5 mm NMR tube. In the case of ion pair titration, the solution also contained 1 molar equivalent of sodium perchlorate. Then small aliquots of a solution of TBAX, containing **1** at a constant concentration, were added, and a spectrum was acquired after each addition. The resulting titration data were analyzed using the BindFit (version 0.5) package, available online at http://supramolecular.org.

**Crystallization and Single-Crystal X-ray Diffraction.** Crystals containing **1** and NaCl that were suitable for X-ray diffraction were obtained by a slow evaporation of a saturated salt solution of **1** in DMSO. Crystals containing a mixture of NaCl and $NaNO_3$ accidently grew from an acetonitrile/methanol solution during diffuse crystallization by diethyl ether. The complex of **1** with NaBr was precipitated form a saturated acetonitrile/methanol solution using diethyl ether. The obtained crystals are denoted as [**1**×NaCl], [**1**×NaCl/$NaNO_3$], and [**1**×NaBr] complexes.

The X-ray measurements of the investigated crystals were performed on a Bruker D8 Venture diffractometer equipped with a TRIUMPH monochromator using Mo K$\alpha$ ($\lambda$ = 0.71073 Å) radiation. The samples were measured at low temperatures yielding either 100(2) K for [**1**×NaCl] and [**1**×NaBr] complexes or 110(2) K for the [**1**×NaCl/$NaNO_3$] compound. Diffraction data were collected with either Bruker APEX2[10] or APEX3[11] programs. The frames were integrated with the Bruker SAINT software package.[12] In the case of the twinned crystal of [**1**×NaCl] with partial overlap of reflections, two twin domains were included in the processing followed by absorption correction using the multiscan method and scaling



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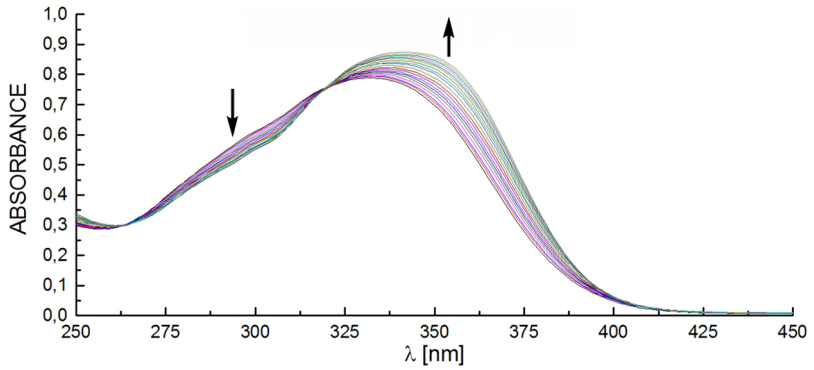


**Figure 2.** Representative UV−vis titration spectra of receptor **1** (upon gradual addition of tetrabutylammonium nitrate). [**1**] = 2.93 × $10^{-5}$ M; optical path length of 10 mm.

performed in TWINABS.[13] In the case of the single crystals of [**1**×NaCl/$NaNO_3$] and [**1**×NaBr], data were scaled and corrected for absorption effects using the multiscan method implemented in SADABS.[14] All the structures were determined and refined with the SHELX software suite[15,16] with the atomic scattering factors taken from the International Tables.[17] The crystal data and final structure refinement parameters are listed in Table 1. The details of single-crystal diffraction experiments, including data collection, integration, and structural refinement, are available in the appropriate part of the Supporting Information. The molecular graphic plots and the geometry analysis of the obtained structures were performed in Mercury CSD 3.10 software.[18]

The crystallographic data have been deposited with the Cambridge Crystallographic Data Center under the following numbers: CCDC 1812264, CCDC 1855570, and CCDC 1855571 for the [**1**×NaCl], [**1**×NaCl/$NaNO_3$], and [**1**×NaBr] complexes, respectively.

## RESULTS AND DISCUSSION

**Receptor Design and Synthesis.** Receptor **1** was designed to simultaneously bind cations and anions with a particular affinity for sodium chloride. Namely, the diarylsquaramide unit, a binding domain that can effectively associate with halide ions,[2,4e] was combined with sodium selective crown ether. The heteroditopic ion pair receptor **2**, comprising a urea-based anion binding domain, and homotopic anion receptor **3**, lacking a crown ether unit, were selected as reference compounds (Figure 1). In the structure of ion pair receptors **1** and **2**, the benzo-15-crown-5-ether is an integral part of the anion binding site; thus, we expected that binding of a sodium cation by this domain would reduce the electron density on the adjacent phenyl ring, increasing the acidity of the squaramide protons and as a consequence reinforcing anion binding. Receptors **1** and **3** were synthesized starting with successive amidation of dimethyl squarate with 3,5-trifluoromethylaniline, followed by 4-aminobenzo-15-crown-5 for **1**, or with aniline for **3**, respectively. Receptor **2** was obtained in two steps, reduction of the nitro group of 4-nitrobenzo-15-crown-5 to the corresponding amine and subsequent reaction with 3,5-trifluoromethylisocyanate (Scheme 1). It should be emphasized that the synthesis of all receptors is straightforward and does not require chromatographic purification. All intermediates and receptors can be simply purified by crystallization and thus are easy to obtain on a large scale.

**Binding Studies.** A quantitative evaluation of the anion and salt binding ability of **1** was performed by UV−vis titrations in acetonitrile. To rule out the self-association event that might be occurring in the range of concentrations under investigation, dilution studies were first performed. The dilution experiments showed a linear dependence of the UV absorption on the concentration, which suggests that receptor **1** does not aggregate in the concentration range studied (1 × $10^{-5}$ to 8 × $10^{-5}$ M). Likewise, test experiments with tetrabutylammonium perchlorate excluded the interaction of receptor **1** with these ions. Adding incremental amounts of various anions (as TBA salts) to a solutions of **1** resulted in bathochromic shifts in the absorption maximum of the receptor, allowing us to calculate stability constants (Figure 2). The association constants calculated by the nonlinear regression analysis of the binding isotherms are summarized in Table 2.

**Table 2. Association Constants for Interactions of Receptors 1 and 2 with Selected Anions and Apparent Association Constants for Interactions of 1 and 2 with Anions in the Presence of 1 equiv of Sodium Perchlorate**[a]

| | **1** | **1** + 1 equiv of $NaClO_4$ | **2** | **2** + 1 equiv of $NaClO_4$ |
|---|---|---|---|---|
| $NO_3^-$ | 2200 | 3600 | 550 | 760 |
| $Br^-$ | 47500 | 82800 | 1200 | 2220 |
| $NO_2^-$ | 79200 | 147000 | 5800 | 8900 |
| $Cl^-$ | $K_{11}$ = 789000 | $K_{11}$ = 1400000 | 9920 | 18600 |
| | $K_{21}$ = 109000 | $K_{21}$ = 166000 | | |
| $PhCOO^-$ | *b* | *b* | 490200 | 353000 |
| $CH_3COO^-$ | *b* | *b* | 1181200 | 907500 |

[a]UV−vis, solvent $CH_3CN$, 293 K, [**1**] = 2.93 × $10^{-5}$ M, [**2**] = 3.36 × $10^{-5}$ M, anions added as TBA salts, where [TBAX] ∼ 3 × $10^{-3}$ M; $M^{-1}$, errors of <10%. [b]Deprotonation.

We found that receptor **1** binds these anions with moderate to very high strength, in the following order: $NO_3^-$ < $Br^-$ < $NO_2^-$ < $Cl^-$. In the case of the interaction of **1** with carboxylate anions such as benzoate or acetate, deprotonation of the receptor was observed. This was supported by $^1$H NMR measurements that displayed a disappearance of signals assigned to the squaramide protons upon addition of these anions.

Strikingly, when receptor **1** was titrated in the presence of 1 equiv of sodium cations (added as $NaClO_4$), all bound anions were found to interact in an enhanced manner, with a 1.6-fold higher association constant. The strong influence of sodium cation association on anion binding was also supported by an analysis of the $TBANO_2$ titration experiment performed in the


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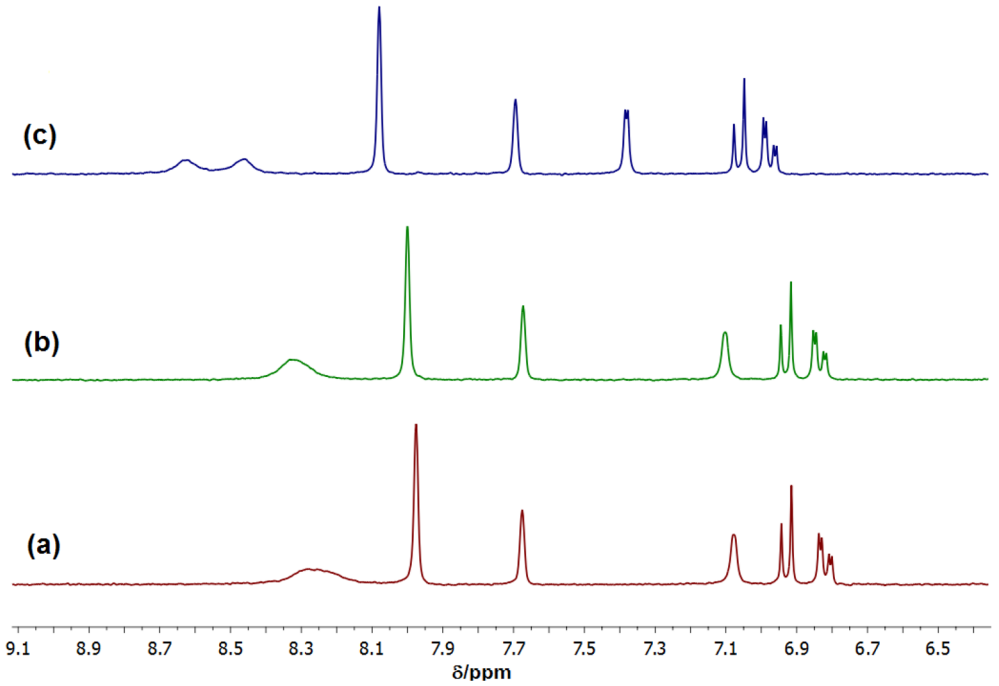


**Figure 3.** Partial $^1$H NMR spectra of (a) receptor **1**, (b) receptor **1** with 2 equiv of $TBAClO_4$, and (c) receptor **1** with 2 equiv of $NaClO_4$ in $CD_3CN$.

absence and presence of 1 and 5 equiv of sodium cations. These experiments showed that as the amount of sodium cations increases (1 and 5 equiv), receptor **1** can bind nitrite anions with 1.86- and 3.60-fold higher association constants, respectively, than in the absence of $Na^+$. Therefore, the data obtained from titrations conducted in the presence of metal cations should be analyzed in terms of the binding cooperativity of ion pairs and should be treated as apparent stability constants, because they are highly dependent on the concentration of metal cations.

Interestingly, in the case of the chloride anion, a very strong interaction with **1** was observed and a mixed 2:1 + 1:1 (receptor:chloride) binding mode was better suited than a 1:1 binding stoichiometry, while 1:1 fitting produced a high error rate and sinusoidal residuals (Supporting Information).[19] This suggests that upon titration of receptor **1** with chloride anions apart from 1:1 complexes, 2:1 complexes (receptor:chloride) are also formed. This was especially pronounced when titration was performed in the presence of sodium cations. The evidence for a binding equilibrium more complex than 1:1 came from titration experiments performed under $^1$H NMR control. We found that upon incremental addition of chloride anions to an acetonitrile solution of receptor **1** containing 1 equiv of sodium cations, the signals corresponding to the aromatic protons were shifted inconsistently. These signals were initially shifted downfield, and after >1.3 equiv of chloride anions had been added, the signals were moved upfield (Supporting Information). This may suggest that in the acetonitrile solution, initially 2:1 and 1:1 complexes are in equilibrium and upon addition of an excess of chloride anions the 1:1 complex becomes the predominant species. To obtain more reliable data and calculate the stability constants for chlorides, we performed UV−vis titration experiments in more competitive media. When titration experiments were conducted in the presence of 0.5% water (pH 3) in acetonitrile, we could determine the association constants for complexes of **1** with chloride salts, fitting the data to the 1:1 stoichiometry. We found that under such conditions chloride anions are recognized less strongly than in pure acetonitrile, with an association constant of 114300 $M^{-1}$. In the presence of 1 equiv of sodium cations, the enhancement of chloride binding was still observed and the apparent stability constant thus obtained was calculated to be 196700 $M^{-1}$.

A similar enhancement of anion binding, as was detected for sodium cations, was observed when receptor **1** was titrated with TBABr in the presence of 1 equiv of lithium perchlorate in acetonitrile. Specifically, in the presence of 1 equiv of lithium cations (added as $LiClO_4$), receptor **1** binds bromide anions even as much as 2 times more strongly than in the absence of $Li^+$, with an apparent association constant ($K_{LiBr}$) of 98600 $M^{-1}$. On the other hand, when the receptor was titrated with TBABr in the presence of 1 equiv of potassium or ammonium cations (added as $KPF_6$ or $NH_4PF_6$, respectively), no enhancement of bromide binding was observed and receptor **1** binds bromide anions less strongly than in the absence of these cations, with the following apparent association constants: $K_{KBr}$ = 44500 $M^{-1}$ and $K_{NH4Br}$ = 43300 $M^{-1}$.

The enhancement of anion binding in the presence of sodium or lithium cations can be explained in terms of the formation of strong 1:1 complexes with receptor **1** and metal cations, cation complexation-induced electrostatic interactions, and the cation complexation-induced increased acidity of squaramide protons that reinforce interactions with anions. Indeed, when sodium cations were added as sodium perchlorate, both of the signals corresponding to squaramide protons were shifted downfield, indicating their higher acidity, and as a consequence increased their ability to recognize anions (Figure 3).[20]

Furthermore, to test cooperativity in ion pair binding, we also investigated the influence of anion binding on sodium association. When sodium cations (added as $NaClO_4$) were


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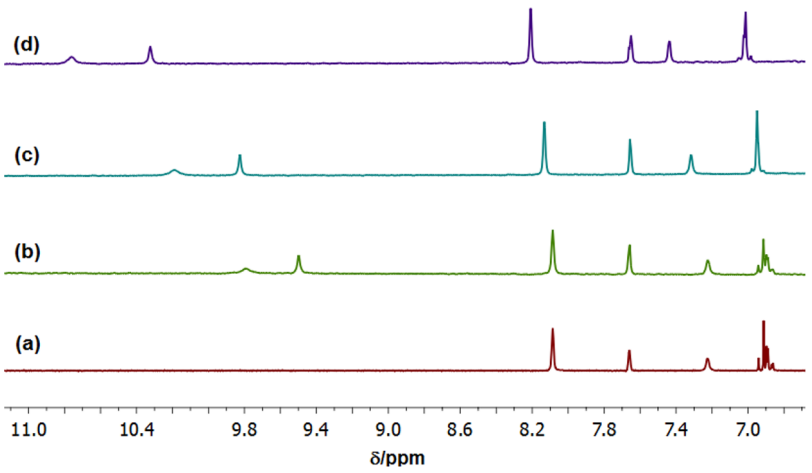


**Figure 4.** Partial $^1$H NMR spectra of a 2.6 mM solution of **1** in $CD_3CN$ with (a) 10% water, (b) 10% aqueous $HClO_4$ (pH 3), (c) 10% aqueous $HClO_4$ (pH 3) and 1 equiv of NaCl, and (d) 10% aqueous $HClO_4$ (pH 3) and 3 equiv of NaCl.

associated with receptor **1** moderately with an association constant $K_{Na^+}$ of 10000 $M^{-1}$, in the presence of 1 equiv of $NO_3^-$, $Br^-$, $NO_2^-$, and $Cl^-$ anions, they were bound in an enhanced manner, namely 1.40, 4.46, 6.50, and 7.56 times more strongly, respectively. This corresponds to the increasing binding strength of receptor **1** with the anions investigated.

To establish the role of the crown ether units in salt binding, monotopic receptor **3** lacking a crown ether binding domain was tested for anions and ion pairs. We found that anion receptor **3** can bind bromide anions like ditopic receptor **1** does with a stability constant $K_{TBABr}$ of 48200 $M^{-1}$. However, the absence of a cation binding domain in receptor **3** has serious implications in terms of ion pair binding. Specifically, in the presence of sodium cations, monotopic receptor **3** binds a bromide anion less strongly than in the absence of sodium cations, with an apparent stability constant $K_{NaBr}$ of 43800 $M^{-1}$.

To confirm the high affinity of the squaramide group of receptor **1** for anions and ion pairs, we decided to vary the anion binding site. For this purpose, analogous, heteroditopic ion pair receptor **2** supported with a urea-based anion binding site was tested. As Table 2 shows, receptor **2** associates with TBA salts of nitrate, bromide, nitrite, and chloride anions with weak to moderate strength. The association constant values for these anions are at least 1 magnitude of order weaker than for squaramide-based receptor **1**. Interestingly, it was found that receptor **2** forms stable complexes with acetate and benzoate anions, which readily caused deprotonation of receptor **1**. When ion pair binding experiments were performed in the presence of sodium cations, we found that, with the exception of carboxylates, all the anions were associated with the receptors more strongly than in the presence of tetrabutylammonium countercations. Nevertheless, even in the presence of sodium cations, urea-based receptor **2** cannot interact with anions as strongly as squaramide **1** or **3**. For example, in the presence of a sodium cation, receptor **2** binds bromide anions moderately with an apparent stability constant of 2200 $M^{-1}$. On the other hand, monotopic receptor **3** and ditopic receptor **1** form complexes that are 1 magnitude of order stronger with bromides, with apparent stability constants of 43800 and 82800 $M^{-1}$, respectively.

To gain more insight into the anion and ion pair binding mechanism, $^1$H NMR titration experiments were conducted. The titration of receptor **1** in acetonitrile with nitrate salts was selected, taking into account the range of the estimated suitable stability constant calculated using the $^1$H NMR technique. We found that, upon incremental addition of tetrabutylammonium nitrate, both of the signals corresponding to squaramide protons were gradually shifted downfield and perturbations in signals corresponding to aromatic protons were also observed. Analyzing the nitrate anion complexation-induced shifts of all protons engaged in anion binding allowed us to calculate the stability constant as $K_{TBANO_3}$ = 2390 $M^{-1}$. This corresponds well with the data obtained from UV−vis titration. Titration of **1** in the presence of 1 equiv of sodium cations with tetrabutylammonium nitrate induced analogous shifts for all mentioned protons of receptor **1**, although the changes were more drastic. We found that in the presence of sodium cations the association of nitrate anions was greatly enhanced, and the stability constant thus obtained was even higher than that obtained from UV−vis titration ($K_{NaNO_3}$ = 5880 $M^{-1}$ from $^1$H NMR vs $K_{NaNO_3}$ = 3600 $M^{-1}$ from UV−vis titrations). This further supports the strong influence of sodium cations on anion binding. In particular, in the case of $^1$H NMR titration, the concentration of receptor **1** is 2 orders of magnitude higher than in the case of UV−vis measurements, which is responsible for the higher fraction of receptor **1** molecules occupied by a sodium cation in the MeCN-$d_3$ solution, namely, 84% at 3.13 × $10^{-3}$ M versus 19% at 2.93 × $10^{-5}$ M. To be as close as possible to unified measurement conditions and reach a comparable fraction of receptor **1** occupied by a sodium cation, a comparative binding study was performed. Specifically, we performed UV−vis titration experiments at 3.36 × $10^{-4}$ M using a 1 mm cuvette and $^1$H NMR titrations at 6.05 × $10^{-4}$ M receptor **1**. The apparent stability constants thus obtained are in good agreement with each other and were calculated to be 4500 and 4800 $M^{-1}$ for UV−vis and $^1$H NMR conditions, respectively.

Taking into account the strong ability of receptor **1** to associate with chloride anions and sodium chloride, titration in the presence of water was conducted under UV−vis control. The addition of 5% water to the solution of receptor **1** in acetonitrile caused a considerable bathochromic shift in the absorption maximum, suggesting the formation of strong hydrogen bonds with water molecules. However, similar


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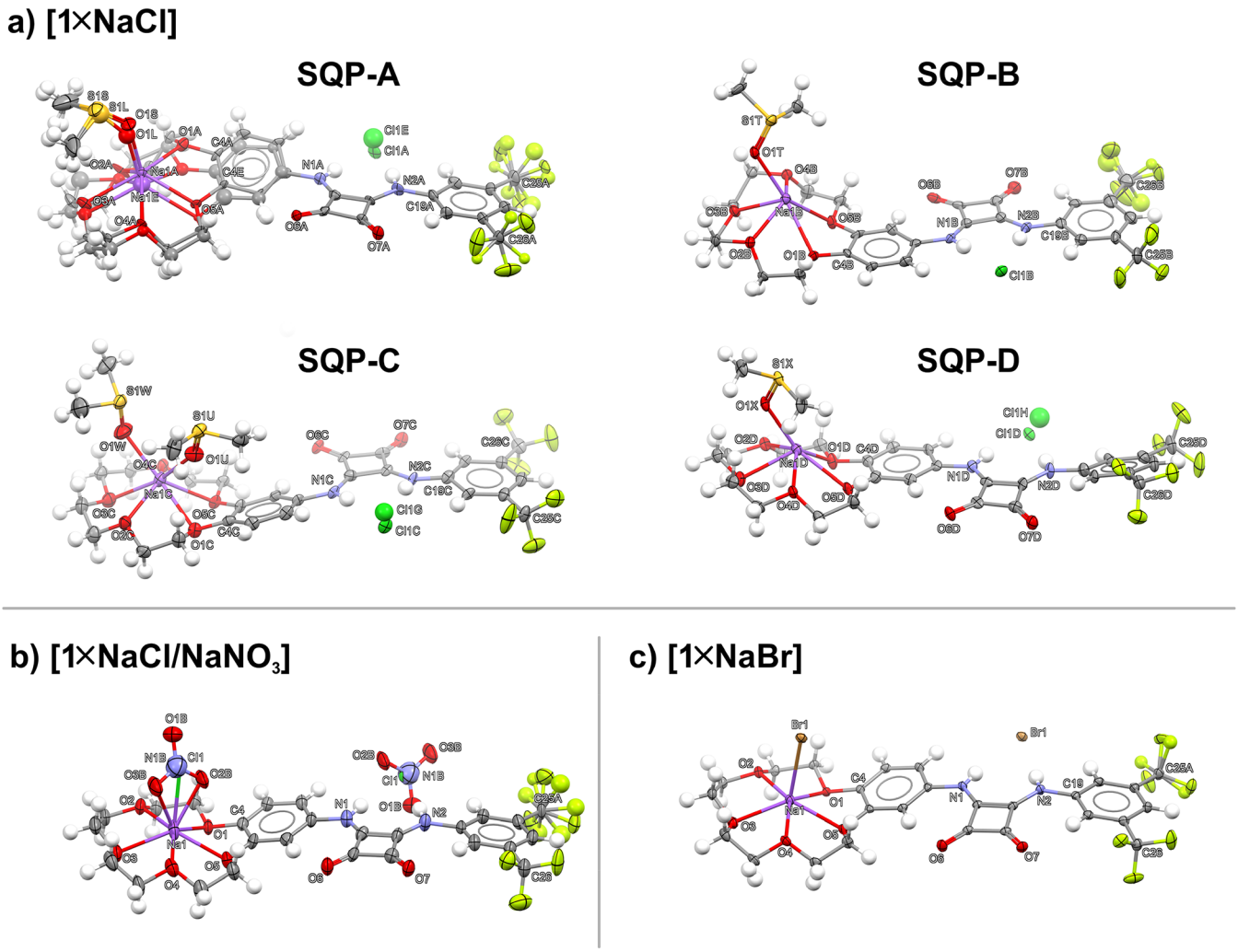


**Figure 5.** Displacement ellipsoid plot at the 50% probability level for structures of (a) [**1**×NaCl], (b) [**1**×NaCl/$NaNO_3$], and (c) [**1**×NaBr].

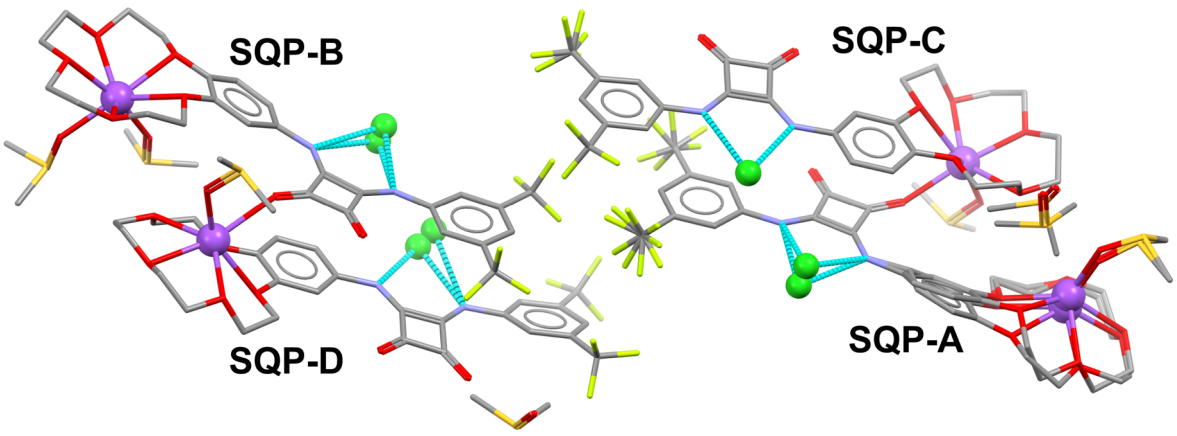


**Figure 6.** Dimers of **SQP** ligands in the crystals of [**1**×NaCl].

changes in the UV−vis spectrum were observed upon addition of 1 equiv of tetrabutylammonium hydroxide to the receptor **1** solution, rather suggestive of a deprotonation event. Indeed, $^1$H NMR experiments revealed that deprotonation takes place under such conditions, and the disappearance of both signals corresponding to squaramide protons is detected (Figure 4a). To protect water-induced deprotonation of receptor **1**, aqueous perchloric acid (pH 3) was used instead of pure water in UV−vis titration experiments.

An aqueous environment opens up the unique opportunity to use sodium chloride instead of salt generated *in situ* and conduct experiments with 5 and 10% water (pH 3) in acetonitrile. We found that in the presence of 5% water, receptor **1** binds chloride anions (added as TBACl) weakly with a binding constant $K_{TBACl}$ of 890 $M^{-1}$. Interestingly, in


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such a competitive mixture of solvents, NaCl is associated more strongly than TBACl, namely with a stability constant $K_{NaCl}$ of 1350 $M^{-1}$. In the presence of 10% water (pH 3), a further decrease in binding strength was observed and only sodium chloride was noticeably recognized using the UV−vis technique. However, the value of the calculated stability constant was too low to be precisely determined using the UV−vis technique ($K_{NaCl}$ = 250 $M^{-1}$ was assumed). Thus, the ability for sodium chloride to be recognized by receptor **1** in the presence of 10% water (pH 3) in acetonitrile was supported by $^1$H NMR measurements. Specifically, upon addition of 1 and 3 equiv of sodium chloride to the solution of receptor **1** in $CD_3CN$, the squaramide protons that initially resonated at $\delta$ = 9.50 and 9.78 ppm were shifted downfield to $\delta$ = 9.82 and 10.20 ppm with the addition of 1 equiv of NaCl and to $\delta$ = 10.32 and 10.76 ppm in the presence of 3 equiv of this salt, respectively (Figure 4). This clearly indicates that receptor **1** is able to interact with sodium chloride in 10% water (pH 3) in acetonitrile. However, upon addition of a larger amount of sodium chloride, precipitation occurs, not enabling the stability constant to be determined by $^1$H NMR spectroscopy.

**X-ray Measurements.** The high affinity of receptor **1** for a variety of Na salts is confirmed by single-crystal X-ray diffraction experiments. During the studies, three solid-state structures of **1** with NaCl, a $NaCl/NaNO_3$ mixture, and NaBr were obtained. The structures are denoted as [**1**×NaCl], [**1**×$NaCl/NaNO_3$], and [**1**×NaBr], respectively. The crystal of [**1**×NaCl] contains in the asymmetric part of the unit cell four ligands named **SQPA**−**SQPD**, four $Na^+/Cl^-$ ion pairs, and seven DMSO molecules (Figures 5 and 6).

In the structure, the crown ether fragment with the $Na^+$ ion in the **SQPA** moiety is disordered over two sites. All but one of the $Cl^-$ anions are also disordered over two positions. The same applies for the two DMSO molecules. In all the ligands, sodium cations and chloride anions interact directly with the corresponding binding domains. Sodium occupies the crown ether cavity and is bonded by five etheric oxygen atoms. The distances between O and Na atoms for all the molecules are in the range from 2.35 to 2.48 Å. The anions are coordinated by N−H groups of the squaramide fragments forming unequal H-bonds with most of the N···Cl distances varying from 2.99 to 3.16 Å. The two protruding distances, concerning a disordered anion in the **SQPD** ligand, are equal to 3.27 and 3.66 Å; however, the latter corresponds to the N−H···Cl contact that is slightly longer than the sum of the van der Waals radii of the H and $Cl^-$ moieties.[18,21] There are also some weak H-bonds between $Cl^-$ anions and aliphatic or aromatic H atoms of neighboring molecules. These contacts, however, seem to be a secondary effect of the packing of the molecules. In the crystal lattice of [**1**×NaCl], ligands are forming **SQPA**···**SQPC** and **SQPB**···**SQPD** dimers with one of the Na ions coordinated by the carbonyl groups of another molecule of **1**, as shown in Figure 6.

In the dimers, the ligands are translated relative to one another, which results in an inequivalent environment of the Na ions. The formation of these dimers is supported by the parallel $\pi-\pi$ stacking interaction between the phenyl moiety of the benzo-15-crown-5-ether unit and the unsaturated squaramide ring. The shortest distances between the LSQ plane fitted to the phenyl ring and a C atom of the squaramide are equal to 3.24 and 3.14 Å for the **SQPA**···**SQPC** and **SQPB**···**SQPD** dimers, respectively. These two molecular aggregates are not chemically identical. In the **SQPA** unit, the sodium cation is coordinated by only one DMSO molecule, whereas in the corresponding **SQP-B** moiety, two DMSO species are bonded to the $Na^+$ ion. In the structure, the two remaining DMSO molecules act as space fillers and form no hydrogen bonds with the other entities. In the crystal, the molecules are packed to form layers parallel to the $(01\bar{1})$ lattice plane with the $CF_3$ groups and some DMSO molecules located between them, as presented in Figure 7a.

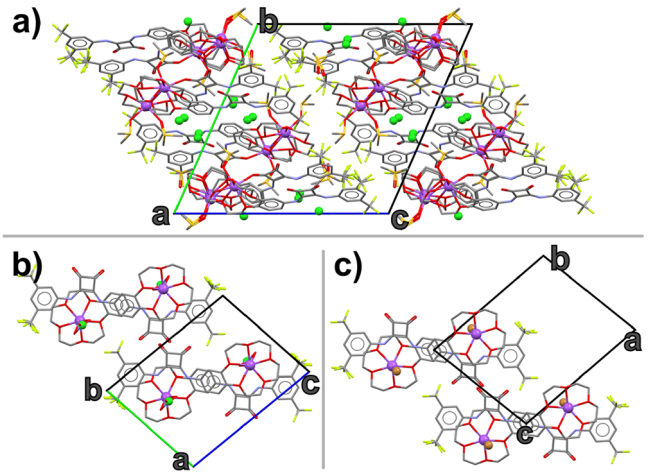


**Figure 7.** Packing diagrams of single-crystal structures of (a) [**1**×NaCl], (b) [**1**×$NaCl/NaNO_3$], and (c) [**1**×NaBr].

The next two structures with **1** and sodium salts, in spite of their different compositions, are very similar. The first one is a crystal containing mixed $Cl^-/NO_3^-$ sites with an occupancy ratio of the anions equal to 0.56(1):0.44(1). The second example is a crystal incorporating $Na^+/Br^-$ ionic pairs. The crystals contain, in the asymmetric part of the unit cell, a **SQP** unit and the corresponding ions. There are no additional solvent molecules present in the crystal lattices. Although the unit cell angles of the mentioned crystals are different (all obtuse vs all acute), these phases can be considered as isostructural, as can be seen by comparing panels b and c of Figure 7 presenting the packing of the molecules. The substitutional disorder in the crystals of [**1**×$NaCl/NaNO_3$] results in a visible increase in the displacement parameters of the atoms (compare panels b and c of Figure 5). In both structures, as in the case of [**1**×NaCl], the $Na^+$ ions are coordinated by the crown ether moieties, whereas anions are bound by the nitrogen atoms of the squaramide unit. Contacts between $Na^+$ cations and O atoms of the crown ether are in the range of 2.34−2.38 Å for [**1**×$NaCl/NaNO_3$] and 2.33−2.37 Å for [**1**×NaBr] complexes and thus are comparable to those observed in the structure of [**1**×NaCl]. Distances between N and halogen anions are equal to 3.20 and 3.33 Å in [**1**×$NaCl/NaNO_3$] and [**1**×NaBr] structures, respectively. The relatively long N···$Cl^-$ distance probably results from the substitutional disorder and averaging of the whole structure. In the mixed crystal, the $NO_3^-$ anion interacts with both N−H groups with N···O distances equal to 2.78 and 2.98 Å. In both crystals, **SQP** moieties form centrosymmetric dimers (Figure 8).

In such aggregates, $Na^+$ cations located in the crown ether cavities are in addition coordinated by the anions. In the dimers, the distances between the LSQ planes of the phenyl rings in the benzo-15-crown-5-ether fragments are 3.52 and 3.56 Å in the [**1**×$NaCl/NaNO_3$] and [**1**×NaBr] crystals,


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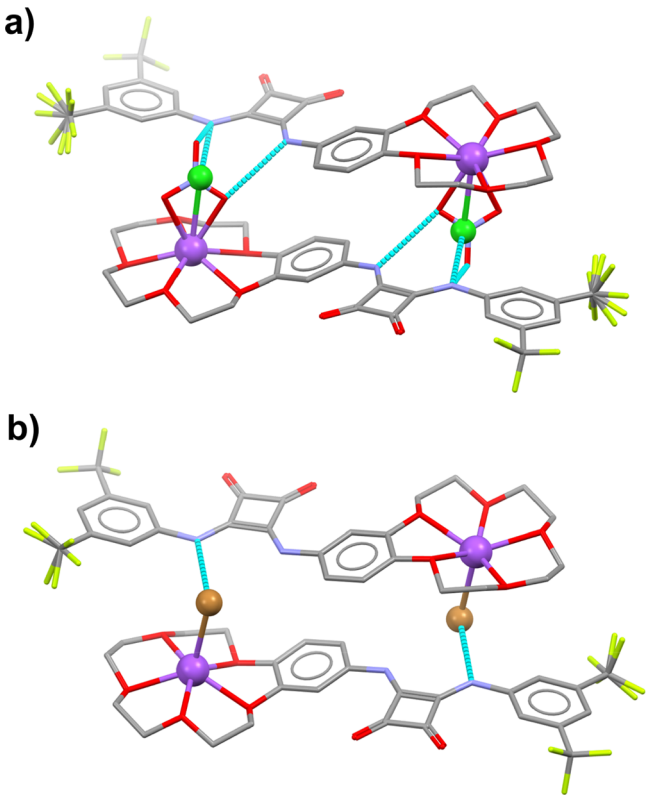


**Figure 8. SQP** ligands forming dimers in the crystals of (a) [**1**×NaCl/$NaNO_3$] and (b) [**1**×NaBr].

respectively. The phenyl rings, however, are visibly displaced; thus, this type of interaction is secondary and probably originates from strong cooperative attraction between the anions and N−H groups. Nevertheless, strong parallel $\pi-\pi$ stacking can be observed between the dimers where the distances from LSQ planes of the phenyl moiety in the benzo-15-crown-5-ether fragments are equal to 3.30 and 3.31 Å in the $Cl^-/NO_3^-$ and $Br^-$ ion-containing structures, respectively. These types of interactions result in the formation of columns of the moieties parallel to the [100] direction (Figure 7b,c).

Interestingly, both structures are similar to the known structure of the $NaNO_3$ complex of a ligand analogous to **2** containing no $CF_3$ groups.[22] In this structure, the molecules also form centrosymmetric dimers, though with ether fragments positioned closer, yet longer amide to $NO_3^-$ distances.

Although the $Na^+$ fits perfectly into the cavity of the 15-crown-5 moiety in all the structures of **1** described here, the cation is bound externally, with the coordination sphere formed by the ether on one side and additional ligands on the other. Such a behavior is typical for $Na^+$ complexes with an ether of such size, as is confirmed by the analysis of the single-crystal structures retrieved from Cambridge Structural Database.[23] The histogram presenting the number of structures depending on the distance from the mean LSQ plane fitted to all the atoms of the ether ring to the $Na^+$ ion is presented in Figure 9. In only a couple of the structures the cation is located approximately in the equatorial plane of the ether, complexed on both sides by small molecules like $H_2O$. In the case of distances between 0.5 and 1.5 Å, the cation is coordinated by the ether on one side only and complexed by additional ligands on the other side. The size and/or number of these ligands increases from the left to the right side of the picture. In the

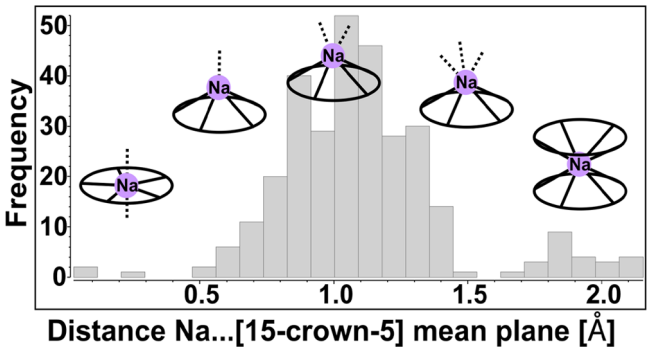


**Figure 9.** Histogram of distances between the $Na^+$ cation and LSQ mean plane fitted to the [15-crown-5] ether ring for the single-crystal structures retrieved from the Cambridge Structural Database.[23]

structures with distances from $Na^+$ to the mean plane of >1.5 Å, the cation is coordinated by two crown ether units on both sides, forming a sandwichlike complex. In the crystals of [**1**×NaCl], the distances are equal to 1.21 Å/1.00 Å, 1.35 Å, 1.16 Å, and 1.08 Å for Na(1A)/Na(1E) in the disordered **SQP-A** moiety, **SQP-B**, **SQP-C**, and **SQP-D** ligands, respectively. In the isostructural crystals of [**1**×NaCl/$NaNO_3$] and [**1**×NaBr], the corresponding distances are 0.58 and 0.54 Å, respectively.

**Extraction Studies.** Ion pair receptors offer substantial advantages in terms of affinity as compared to corresponding single-ion receptors and can be utilized under interfacial conditions as efficient extractants.[24] Therefore, we tested receptors **1**−**3** in an extraction of sodium chloride from the aqueous to the organic phase. To be as close as possible to the conditions that correlate well with the transport abilities of squaramide-based anion receptors toward lipid bilayers,[8b] we performed liquid−liquid extractions using a 0.5 M aqueous solution of sodium chloride and 1 mM solutions of receptors in deuterated nitrobenzene. A comparison of the $^1$H NMR spectrum of free receptor **1** in wet nitrobenzene revealed significant changes in the resonance signals of both squaramide protons after being in contact with a 0.5 M aqueous solution of NaCl. The protons that initially resonated at $\delta$ = 9.32 and 9.72 ppm were shifted downfield $\Delta\delta$ = 0.72 and 0.79 ppm, respectively (Figure 6). This clearly indicates the ability of **1** to extract sodium chloride from the aqueous phase and form complexes in the organic layer. This is supported by electrospray ionization mass spectrometric measurements of the extracted organic solution, which clearly shows characteristic peaks appearing at $m/z$ 625.5 [**1** + $Cl^-$] and $m/z$ 647.5 [**1** − $H^+$ + NaCl] (Supporting Information). Furthermore, the organic phase was then back-extracted into $H_2O$. The $^1$H NMR spectrum of the nitrobenzene phase after being in contact with water is essentially identical to the spectrum of the free receptor (Figure 10). In contrast, almost no discernible chemical shift changes were observed in the $^1$H NMR spectrum of the nitrobenzene phase containing receptor **2** or monotopic anion receptor **3** after intensive washing with a 0.5 M aqueous NaCl solution (Figure 11).

To quantify the sodium content in the organic phase and calculate the extraction efficiency in the experiments described above, we used atomic absorption spectroscopy (AAS).[25] The content of sodium in 0.5 mM solutions of receptors in nitrobenzene obtained after extraction with the 0.5 M NaCl solution was determined to be 24 mg/L for **1**, which corresponds to a 22% extraction efficiency and negligible for


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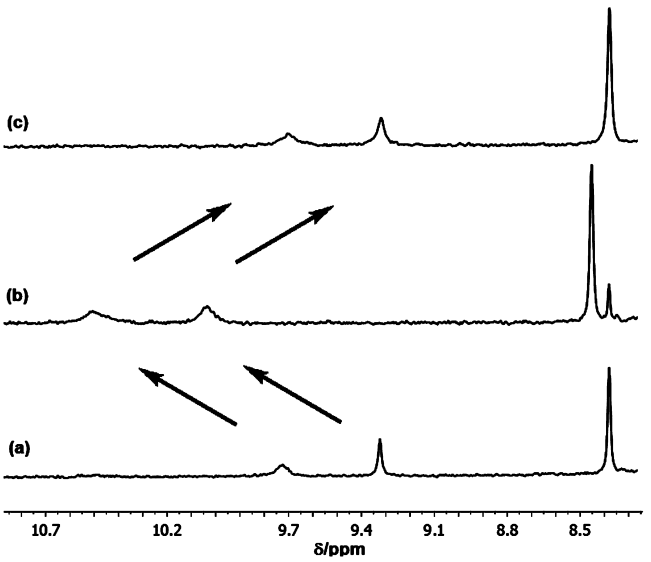


**Figure 10.** Partial $^{1}$H NMR spectra of receptor **1** (a) at 1.0 mM in wet $PhNO_2$-$d_5$, (b) after NaCl extraction from the aqueous phase, and (c) after back-extraction to distilled water.

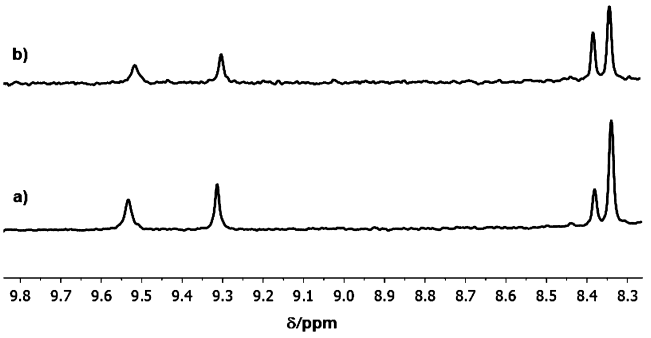


**Figure 11.** Partial $^{1}$H NMR spectra of receptor **3** (a) at 1.0 mM in wet $PhNO_2$-$d_5$ and (b) after NaCl extraction from the aqueous phase.

**2**, **3**, or 4-nitrobenzo-15-crown-5-ether.[26] When a dual-receptor strategy was employed, i.e., extraction of NaCl from the aqueous phase with a binary mixture of anion receptor **3** and 4-nitrobenzo-15-crown-5-ether in nitrobenzene, the extraction efficiency was significantly reduced and determined to be 4%. This clearly shows that the assembly of a strong anion binding domain with a directly linked crown ether in the structure of heteroditopic receptor **1** is needed for the preparation of an effective salt extractant. The ability not only to take up but also to release sodium chloride by receptor **1** was confirmed by the back-extraction experiment, which showed a decrease in the sodium cation concentration in the organic phase after washing with water. Taking these results together, we concluded that squaramide-based ion pair receptor **1** is capable of extracting sodium chloride from aqueous media, in contrast to urea-based ion pair receptor **2** or squaramide-based anion receptor **3**.

## CONCLUSION

In summary, the squaramide-based ion pair receptor was synthesized and characterized. On the basis of titration experiments and single-X-ray crystal diffraction analyses, we demonstrated the strong ability of receptor **1** to form complexes with sodium chloride, even in the presence of water. We demonstrated that the crown ether unit in the receptor **1** structure is responsible for reinforcing anion binding in the presence of sodium cations. In contrast to urea-based ion pair receptor **2** and monotopic receptor **3** lacking a crown ether unit, squaramide-based ditopic receptor **1** can extract sodium chloride from the aqueous to the organic phase, as shown independently by $^{1}$H NMR and MS measurements and supported quantitatively by AAS. These measurements clearly show that receptor **1** is a promising candidate for transporting sodium cations and chloride anions simultaneously across membranes. To the best of our knowledge, compound **1** is the first example of such a simple and effective, non-multimacrocyclic ion pair receptor capable of recognizing sodium chloride in the presence of water and extracting it from the aqueous to the organic phase.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.inorgchem.8b02163.

$^{1}$H and $^{13}$C NMR spectra, UV−vis and $^{1}$H NMR titration spectra, UV−vis and NMR binding isotherms, extraction procedures, and crystal data of [**1**×NaCl], [**1**×NaCl/$NaNO_3$], and [**1**×NaBr] complexes (PDF)

### Accession Codes

CCDC 1812264 and 1855570−1855571 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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The authors declare no competing financial interest.

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## REFERENCES

(1) (a) Wurm, F. R.; Klok, H.-A. Be squared: Expanding the Horizon of Squaric Acid-Mediated Conjugations. *Chem. Soc. Rev.* **2013**, *42*, 8220−8236. (b) Storer, R. I.; Aciro, C.; Jones, L. H. Squaramides: Physical Properties, Synthesis and Applications. *Chem. Soc. Rev.* **2011**, *40*, 2330−2346. (c) Xiaohong, Q.; Can, J.; Xiaoning, Z.; Yan, J.; Chen, L.; Leyong, W. Squaramide Derivatives and Their Applications in Ion Recognition. *Progress in Chemistry* **2014**, *26*, 1701−1711. (d) Alemán, J.; Parra, A.; Jiang, H.; Jørgensen, K. A. Squaramides: Bridging from Molecular Recognition to Bifunctional Organocatalysis. *Chem. - Eur. J.* **2011**, *17*, 6890−6899.

(2) Amendola, V.; Bergamaschi, G.; Boiocchi, M.; Fabbrizzi, L.; Milani, M. The Squaramide versus Urea Contest for Anion Recognition. *Chem. - Eur. J.* **2010**, *16*, 4368−4380.



DOI: 10.1021/acs.inorgchem.8b02163
*Inorg. Chem.* XXXX, XXX, XXX−XXX

(3) (a) Frontera, A.; Morey, J.; Oliver, A.; Piña, M. N.; Quiñonero, D.; Costa, A.; Ballester, P.; Deyà, P. M.; Anslyn, E. V. Rational Design, Synthesis, and Application of a New Receptor for the Molecular Recognition of Tricarboxylate Salts in Aqueous Media. *J. Org. Chem.* **2006**, *71*, 7185−7195. (b) Qin, L.; Hartley, A.; Turner, P.; Elmes, R. B. P.; Jolliffe, K. A. Macrocyclic Squaramides: Anion Receptors with High Sulfate Binding Affinity and Selectivity in Aqueous Media. *Chem. Sci.* **2016**, *7*, 4563−4572. (c) Prohens, R.; Tomàs, S.; Morey, J.; Deyà, P. M.; Ballester, P.; Costa, A. Squaramido-Based Receptors: Molecular Recognition of Carboxylate Anion in Highly Competitive Media. *Tetrahedron Lett.* **1998**, *39*, 1063−1066. (d) Quiñonero, D.; López, K. A.; Deyà, P. M.; Piña, M. N.; Morey, J. Synthetic Tripodal Squaramido-Based receptors for the Complexation of Antineoplastic Folates in Water. *Eur. J. Org. Chem.* **2011**, *2011*, 6187−6194.

(4) (a) Al-Sayah, M. H.; Branda, N. R. Calorimetric and NMR Binding Studies of Hydrogen-Bonding Receptors for Carboxylates. *Thermochim. Acta* **2010**, *503*−*504*, 28−32. (b) Ramalingam, V.; Domaradzki, M. E.; Jang, S.; Muthyala, R. S. Carbonyl Groups as Molecular Valves to Regulate Chloride Binding to Squaramides. *Org. Lett.* **2008**, *10*, 3315−3318. (c) Rotger, C.; Soberats, B.; Quiñonero, D.; Frontera, A.; Ballester, P.; Benet-Buchholz, J.; Deyà, P. M.; Costa, A. Crystallographic and Theoretical Evidence of Anion-$\pi$ and Hydrogen-Bonding Interactions in Squaramide-Nitrate salt. *Eur. J. Org. Chem.* **2008**, *2008*, 1864−1868. (d) Li, Y.; Yang, G.-H.; Shen, Y.-Y.; Xue, X.-S.; Li, X.; Cheng, J.-P. *N*-*tert*-Butyl Sulfinyl Squaramide Receptors for Anion Recognition through Assisted *tert*-Butyl C-H Hydrogen Bonding. *J. Org. Chem.* **2017**, *82*, 8662−8667. (e) Amendola, V.; Fabbrizzi, L.; Mosca, L.; Schmidtchen, F.-P. Urea-, Squaramide-, and Sulfonamide-Based Anion Receptors: a Thermodynamic Study. *Chem. - Eur. J.* **2011**, *17*, 5972−5981. (f) Gaeta, C.; Talotta, C.; Della Sala, P.; Margarucci, L.; Casapullo, A.; Neri, P. Anion-Induced Dimerization in p-Squaramidocalix[4]arene Derivatives. *J. Org. Chem.* **2014**, *79*, 3704−3708.

(5) Rostami, A.; Wei, C. J.; Guérin, G.; Taylor, M. S. Anion Detection by a Fluorescent Poly(squaramide): Self-Assembly of Anion-Binding Sites by Polymer Aggregation. *Angew. Chem., Int. Ed.* **2011**, *50*, 2059−2062.

(6) (a) Elmes, R. B. P.; Jolliffe, K. A. Amino Acid-Based Squaramides for Anion Recognition. *Supramol. Chem.* **2015**, *27*, 321−328. (b) Rostami, A.; Colin, A.; Li, X. Y.; Chudzinski, M. G.; Lough, A. J.; Taylor, M. S. N. *N*′-Diarylsquaramides: General, High-Yielding Synthesis and Applications in Colorimetric Anion Sensing. *J. Org. Chem.* **2010**, *75*, 3983−3992. (c) Neus Piña, M.; Rotger, M. C.; Costa, A.; Ballester, P.; Deyà, P. M. Evaluation of Anion Selectivity in Protic Media by Squaramide-Cresol Red Ensembles. *Tetrahedron Lett.* **2004**, *45*, 3749−3752. (d) Edwards, S. J.; Valkenier, H.; Busschaert, N.; Gale, P. A.; Davis, A. P. High-Affinity Anion Binding by Steroidal Squaramide Receptors. *Angew. Chem., Int. Ed.* **2015**, *54*, 4592−4596. (e) Jin, C.; Zhang, M.; Deng, C.; Guan, Y.; Gong, J.; Zhu, D.; Pan, Y.; Jiang, J.; Wang, L. Novel Calix[4]arene-Based Receptors with Bis-Squaramide Moieties for Colorimetric Sensing of Anions via Two Different Interaction Modes. *Tetrahedron Lett.* **2013**, *54*, 796−801. (f) Tomàs, S.; Rotger, M. C.; González, J. F.; Deyà, P. M.; Ballester, P.; Costa, A. Squaramide-Based Receptors: Synthesis and Application to the Recognition of Polyalkyl Ammonium Salts. *Tetrahedron Lett.* **1995**, *36*, 2523−2526. (g) Liu, Y.; Qin, Y.; Jiang, D. Squaramide-Based Tripodal Ionophores for Potentiometric Sulfate-Selective Sensor with High Selectivity. *Analyst* **2015**, *140*, 5317−5323. (h) Jin, C.; Zhang, M.; Wu, L.; Guan, Y.; Pan, Y.; Jiang, J.; Lin, C.; Wang, L. Squaramide-Based Tripodal Receptors for Selective Recognition of Sulfate Anion. *Chem. Commun.* **2013**, *49*, 2025−2027. (i) Tomàs, S.; Prohens, R.; Vega, M.; Rotger, M. C.; Deyà, P. M.; Ballester, P.; Costa, A. Squaramido-Based Receptors: Design, Synthesis, and Application to the Recognition of Tetraalkyloammonium Compounds. *J. Org. Chem.* **1996**, *61*, 9394−9401. (j) Jin, C.; Zhang, X.; Wu, X.; Zhang, M.; Jiang, J.; Lin, C.; Wang, L. The Recognition of n-Alkyl Phosphonic or Carboxylic Acid by Mono-Squaramide-Functionalised Pillar[5]arenes. *Supramol. Chem.* **2015**, *27*, 329−335. (k) Elmes, R. B. P.; Turner, P.; Jolliffe, K. A. Colorimetric and Luminescent Sensors for Chloride: Hydrogen Bonding vs Deprotonation. *Org. Lett.* **2013**, *15*, 5638−5641.

(7) (a) Załubiniak, D.; Zakrzewski, M.; Piątek, P. Highly Effective Ion-Pair Receptors Based on 2,2-Bis(aminomethyl)-propionic Acid. *Dalton Trans.* **2016**, *45*, 15557−15564. (b) Zdanowski, S.; Piątek, P.; Romański, J. An Ion Pair Receptor Facilitating the Extraction of Chloride Salt from the Aqueous to the Organic Phase. *New J. Chem.* **2016**, *40*, 7190−7196. (c) Frontera, A.; Orell, M.; Garau, C.; Quiñonero, D.; Molins, E.; Mata, I.; Morey, J. Preparation, Solid-State Characterization, and Computational Study of a Crown Ether Attached to a Squaramide. *Org. Lett.* **2005**, *7*, 1437−1440. (d) Ambrosi, G.; Formica, M.; Fusi, V.; Giorgi, L.; Guerri, A.; Micheloni, M.; Paoli, P.; Pontellini, R.; Rossi, P. A New Macrocyclic Cryptand with Squaramide Moieties: an Overstructured $Cu^{II}$ Complex that Selectively Binds Halides: Synthesis, Acid/Base- and Ligational Behavior, and Crystal Structures. *Chem. - Eur. J.* **2007**, *13*, 702−712. (e) Ambrosi, G.; Formica, M.; Fusi, V.; Giorgi, L.; Macedi, E.; Micheloni, M.; Paoli, P.; Pontellini, R.; Rossi, P. A Macrocyclic Ligand as Receptor and $Zn^{II}$-Complex Receptor for Anions in Water: Binding Properties and Crystal Structures. *Chem. - Eur. J.* **2011**, *17*, 1670−1682.

(8) (a) Yang, Y.; Wu, X.; Busschaert, N.; Furuta, H.; Gale, P. A. Dissecting the Chloride-Nitrate Anion Transport Assay. *Chem. Commun.* **2017**, *53*, 9230−9233. (b) Busschaert, N.; Kirby, I. L.; Young, S.; Coles, S. J.; Horton, P. N.; Light, M. E.; Gale, P. A. Squaramides as Potent Transmembrane Anion Transporters. *Angew. Chem., Int. Ed.* **2012**, *51*, 4426−4430. (c) Cai, X.-J.; Li, Z.; Chen, W.-H. Tripodal Squaramide Conjugates as Highly Effective Transmembrane Anion Transporters. *Bioorg. Med. Chem. Lett.* **2017**, *27*, 1999−2002.

(9) Busschaert, N.; Park, S.-H.; Baek, K.-H.; Choi, Y. P.; Park, J.; Howe, E. N. W.; Hiscock, J. R.; Karagiannidis, L. E.; Marques, I.; Félix, V.; Namkung, W.; Sessler, J. L.; Gale, P. A.; Shin, I. A Synthetic Ion Transporter that Disrupts Autophagy and Induces Apoptosis by Perturbing Cellular Chloride Concentrations. *Nat. Chem.* **2017**, *9*, 667−675.

(10) *APEX2*; Bruker AXS Inc.: Madison, WI, 2013.

(11) *APEX3*; Bruker AXS Inc.: Madison, WI, 2017.

(12) *SAINT*; Bruker AXS Inc.: Madison, WI, 2017.

(13) *TWINABS*; Bruker AXS Inc.: Madison, WI, 2012.

(14) *SADABS*; Bruker AXS Inc.: Madison, WI, 2016.

(15) Sheldrick, G. M. SHELXT - Integrated Space-Group and Crystal-Structure Determination. *Acta Crystallogr., Sect. A: Found. Adv.* **2015**, *71*, 3−8.

(16) Sheldrick, G. M. Crystal Structure Refinement with SHELXL. *Acta Crystallogr., Sect. C: Struct. Chem.* **2015**, *71*, 3−8.

(17) Cowley, J. M. *International Tables for Crystallography*; Wilson, A. J. C., Ed.; Kluwer: Dordrecht, The Netherlands, 1992; Vol. *C*, pp 223−245.

(18) Macrae, C. F.; Bruno, I. J.; Chisholm, J. A.; Edgington, P. R.; McCabe, P.; Pidcock, E.; Rodriguez-Monge, L.; Taylor, R.; van de Streek, J.; Wood, P. A. Mercury CSD 2.0 - New features for the Visualization and Investigation of Crystal Structures. *J. Appl. Crystallogr.* **2008**, *41*, 466−470.

(19) Ulatowski, F.; Dąbrowa, K.; Bałakier, T.; Jurczak, J. Recognizing the Limited Applicability of Job Plots in Studying Host-Guest Interactions in Supramolecular Chemistry. *J. Org. Chem.* **2016**, *81*, 1746−1756.

(20) (a) Mäkelä, T.; Kiesilä, A.; Kalenius, E.; Rissanen, K. Ion-Pair Complexation with Dibenzo[21]crown-7 and Dibenzo[24]crown-8 Bis-Urea Receptors. *Chem. - Eur. J.* **2016**, *22*, 14264−14272. (b) Mäkelä, T.; Rissanen, K. Ion Pair Complexes and Anion Binding in the Solution of a Ditopic Receptor. *Dalton Trans* **2016**, *45*, 6481−6490. (c) Karbarz, M.; Romański, J. Dual Sensing by Simple Heteroditopic Salt Receptors Containing an Anthraquinone Unit. *Inorg. Chem.* **2016**, *55*, 3616−3623. (d) Mäkelä, T.; Kalenius, E.; Rissanen, K. Cooperatively Enhanced Ion Pair Binding with a Hybrid Receptor. *Inorg. Chem.* **2015**, *54*, 9154−9156.



DOI: 10.1021/acs.inorgchem.8b02163
*Inorg. Chem.* XXXX, XXX, XXX−XXX

(21) Bondi, A. Van der Waals Volumes and Radii. *J. Phys. Chem.* **1964**, *68*, 441−451.
(22) Barboiu, M.; Vaughan, G.; van der Lee, A. Self-Organized Heteroditopic Macrocyclic Superstructures. *Org. Lett.* **2003**, *5*, 3073−3076.
(23) Groom, C. R.; Bruno, I. J.; Lightfoot, M. P.; Ward, S. C. The Cambridge Structural Database. *Acta Crystallogr., Sect. B: Struct. Sci., Cryst. Eng. Mater.* **2016**, *72*, 171−179.
(24) (a) Wintergerst, M. P.; Levitskaia, T. G.; Moyer, B. A.; Sessler, J. L.; Delmau, L. H. Calix[4]pyrrole: A New Ion-Pair Receptor As Demonstrated by Liquid-Liquid Extraction. *J. Am. Chem. Soc.* **2008**, *130*, 4129−4139. (b) White, D. J.; Laing, N.; Miller, H.; Parsons, S.; Tasker, P. A.; Coles, S. Ditopic Ligands for the Simultaneous Solvent Extraction of Cations and Anions. *Chem. Commun.* **1999**, 2077−2078. (c) Kim, S. K.; Lynch, V. M.; Young, N. Y.; Hay, B. P.; Lee, C.-H.; Kim, J. S.; Moyer, B. A.; Sessler, J. S. KF and CsF Recognition and Extraction by a Calix[4]crown-5 Strapped Calix[4]pyrrole Multitopic Receptor. *J. Am. Chem. Soc.* **2012**, *134*, 20837−20843. (d) He, Q.; Zhang, Z.; Brewster, J. T.; Lynch, V. M.; Kim, S. K.; Sessler, J. L. Hemispherand-Strapped Calix[4]pyrrole: An Ion-pair Receptor for the Recognition and Extraction of Lithium Nitrite. *J. Am. Chem. Soc.* **2016**, *138*, 9779−9782. (e) Romański, J.; Piątek, P. Selective Ammonium Nitrate Recognition by a Heteroditopic Macrotricyclic Ion-Pair Receptor. *J. Org. Chem.* **2013**, *78*, 4341−4347. (f) He, Q.; Williams, N. J.; Oh, J. H.; Lynch, V. M.; Kim, S. K.; Moyer, B. A.; Sessler, J. L. Selective Solid−Liquid and Liquid−Liquid Extraction of Lithium Chloride Using Strapped Calix[4]pyrroles. *Angew. Chem., Int. Ed.* **2018**, *57*, 11824. (g) Mahoney, J. M.; Beatty, A. M.; Smith, B. D. Selective Solid-Liquid Extraction of Lithium Halide Salts Using a Ditopic Macrobicyclic Receptor. *Inorg. Chem.* **2004**, *43*, 7617−7621. (h) Mahoney, J. M.; Nawaratna, G. U.; Beatty, A. M.; Duggan, P. J.; Smith, B. D. Transport of Alkali Halides through a Liquid Organic Membrane Containing a Ditopic Salt-Binding Receptor. *Inorg. Chem.* **2004**, *43*, 5902−5907.
(25) The extraction efficiency is defined as the fraction of receptor molecules occupied by the complex in the organic phase.
(26) The extraction efficiency was determined to be 72% for extraction of solid NaCl with a nitrobenzene solution of receptor **1**. In the case of extraction of a more lipophilic salt such as sodium nitrate, the extraction efficiency was higher and was determined to be 37 and 87% under liquid−liquid and solid−liquid conditions, respectively. This demonstrates that under interfacial conditions the selectivity of receptor **1** is consistent with the Hofmeister bias. Similarly, in the case of extraction of an aqueous solution of chloride salts consisting of fewer (LiCl) and more (KCl) lipophilic cations (with respect to $Na^+$) with a nitrobenzene solution of **1**, the extraction efficiency was determined to be 3 and 53%, respectively (selectivity order LiCl < NaCl < KCl). Interestingly, under solid−liquid conditions, the selectivity order is strongly reversed and the extraction efficiency is determined to be 54 and 84% for KCl and LiCl, respectively (selectivity order KCl < NaCl < LiCl).


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