Inorganic Chemistry

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Cooperative Transport and Selective Extraction of Sulfates by a Squaramide-Based Ion Pair Receptor: A Case of Adaptable Selectivity

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Cite This: https://dx.doi.org/10.1021/acs.inorgchem.0c02114 Read Online

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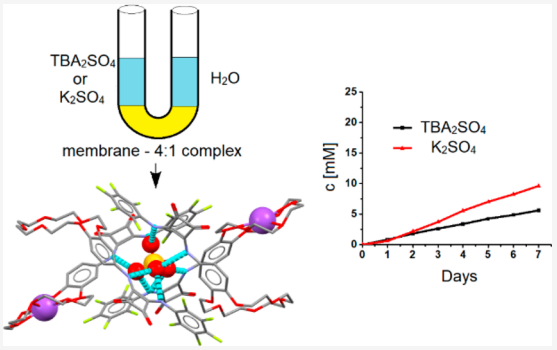
ABSTRACT: The use of a squaramide-based ion pair receptor offers a solution to the very challenging problem of extraction and transport of extremely hydrated sulfate salt. Herein we demonstrate for the first time that a neutral receptor is able not only to selectively extract but also to transport sulfates in the form of an alkali metal salt across membranes and to do so in a cooperative manner while overcoming the Hofmeister bias. This was made possible by an enhancement in anion binding promoted by cation assistance and by diversifying the stoichiometry of receptor complexes with sulfates and other ions. The existence of a peculiar 4:1 complex of receptor **2** with sulfates in solution was confirmed by UV−vis and ^{1}H NMR titration experiments, DOSY and DLS measurements, and supported by solid-state X-ray measurements. By varying the separation technique and experimental conditions, it was possible to switch the depletion of the aqueous layer into extremely hydrophilic or less lipophilic salts, thus obtaining the desired selectivity.



INTRODUCTION

Ion recognition, extraction, and transport are among the particular and still challenging tasks of modern supramolecular chemistry. They are extremely important because they are closely related to real problems including the regulation of ion transport in organisms, their detection, water treatment, and waste disposal.[1] Research has shown that one solution to these problems may involve the use of monotopic anion receptors possessing binding domains capable of interacting with negatively charged species. This group of compounds comprises squaramides, which are a special class of monotopic anion receptors able to interact with anions more effectively than their urea or thiourea analogues.[2] However, monotopic receptors are capable of interacting with one type of ion (anions), which in the presence of strongly coordinating counterions (cations) may lose their effectivity in ion binding due to the formation of ion pairs out of the receptor's binding site.[3] To eliminate this dysfunction, ion pair receptors, compounds capable of simultaneously binding anions and cations, have been proposed and recently intensively investigated.[4] Cooperative binding by heteroditopic receptors can be achieved by properly oriented binding domains within a receptor platform.

Unexpectedly, within this group of compounds, only a few examples of ditopic ion pair receptors possessing a squaramide unit as an anion binding domain can be distinguished.[5] Our contribution in this field has involved the design of squaramide-based ion pair receptors which are so effective that they can be used in liquid−liquid extraction (LLE) of salts from the aqueous layer to the organic phase, including the selective extraction of extremely hydrophilic sulfate salts (ΔG_h° = −1080 kJ/mol).[6,7] Selective sulfate removal is a nontrivial task and involves defeating the hydration energy of anions and overcoming the Hofmeister series to preferentially extract these ions to the organic phase even in the presence of less hydrated anions (e.g., nitrates ΔG_h° = −306 kJ/mol).[7,8] This task is highly desired, e.g., in the context of the storage of radioactive waste after nuclear processes containing sulfates.[9] Sulfates cause corrosion of glass melters and the constituent electrodes, and due to their low solubility in borosilicate glass, they are responsible for problems with vitrification, resulting in reduced durability of glass logs and thus entailing a safety hazard upon storage.

To date, however, few examples of receptors capable of overcoming the Hofmeister series and allowing the selective extraction (LLE) of sulfates from aqueous solutions have been developed. The group of these compounds mainly includes anion receptors: macrocyclic calix[*n*]pyrroles, TREN-based hexaurea, diiminoguanidine, and more recently macrocyclic

Received: July 16, 2020

squaramide derivatives.[10] Some of these receptors were found to recognize sulfate salts in unusual manner via contact ion pair interactions.[11] However, this approach requires the assistance of lipophilic counterions during the extraction or transport processes. The solution proposed by our group, however, relies on using squaramide-based ion pair receptors and the formation of 4:1 complexes with sulfates, rather than 1:1 complexes with other salts tested.[6] This facilitated the selective extraction of sulfates from aqueous to organic phase even in the presence of alkali potassium cations. However, due to the insufficient solubility of such a receptor in chloroform, in extraction experiments its suspension was used. We found that complete dissolution and phase separation was observed only after such a suspension was contacted with an aqueous solution of potassium sulfate, which was not the case for the other salts tested. This characteristic was interpreted as a component that causes the selectivity of sulfate extraction in the presence of other salts whose complexes were not soluble in the organic layer. In order to verify whether more complex equilibria (like that in the case of the interaction of sulfates with squaramides) are the main driving force for the selective extraction process, in the present study we eliminated the solubility drawback and developed and tested squaramide-based ion pair receptors equipped with a pentafluorophenyl unit, soluble in chloroformic phase. Ion pair receptor bearing pentafluorophenyl unit was recently found to be selective in solid−liquid extraction of potassium bromide.[12] We proved, however, that replacing urea with a squaramide function in the ion pair receptor structures opens up its potential to act under liquid−liquid conditions.[6] By comparing ditopic receptors to a monotopic one, the impact of the presence of a cation binding domain and the ability to simultaneously bind cations and anions on the extraction process were also established. The ability of neutral ion pair receptor **2** not only to selectively extract but also to transport them in a selective and adaptable manner across membranes without the assistance of lipophilic cation was successfully developed for the first time.

EXPERIMENTAL SECTION

All reagents and chemicals were reagent-grade and purchased commercially. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 300 MHz spectrometer. ^{1}H NMR chemical shifts δ are reported in parts per million referenced to residual solvent signal (deuterated dimethyl sulfoxide (DMSO-d_6 or $CDCl_3$). Mass spectra were measured on Quattro LC Micromass or Shimadzu LCMS-IT-TOF unit.

Preparation of Compound M1. Compound **M1** was synthesized according to the literature procedure with small modifications.[13] 2,3,4,5,6-Pentafluoroaniline (2.01 g, 11.3 mmol) was added to a solution of dimethyl squarate (1.63 g, 11.5 mmol) in MeOH (20 mL). After being stirred for 48 h at room temperature, the reaction mixture was concentrated and purified by silica gel column chromatography (5% methanol in chloroform) to give compound **M1** as a white solid (2.65 g, 9.01 mmol, 80% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.11 (s, 1H), 4.32 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d6) δ 190.5, 187.5, 184.9, 183.1, 180.0, 170.8, 167.4, 142.9−140.7 (m), 138.6−135.8 (m), 113.5−112.7, 60.8. HRMS (ESI): m/z calcd for $C_{11}H_4O_3NF_5Na$ $[M + Na]^+$: 316.0009. Found 316.0003.

Preparation of Receptor 1. To a degassed solution of 4-nitrobenzo-15-crown 5-ether (0.407 g, 1.3 mmol) in 10 mL of a THF/MeOH mixture (1/4) was added 10 mg of 10% Pd/C. The reaction mixture was kept under a H_2 atmosphere (balloon pressure) at room temperature overnight. Then, 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 (0.368 g). The obtained 4-aminobenzo-18-crown 5-ether was used in the next step without further purification. To the solution of 4-aminobenzo-18-crown 5-ether (0.368 g, 1.3 mmol) in methanol (10 mL) was added compound **M1** (0.381 g, 1.3 mmol) at room temperature. After being stirred for 48 h, the reaction mixture was concentrated and residue was purified by silica gel column chromatography (2% methanol in chloroform) to give receptor **1** as a yellow solid (0.582 g, 1.07 mmol, 82% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.92 (s, 2H), 7.06 (s, 1H), 7.00−6.85 (m, 1H), 6.85−6.72 (m, 1H), 4.12−3.95 (m, 4H), 3.85−3.70 (m, 4H), 3.68−3.55 (m, 8H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 184.2, 183.4, 167.0, 166.8, 149.1, 145.3, 141.5−140.5 (m), 140.5−135.2 (m), 132.9, 117.0−115.5 (m), 115.1, 111.8, 106.6, 70.7, 70.7, 70.1, 70.0, 69.4, 69.3, 69.0, 68.6. HRMS (ESI): calcd for $C_{24}H_{21}F_5N_2O_7Na$ $[M + Na]^+$: 567.1167. Found: 567.1171.

Preparation of Receptor 2. 4-Aminobenzo-18-crown 6-ether (0.622 g, 1.9 mmol) was reacted with compound **M1** (0.557 g, 1.9 mmol) according to procedure described for receptor **1** to yield receptor **2** as a light beige solid (0.823 g, 1.4 mmol, 74% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.65 (s, 2H), 7.36 (s, 1H), 7.25−6.85 (m, 2H), 4.17−3.95 (m, 4H), 3.90−3.70 (m, 4H), 3.65−3.45 (m, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.2, 182.2, 166.5, 166.0, 148.8, 144.4, 144.4−140.5 (m), 140.5−135.0 (m), 132.8, 115.5−114.3 (m), 113.6, 110.4, 104.8, 70.0, 69.1, 68.9, 68.4, 67.9. HRMS (ESI): calcd for $C_{26}H_{25}F_5N_2O_8Na$ $[M + Na]^+$: 611.1429. Found: 611.1422.

Preparation of Receptor 3. To a solution of compound **M1** (0.337 g, 1.15 mmol) in MeOH (5 mL) was added aniline (0.11 mL, 1.2 mmol), and the mixture was stirred 24 h at room temperature. 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 compound (0.321 g, 0.91 mmol, 79% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.00 (s, 2H), 7.45−7.28 (m, 4H), 7.18−7.00 (m, 1H). ^{13}C NMR (75 MHz, DMSO) δ 184.5, 183.1, 166.9, 166.8, 144.5−139.2 (m), 138.9, 137.8−135.2 (m), 129.7, 124.2, 119.7, 115.5−113.0 (m). HRMS (ESI): calcd for $C_{16}H_7F_5N_2O_2Na$ $[M + Na]^+$: 377.0325. Found: 377.0329.

UV−Vis Titration Experiments. UV−vis analyses were performed using Thermo Spectronic Unicam UV500 Spectrophotometer in CH_3CN solution at 298 K. To 10 mm cuvette was added 2.5 mL of freshly prepared solution of studied receptor (receptor **1**, 2.85×10^{-5} M; receptor **2**, 2.63×10^{-5} M; receptor **3**, 2.16×10^{-5} M), and in case of ion pair binding studies 1 mol equiv of cation (KPF_6 or $NaClO_4$) was added prior to titrations. Small aliquots of ca. 1.5×10^{-3} M of solution of anions were added (added as TBA salts: TBAX; containing receptor **1**, **2**, or **3** at the same concentration as that in the cuvette), and a spectrum was acquired after each addition. The resulting titration data were analyzed using BindFit (v0.5) package, available online at http://supramolecular.org.

^{1}H NMR Titration Experiments. The ^{1}H NMR titration was carried out on a Bruker AVANCE III HD 300 MHz spectrometer, at 298 K in CD_3CN. In each case, 500 μL of freshly prepared ca. 3 mM solution of receptor was added to a 5 mm NMR tube. In the case of ion pair titration receptor was first pretreated with 1 equiv of $NaClO_4$ or KPF_6 (referenced to receptor). Then, small aliquots of a solution of TBAX (containing the receptor at constant concentration) were added, and a spectrum was acquired after each addition. The resulting titration data were analyzed using BindFit (v0.5) package, available online at http://supramolecular.org.

^{1}H NMR DOSY experiments were conducted at 298 K on a Bruker AVANCE III HD 500 MHz spectrometer with a residual solvent signal as an internal standard.

Atomic emission measurements were carried out using PerkinElmer AAnalyst 300 spectometer.

Ion chromatography data were recorded on a Metrohm ion chromatograph model 930 Compact IC Flex equipped with conductivity detector and Metrosep A Supp 5−250/4.0 column.

Dynamic light scattering (DLS) analyses were carried out using a Malvern Zetasizer instrument (Nano ZS, UK) equipped with a 4 mW helium−neon laser of light wavelength 632.8 nm was used. The

https://dx.doi.org/10.1021/acs.inorgchem.0c02114
Inorg. Chem. XXXX, XXX, XXX−XXX

Table 1. Crystal Data and Structure Refinement Parameters for Obtained Complexes of 2 with Various Salts

	2 + KNO_3	2 + KCl/NaCl	2 + Na_2SO_4
formula	$C_{56}H_{60}F_{10}K_2N_6O_{23}$	$C_{52}H_{50}Cl_2F_{10}K_{1.31}N_4Na_{0.69}O_{16}$	$C_{457.20}H_{460}F_{80}N_{52}Na_8O_{147.20}S_4$[a]
	2 × **2** + 2 × KNO_3 + Et_2O	2 × **2** + 1.31 × KCl + 0.69 × NaCl	16 × **2** + 4 × Na_2SO_4 + 20 × MeCN + 1.2 × MeOH + 2 × H_2O[a]
M_x/g mol^{-1}	1453.30	1315.02	10870.50
T/K	130.0(5)	100.0(5)	100.0(5)
λ/Å	1.54178	1.54178	0.71073
crystal size/mm^3	0.038 × 0.241 × 0.294	0.024 × 0.168 × 0.295	0.148 × 0.201 × 0.357
space group	$P2_1/c$	$P2_1/c$	$C2/c$
unit cell dimensions	a = 19.5699 (6) Å	a = 18.1253 (5) Å	a = 12.0787 (9) Å
	b = 7.9685 (3) Å	b = 7.8928 (2) Å	b = 43.414 (3) Å
	c = 20.9742 (7) Å	c = 19.8048 (5) Å	c = 23.9907 (18) Å
	β = 104.0030 (13)°	β = 90.0610 (12)°	β = 95.624 (3)°
V/Å^3, Z	3173.58 (19), 2	2833.26 (13), 2	12519.8 (16), 1
D_x/g cm^3	1.521	1.541	1.442
μ/mm^{-1}	2.324	2.885	0.148
F(000)	1500	1349	5617
diffractometer	Bruker D8 Venture	Bruker D8 Venture	Bruker D8 Venture
radiation source	Incoatec IμS tube	Incoatec IμS tube	Fine focus sealed tube
θ_{min}, θ_{max}	2.33, 66.50°	2.44, 66.48°	2.20, 25.05°
index ranges	$-23 \le h \le 23$	$-21 \le h \le 21$	$-14 \le h \le 14$
	$-9 \le k \le 9$	$-9 \le k \le 9$	$-51 \le k \le 51$
	$-24 \le l \le 24$	$-23 \le l \le 22$	$-28 \le l \le 28$
reflections collected/ independent	42667/5591 (R_{int} = 0.0380)	30223/4996 (R_{int} = 0.0323)	119249/11108 (R_{int} = 0.0364)
completeness	99.9%	99.8%	99.9%
absorption correction	multi-scan	multi-scan	multi-scan
T_{max}, T_{min}	0.917, 0.548	0.934, 0.483	0.978, 0.949
refinement method	full-matrix LSQ on F^2	full-matrix LSQ on F^2	full-matrix LSQ on F^2
data/restraints/ parameters	5591/132/523	4996/51/455	11108/72/933
goodness of fit on F^2	1.033	1.032	1.099
final R indices	5166 data; $I > 2\sigma(I)$	4685 data; $I > 2\sigma(I)$	9555 data; $I > 2\sigma(I)$
	R_1 = 0.0482, wR_2 = 0.1410	R_1 = 0.0363, wR_2 = 0.0930	R_1 = 0.0484, wR_2 = 0.1047
	all data	all data	all data
	R_1 = 0.0506, $wR2$ = 0.1442	R_1 = 0.0384, $wR2$ = 0.0944	R_1 = 0.0576, wR_2 = 0.1099
extinction coefficient			0.00026(3)
$\Delta\rho_{max}$, $\Delta\rho_{min}$	0.308, −0.318 e Å^{-3}	0.284, −0.208 e Å^{-3}	0.721, −0.302 e Å^{-3}

[a]Hydrogen atoms of partial occupancy disordered water and methanol moieties not assigned.

scattering angle was set to 173° at 25 °C. The hydrodynamic diameter distributions were obtained by volume using the software package of the apparatus. Each curve represents the average of 3 measurements (16 runs each). Prior to analyses, all solutions were filtered and degassed.

Crystallization and Single-Crystal X-ray Diffraction. The phases suitable for single-crystal X-ray diffraction experiment were prepared by slow diffusion of diethyl ether to acetonitrile or acetonitrile/methanol solution containing **2** and the appropriate inorganic salt. The samples were measured at lowered temperatures on Bruker D8 Venture single-crystal diffractometer equipped with PhotonII detector. Data were collected, integrated, and scaled with the help of Bruker software,[14−16] then solved and refined in SHELX software package.[17−19] Data collection and refinement parameters for the measured samples are grouped in a suitable part of the Supporting Information together with figures displaying atomic displacement parameters and packing diagrams. These figures were prepared in Mercury 4.1 software.[20] CCDC 1988974−1988976 contain the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures. The crystal data and final structure refinement parameters are collected in Table 1.

RESULTS AND DISCUSSION

Receptor Design and Synthesis. Ion pair receptors **1** and **2** as well as monotopic anion receptor **3** (Figure 1) were

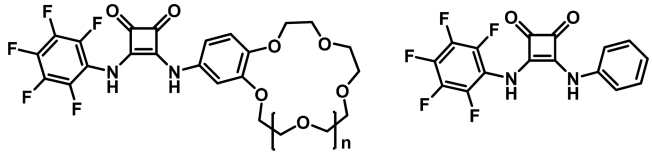


Figure 1. Structure of receptors **1**−**3**.

synthesized in a modular fashion as outlined in Scheme 1. Briefly, pentafluoroaniline and dimethyl squarate were coupled to afford monoester module. This module was reacted further with a second equivalent of amine (amino benzocrown ethers or aniline) to furnish receptors **1**−**3**.

Binding Studies. Initial evidence that receptors **1** and **2** could bind ion pairs with significantly enhanced affinity relative to the monotopic anion receptor **3** came from UV−vis spectroscopic titration experiments carried out in acetonitrile. To verify this assumption, we carried out selected titrations of receptors **1**−**3** with chloride anions (as tetrabutylammonium salt) in the presence and absence of cations (added as $NaClO_4$ or KPF_6). Indeed, while all receptors were able to bind the chloride anion with a similar stability constant (K_{TBACl} = 1.88

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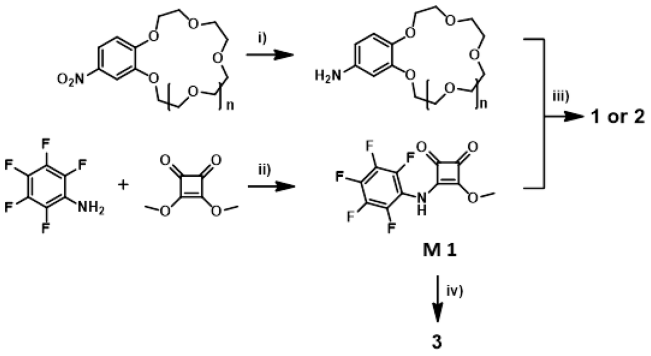
Scheme 1. Synthesis of Receptors 1−3[a]



[a]Reagents and conditions: (i) H_2, Pd/C, MeOH/THF, 12 h, room temperature, quantitative; (ii) methanol, 48 h, room temperature, 80%; (iii) methanol, 48 h, room temperature, 82 and 74% for **1** and **2**, respectively; (iv) aniline, methanol, 24 h, room temperature, 79%.

$\times 10^5$, 2.00×10^5, and 2.01×10^5 M^{-1} for interaction of chloride anions with **1**, **2** and **3**, respectively), only in the case of receptors **1** and **2** equipped with the cation binding domain was stronger binding observed in the presence of cations ($K_{NaCl} = 3.03 \times 10^5$ M^{-1} for interaction of **1**; $K_{NaCl} = 3.58 \times 10^5$ M^{-1} and $K_{KCl} = 4.92 \times 10^5$ M^{-1} for interaction of **2** with *in situ* generated salts). The same trend was observed for the other salts tested, with the exception of acetate and benzoate anions, which induce deprotonation of receptors (Table 2). The increase in stability constants correlates well with the order of increased affinity of cations to the macrocyclic cavity of esters: Receptor **2** equipped with a benzo-18-crown unit binds chloride anion more strongly in the presence of sodium cations than does receptor **1**, while the highest enhancement in ion pair binding was noted for the interaction of **2** with *in situ* generated potassium chloride. This is supported by the increased stability constants determined for complexes of receptors **1** and **2** with cations. Specifically, we found that receptor **1** binds sodium cations with stability constants of $K_{Na^+} = 1.77 \times 10^4$ M^{-1}, while receptor **2** recognized this cation more strongly with $K_{Na^+} = 3.73 \times 10^4$ M^{-1}. The highest interaction was observed for complexes of **2** with potassium cation, which produces stability constants of $K_{K^+} = 4.71 \times 10^4$ M^{-1}. However, the lack of a cation-binding domain in the structure of receptor **3** resulted in a decrease in the apparent stability constants for anions when titrations were performed in the presence of sodium or potassium cations ($K_{NaCl} = 1.65 \times 10^5$ M^{-1} and $K_{KCl} = 1.66 \times 10^5$ M^{-1} for receptor **3**).

Interestingly, the high affinity of receptors toward chlorides allowed for interaction with these salts even in the presence of 5% water in acetonitrile, conditions where sodium or potassium chloride can be directly used instead of *in situ* generated salts. In such competitive media, receptor **2** was able to interact much more strongly with sodium or potassium chloride than with tetrabutylammonium chloride ($K_{TBACl} = 1.53 \times 10^3$ M^{-1}, $K_{NaCl} = 4.33 \times 10^3$ M^{-1}, and $K_{KCl} = 5.94 \times 10^3$ M^{-1}). However, when we carried out titration experiments in acetonitrile with receptors **1**−**3** and sulfate anions, we could not fit the obtained data to the appropriate binding model, suggesting that more complex equilibria are present under experimental conditions. Thus, ^{1}H NMR titrations in CD_3CN were carried out to support the aforementioned findings. We first tested halide salts. The isotherms obtained from the titration experiments carried out with bromide salts (bromides were chosen due to expected range of values of K_a's suitable for NMR measurements) could be simply fitted to the 1:1 binding model, producing comparable apparent stability constants like those in the case of experiments under UV−vis control ($K_{TBABr} = 1.18 \times 10^4$ M^{-1} and $K_{NaBr} = 2.49 \times 10^4$ M^{-1} for receptor **1** and $K_{TBABr} = 1.15\times 10^4$ M^{-1} and $K_{KBr} = 3.43 \times 10^4$ M^{-1} for receptor **2**). In contrast, upon addition of incremental equivalents of sulfate anions into the receptor solutions, inconsistent perturbations in signals were noticed, with signals corresponding to the aromatic protons as well as to the crown ethers moving downfield or upfield, back and forth. To confirm that this was a manifestation of the formation of complexes with higher stoichiometry which should significantly affect the diffusion coefficient, we performed comparative studies using ^{1}H NMR DOSY experiments. Specifically, we compared the change in the diffusion coefficients of receptors **1**−**3** in CD_3CN after the addition of 1 equiv of bromide or sulfate anions (added as TBA salts). We found that only the addition of the latter anions causes a significant drop in diffusion coefficients, in the range of 30.3−34.3%, suggesting that a large complex is formed. In contrast, the presence of bromide anions affects the change in the diffusion coefficients of the receptors only weakly, which may evidence the formation of smaller complexes of receptors with bromides, most likely with 1:1 stoichiometry. The obtained data are in good agreement with approximate diffusion coefficients for 1:1 R × Br^- complexes (calculated according to the equation $\frac{D_1}{D_2} = \sqrt{\frac{M_2}{M_1}}$ for rod-like molecules) and 4:1 4R × SO_4^{2-} complexes (calculated according to the equation $\frac{D_1}{D_2} = \sqrt[3]{\frac{M_2}{M_1}}$ for spherical molecules)

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[a]

	1	**1** + 1 equiv of $NaClO_4$	**2**	**2** + 1 equiv of $NaClO_4$	**2** + 1 equiv of KPF_6
Cl^-	1.88×10^5	3.03×10^5	2.00×10^5	3.58×10^5	4.92×10^5
Br^-	1.25×10^4	2.52×10^4	1.21×10^4	3.96×10^4	4.05×10^4
I^-	2.13×10^3	3.35×10^3	2.51×10^3	3.02×10^3	4.67×10^3
NO_2^-	7.39×10^4	1.15×10^5	7.51×10^4	1.10×10^5	1.23×10^5
NO_3^-	1.60×10^3	2.40×10^3	1.53×10^3	2.21×10^3	2.53×10^3
HSO_4^-	6.80×10^3	7.75×10^3	7.12×10^3	7.64×10^3	8.05×10^3

[a]In the presence of 1 equiv of sodium perchlorate or potassium hexafluorophosphate UV−vis, solvent CH_3CN, temperature 293 K, [**1**] = 2.85×10^{-5} M, [**2**] = 2.63×10^{-5} M, [**3**] = 2.16×10^{-5} M, anions added as TBA salts [TBAX] ~ 1.5×10^{-3} M. Estimated errors < 10% (Supporting Information). Stability constants for receptor **3**: $K_{TBACl} = 2.01 \times 10^5$ M^{-1} for Cl^- and $K_{NaCl} = 1.65 \times 10^5$ M^{-1} for Cl^- in the presence of 1 equiv of Na^+ and $K_{KCl} = 1.66 \times 10^5$ M^{-1} for Cl^- in the presence of 1 equiv of K^+.

https://dx.doi.org/10.1021/acs.inorgchem.0c02114
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Table 3. Summarized Results of DOSY NMR Experiments for Receptors 1−3[a]

	1		2		3	
	$D \times 10^{-9}$ m^2 s^{-1}	Δ (%)	$D \times 10^{-9}$ m^2 s^{-1}	Δ (%)	$D \times 10^{-9}$ m^2 s^{-1}	Δ (%)
R	1.17		1.12		1.53	
R + 1 equiv of TBABr	1.13	2.8	1.08	3.7	1.44	6.2
calculated	1.09		1.05		1.39	
R + 1 equiv of TBA_2SO_4	0.81	30.3	0.73	32.0	1.01	34.3
calculated	0.72		0.70		0.95	

[a]In CD_3CN and for their *in situ* generated complexes with bromide and sulfate anions.

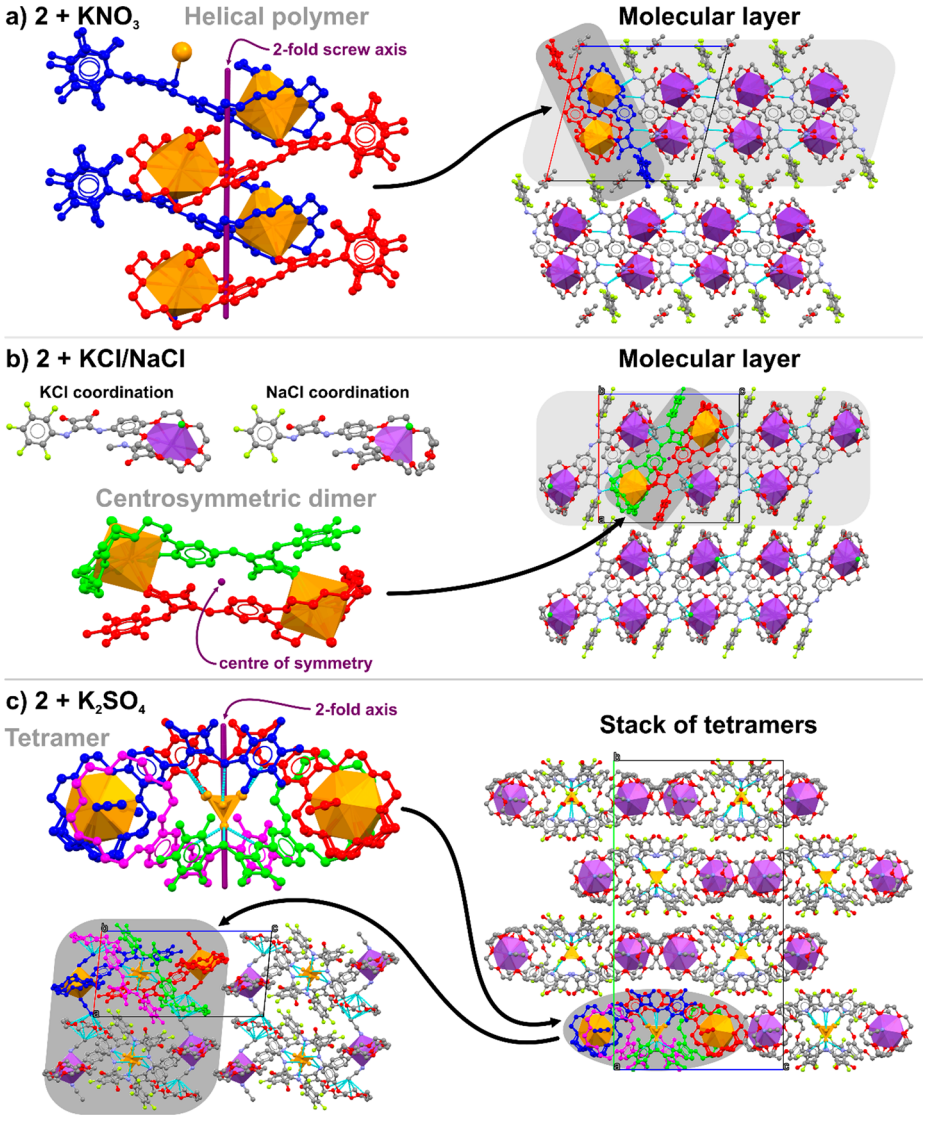

Figure 2. Molecular aggregates and their arrangements in the crystals of **2** × KNO_3 (a), **2** × KCl/NaCl (b), and **2** × K_2SO_4 (c). Hydrogen atoms are omitted for clarity.

(Table 3).[21] This confirms the presence of large complexes of squaramides with sulfate anions in solution.

Crystallization and Single-Crystal X-ray Diffraction. Our findings were further corroborated by analyses of receptor **2** complexes with ion pairs in the solid state by means of X-ray measurements. In the presence of potassium nitrate, crystals containing 1:1 ratio of inorganic salt and receptor **2** were formed. Such behavior could be expected based on the complexation experiments in the liquid phase. In the structure, the fluorinated phenyl ring of the receptor is disordered over two positions. Also, nitrate anions occupy two alternative but closely located sites. The K^+ moiety bound by the crown ether ring is coordinated from one side by the disordered nitrate anion and by the O(7) carbonyl part of the squaramide unit from the opposite side. The distances between the K^+ cation and the O atoms in the crown ether part range from 2.63 to 2.82 Å. In the case of nitrate the distances for highly occupied (93%) fragment yields 2.74 and 2.83 Å, whereas for the carbonyl group the distance is equal to 2.76 Å. Such strongly coordinated moieties form 1D helical polymers with 2-fold

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symmetry. These polymers, due to strong hydrogen bonds between NO_3^- ions and amide groups of the anion binding site (N···O distances equal to 2.68 and 2.82 Å), are grouped together forming molecular layers parallel to the (100) lattice plane. Between these layers, in channels walled by fluorinated phenyl ring, disordered diethyl ether molecules are located. Both the helical polymer of **2** with NO_3^- and molecular layers are presented in Figure 2a. Surprisingly, the formation of helical structures in the crystals of **2** and KNO_3 is similar to the case of 1:1 KCl salt complex with a squaramide-based, same-sized crown ether receptor containing a ferrocene signaling unit instead of the fluorinated phenyl moiety.[5e]

Crystallization of **2** and KCl instead of the planned complex serendipitously gave a nonstoichiometric mixed KCl/NaCl salt complex but still with a 1:1 receptor/anion ratio. As only pure reagents were used during all the steps, one of the reasonable explanations for such behavior is slow Na^+ diffusion from the glassware, especially given that the crystal growth process took quite a long time, combined with the energetically preferred formation of mixed instead of simple crystals. Because of mixed cationic composition the structure is disordered and contains 0.655(2):0.345(2) K^+/Na^+ ions ratio. Both these ions are located in the crown ether part. Because sodium is slightly too small for the 18-crown-6 unit, it is nonsymmetrically coordinated by five O ether atoms, resulting in disorder of part of the noncoordinating crown ether moiety. Both cations are additionally coordinated from two sides by a Cl^- anion and O(8) atom of the carbonyl group; thus, the pattern of the interaction is almost identical as in the **2** × KNO_3 complex. However, due to differences of the ionic radii of Na^+ and K^+ the chloride and carbonyl ligands are disordered as well. The distances to potassium ion and oxygen in the crown ether ring are in the range of 2.71−2.86 Å, whereas for sodium the corresponding distances are 2.45−2.78 Å. An understandable discrepancy is also visible for distances to the carbonyl O atom and chloride anion, which are 2.46 and 2.84 Å for sodium and 2.67 and 3.05 Å for potassium, respectively. Unlike in the case of complex **2** with KNO_3, in the structure containing **2** and KCl/NaCl, organic molecules form centrosymmetric dimers which further interact via Cl^-···H−N hydrogen bonds to develop molecular layers parallel to the (100) lattice plane. Distances between anions and amide nitrogen atoms of the squaramide moiety are in range of 3.05 −3.13 Å. Molecular diagrams presenting ion complexation, the formation of centrosymmetric dimers, and molecular layers in the structure of **2** with KCl/NaCl are given in Figure 2b. A similar centrosymmetric dimer formation can be observed for an ion pair receptor complex analogous to **2** (but containing a 15-crown-5 ether unit and 3,5-bis(trifluoromethyl)phenyl moiety) with a mixed $NaNO_3$/NaCl salt.[5f] However, in this Na^+ case due to the lack of additional coordination of the central ion by the carbonyl oxygen fragment, there is no further hydrogen-bond aggregation of the dimers into molecular layers.

However, the same receptor **2** with K_2SO_4 salt gives a structure distinctly different from the examples described above. The crystal lattice contains one sulfate anion coordinated by four receptor molecules, with every second organic molecule complexing potassium in the crown ether unit. Such a supramolecular complex is located on a 2-fold symmetry axis with the anion equally disordered over two possible orientations. The sulfate anion is coordinated by the squaramide N−H binding domains, resulting in hydrogen bond formation with N···O distances ranging from 2.66 to 3.02 Å. Sulfate complexation by **2**, giving a 1:4 ratio of anion and ionic pair receptor both in solution and in the solid state, was also observed for a similar squaramide-based system, which seems to be promising in competitive extraction of sulfates from aqueous media.[6a] The structure of **2** and K_2SO_4 contains K^+ ion complexed by the crown ether ring disordered over three alternative positions. The central cation is additionally coordinated from two sides by acetonitrile molecules. In the crystal disordered methanol, additional CH_3CN and water molecules are also present. The tetramer of receptor **2** and sulfate anion is significantly flattened with acetonitrile CH_3 groups weakly coordinated by empty crown ether moieties. Similar coordination of the acetonitrile by empty crown ethers of receptors in neighboring tetramers results in formation of stacks of tetramers parallel to the [100] direction plane. Views of the tetramer coordinating SO_4^{2-} anion and weak intermolecular interactions in the structure of **2** × K_2SO_4 are presented in Figure 2c.

Extraction Studies. Taking into account the different stoichiometry of the complexes formed with selected salts and the good solubility of salt receptors in chloroform, we conducted qualitative extraction tests to verify whether the ion pair receptors can operate under interfacial conditions and are able to extract salts from aqueous solution into organic phase. Specifically, we have treated the solution of receptors **1** and **2** in chloroform or deuterated chloroform with aqueous solution of sodium or potassium salts of Br^-, NO_3^-, Cl^-, and SO_4^{2-} and tracked the formation of complexes with salts in organic phase using UV−vis or ^1H NMR analyses (Figures 3 and 4).

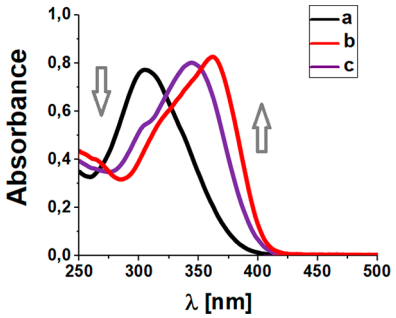

Figure 3. UV−vis spectra of receptor **2** at 3 × 10^{-5} M (a) in wet $CHCl_3$; (b) after KBr (50 mM) extraction from the aqueous phase; (c) after K_2SO_4 (50 mM) extraction from the aqueous phase.

We noticed a considerable bathochromic shift in the UV−vis spectrum after contacting a wet chloroformic solution of **2** with all aqueous solutions of potassium salts, including extremely hydrophilic sulfates, as well as for the extraction of chloroformic solution of **2** with aqueous solution of NaCl. This demonstrates that receptor **2** is able to form complexes in organic phase extracting ions from aqueous solution. Further support came from ^1H NMR measurements showing that the signals in the NMR spectrum corresponding to the squaramide protons as well to the aromatic ones were shifted downfield after the solution of **2** in wet $CDCl_3$ was contacted with aqueous solution of salts, indicating interaction with anions. Specifically, the signals corresponding to the squaramide protons, which initially resonated at 8.95 and 9.32 ppm, were shifted downfield after extraction with aqueous solution of KBr or K_2SO_4 to 9.92 and 10.33 ppm or 10.00 and 10.27

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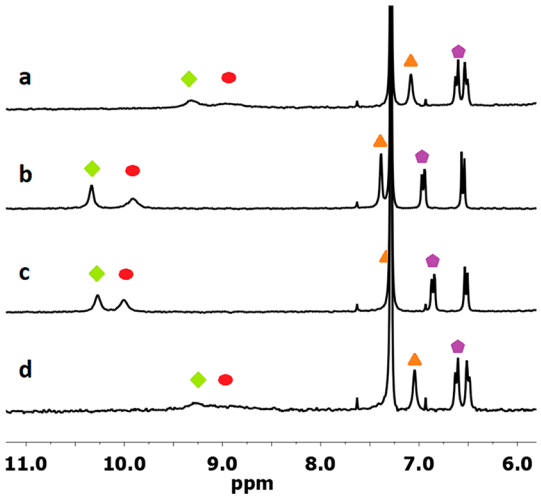

Figure 4. Partial ^{1}H NMR spectra of receptor **2** at 3 mM (a) in wet $CDCl_3$; (b) after KBr (50 mM) extraction from the aqueous phase; (c) after K_2SO_4 (50 mM) extraction from the aqueous phase; (d) after back extraction of solution to distilled water.

ppm, respectively. Less pronounced, yet observable changes (Δppm in the range 0.03−0.07 ppm) were found for signals assigned to the crown ether protons, suggesting that potassium cation also occupies the crown ether cavity. After back-extraction experiments, the signals returned to the initial position, which confirms salt release and suggests that receptor **2** may act as a suitable salt transporter. We found that receptor **1** was ineffective under interfacial conditions, and no evident spectral changes were noted after the solution of **1** in wet chloroform was treated with aqueous solutions of salts. Interestingly, anion receptor **3** is not soluble in chloroform, which implies that the presence of the cation binding domain in receptors **1** and **2** is not only responsible for the enhancement in anion biding in the presence of cations but also facilitates solubility of ion pair receptors in lipophilic media.

In order to establish the extraction efficiency, which was defined as the occupancy ratio of receptor **2** with cation, we applied atomic emission spectroscopy (AES) and quantified the potassium content in organic phase. Specifically, we carried out extractions of 0.5 M aqueous solution of selected potassium salts with 1 mM solution of **2** in chloroform. The obtained results clearly demonstrate the presence of potassium cations in the chloroformic phase after each extraction experiment. We found that increased extraction efficiency in the case of potassium halides follows decreased hydration energy of extracted anions. Specifically, after extraction of potassium chloride, bromide, and iodide the content of receptor **2** molecule occupied with potassium cation was calculated to be 51, 58, and 61%, respectively. The lowest content of potassium cation in the organic layer (extraction efficiency equal to 45%) was noted after extraction of aqueous solution of potassium sulfate with **2** in chloroform. However, taking into consideration the 4:1 stoichiometry for complexes of **2** with sulfates, where only two of four ligands are occupied by cation, the yield of extraction can be calculated at 90%.

To verify this assumption and to evidence the disparity in the stoichiometry of complexes formed in the organic layer after extraction, ^{1}H NMR DOSY analyses were applied once again. We measured the diffusion coefficients of receptor **2** in wet $CDCl_3$ and after extraction with aqueous solutions of KBr and K_2SO_4. The obtained results clearly demonstrate that large species are formed only after contacting of receptor **2** with potassium sulfate. The drop in diffusion coefficient value in this case was calculated to be ΔD = 21%, from $D = 0.53 \times 10^{-9}$ m^2 s^{-1} for **2** in wet $CDCl_3$ to $D = 0.43 \times 10^{-9}$ m^2 s^{-1} after contact with aqueous solution of K_2SO_4. In contrast, after the extraction of chloroformic solution of **2** with an aqueous solution of KBr the change was less pronounced, and the diffusion coefficient after extraction was found to be $D = 0.52 \times 10^{-9}$ m^2 s^{-1} (ΔD ca. 2%). The changes in the size of receptor **2** and supramolecular complexes formed in wet chloroform after extraction were also measured by means of DLS measurements. The value of the solvodynamic diameter was found to be d = 1.2 nm for receptor **2** in wet chloroform, and after extraction with aqueous solution of KBr or K_2SO_4, it increased to 1.4 or 2.0 nm, respectively (see the Supporting Information). This is in accordance with DOSY experiments and provides confirmation that the largest assembly is formed in organic phase after contacting with aqueous K_2SO_4 solution.

Next, we estimated the selectivity of receptor **2** under interfacial conditions, tracking the loss of particular anions in the aqueous source phase after extraction. Specifically, we carried out extraction experiments using a 5 mM aqueous solution of K_2SO_4, an aqueous binary mixture consisting of KNO_3 and K_2SO_4 (5 mM each), an aqueous mixture of more complicated potassium salts (KCl, KBr, KNO_3, KNO_2, KH_2PO_4, and K_2SO_4, 5 mM each), and a 20 mM solution of **2** in chloroform. The drop in anion concentrations in aqueous phase after extraction was monitored using the ion chromatography technique. The obtained results demonstrated the aforementioned findings that receptor **2** is able to extract potassium sulfate from aqueous into organic phase and do so even from diluted samples. Under such conditions, the sulfate concentration decrease in the aqueous phase was 45%, which assuming a 4:1 (receptor/sulfate) complex stoichiometry and 4 times higher receptor **2** concentration in chloroform than potassium sulfate in aqueous phase, corresponds to the same extraction yield. More importantly, competitive extraction experiments showed that by using receptor **2**, it is possible to overcome the Hofmeister bias and extract extremely hydrophilic sulfate salts in the presence of lipophilic nitrates: After extraction of binary mixtures of KNO_3 and K_2SO_4 with **2** in chloroform, the drop in concentration was calculated to be 12 and 44% for nitrates and for sulfates, respectively. Taking into account the stoichiometry of complexes formed (1:1 for nitrates and 4:1 for sulfates), the extraction yield was calculated to be 3 and 44% for nitrates and sulfates, respectively (see the Supporting Information). Furthermore, the selectivity and effectivity of receptor **2** toward sulfate was maintained even when the spectrum of potassium salts in the aqueous mixture was extended to nitrites, bromides, chlorides, and dihydrogen phosphates (Figure 5). This demonstrates that the main driving force for selective sulfate extraction is the formation of higher stoichiometry complexes of **2** with sulfates, rather than 1:1 complexes for other monovalent anions. This enables the formation of an inorganic−organic (sulfate-receptor) core−shell-like assembly, thereby selectively smuggling the extremely hydrophilic sulfate anion into the organic phase. However, basic anions such as acetate, benzoate, or hydrogen phosphate promote deprotonation of **2**, which causes no phase separation during the extraction experiments.

Nevertheless, the system has some disadvantages because the replacement of the potassium cation with a sodium ion in

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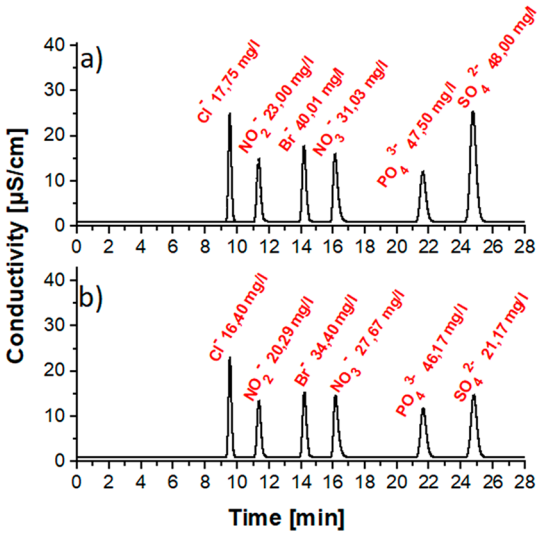

Figure 5. Chromatograms obtained during extraction experiments after 10-fold dilution: (a) source phase, (b) after extraction with 20 mM of **2** in $CHCl_3$.

extraction experiments significantly reduced the receptor's efficiency toward sulfates. When the source of sulfates was changed to sodium salt (5 mM Na_2SO_4 in water), the sulfate concentration in aqueous phase after extraction with solution of 20 mM receptor **2** in chloroform decreased only by 1%. This suggests that apart from the binding ability toward cations, the hydration energy of the cation may affect the receptor behavior under interfacial conditions. Verification of this hypothesis came from extraction experiments carried out for aqueous solution of 5 mM of sulfates added as a mixture of sodium and tetrabutylammonium salts. Specifically, in the presence of the lipophilic TBA cation, receptor **2** was able to extract sulfates from aqueous to organic phase more efficiently, and the drop in sulfate concentration was calculated to be 12%. Further enhancement in sulfate extraction was achieved when TBA_2SO_4 was used as a sulfate source (22%). In no case, however, was the efficiency achieved as for the extraction of potassium sulfate, showing the cooperation in extraction using this salt.

Transport across Membrane. Finally, taking into consideration the ability of receptor **2** not only to extract but also to release sulfate anion, we carried out transport experiments using the U-tube technique. Very recently, Jolliffe and co-workers have successfully demonstrated the ability of neutral, cyclic squaramide to transport sulfate ion across a bulk chloroform layer via an anion exchange mechanism with nitrate.[10h] However, because it uses an anion receptor as a transporter, this process and all those reported so far in the literature required the assistance of lipophilic counterion.[10] We envisioned that by using receptor **2** it would be possible to eliminate this drawback, and for the first time, transport sulfates in the form of alkali metal salts across a membrane. For comparative purposes, we investigated the U-tube transport experiments with both scenarios where the aqueous source phase contained a 50 mM solution of TBA_2SO_4 or K_2SO_4 and the bulk chloroform phase contained 5 mM receptor **2**. The sulfate concentration in the receiving phase was monitored by conductometry. We found that receptor **2** is able to transport tetrabutylammonium sulfate, and the yield of this process (defined as the ratio of sulfate concentration in the receiving layer to half the concentration in the initial source phase) after 7 days was calculated to be 22%. Unprecedently, the analogous experiment with potassium sulfate revealed the ability of neutral receptor **2** to transport sulfate in the form of an alkali metal salt across a membrane. Moreover, in this case the yield of transport was remarkably higher than that for TBA_2SO_4 transport, and after 7 days, it was found to be 38.5%. This clearly demonstrates the cooperativity in ion pair transport across membranes and enables not only the transport of K_2SO_4 by receptor **2** but also enhances sulfate anion transport with the assistance of potassium cation (Figure 6). When we

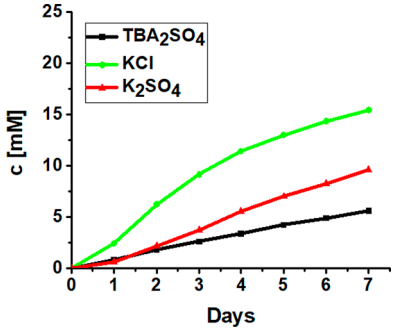

Figure 6. Sulfate transport by **2** across a bulk chloroform membrane determined by the sulfate concentration in the receiving phase. Source phase: 50 mM solution of TBA_2SO_4, K_2SO_4, or KCl in water; organic phase: 5 mM **2** in $CHCl_3$; receiving phase: water.

extended the time for the potassium sulfate transport experiment to 14 days, the yield was even higher, reaching 63%. Interestingly, receptor **2** is also an efficient chloride transporter, which also makes it an excellent candidate in the treatment of channelopathy.[22] The transport experiments with potassium chloride in the source phase proved to be an even more efficient process than in the case of K_2SO_4 transport. After 7 and 14 days, the yield of the process was calculated to be 62 and 80%, respectively (Figure 6).

Comparison of the data from extraction and transport experiments implies that the ability of receptor **2** to separate salts can be achieved in a tailored manner by using the appropriate technique. Due to the relatively stable complexes of receptor **2** with sulfates, the extraction process favors selective separation of these salts. For the same reason (stability), the transport of sulfates across the membrane, which requires the release of the ion from the complex, should be hampered, and other salts which form less stable complexes with receptor **2** should be transported more effectively. To conclusively confirm this assumption, competitive U-tube transport experiments were carried out under ion chromatography control. Indeed, when the source phase contained binary mixtures (50 mM each) of KNO_3/K_2SO_4 or KCl/K_2SO_4, the transport of chloride or nitrate salt across the membrane was more efficient than that of potassium sulfate (Figure 7C,D). However, from the point of view of nuclear waste disposal, selective sulfate extraction is necessary, preferably in a continuous process. Thus, we modified transport experiments and instead of using water as a receiving phase, aqueous solutions of specific salts were used. For the competitive KNO_3/K_2SO_4 or KCl/K_2SO_4 transport experiments, an aqueous solution of KNO_3 or KCl was used as a receiving phase, respectively. As a consequence, the transport of lipophilic salts was "frozen" by reaching equilibrium and

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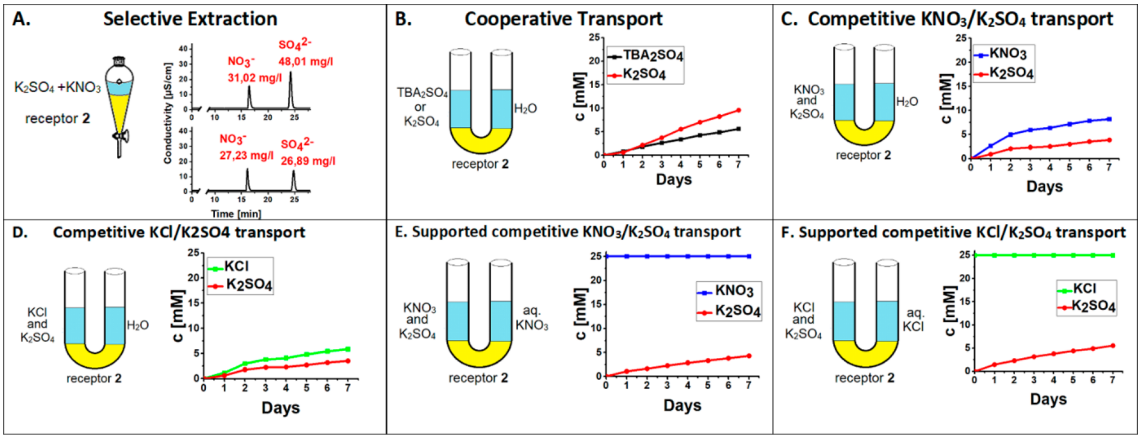

Figure 7. Schematic illustration of the ability of receptor **2** to remove specific salts from aqueous solutions by varying the separation techniques and experimental conditions. (A) Extraction experiment: top and bottom chromatograms refer to initial aqueous phase and after extraction with the solution of **2** in chloroform, respectively. (B–F) Transport experiments: the concentration of specific salts on the charts refers to the receiving phase.

facilitated the selective transport of sulfates in the presence of more lipophilic salts in a continuous process (Figure 7E,F). The capabilities of receptor **2** are schematically depicted on Figure 7, and the drop of salt concentration in the source phase by using appropriate technique is presented on Figure 8. This

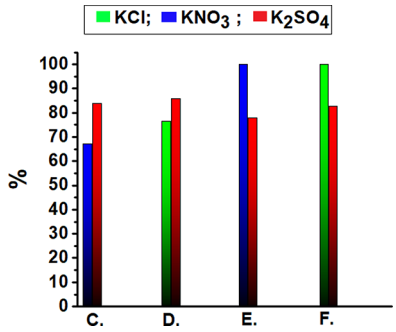

Figure 8. Drop-in salt concentration in the source phase after 7 days of transport experiments illustrated in Figure 7: C, competitive KNO_3/K_2SO_4 transport; D, competitive KCl/K_2SO_4 transport; E, supported competitive KNO_3/K_2SO_4 transport; and F, supported competitive KCl/K_2SO_4 transport.

clearly indicates the unique properties of receptor **2** and the possibility of its use for the selective transport of selected salts, even those which are extremely hydrophilic, in an adaptable manner by varying the separation technique and experimental conditions.

CONCLUSION

Squaramide-based ion pair receptors **1** and **2** and anion receptor **3**, possessing a pentafluorophenyl unit conferring lipophilicity and assuring acidity of the anion binding domain, were synthesized in modular fashion. Contrary to monotopic receptor **3**, ditopic receptors **1** and **2** were able to bind anions more strongly in the assistance of alkali metal cations. The high affinity of these receptors for ions was successfully used in salt recognition even in highly competitive aqueous media. Squaramides **1**–**3** were found to form 4:1 complexes with sulfates, rather than 1:1 complexes as with other monovalent anions. The difference in stoichiometry of the complexes was confirmed by means of UV–vis and ^{1}H NMR titration experiments, DOSY, DLS, and solid-state X-ray measurements. The formation of 4:1 complexes of receptor **2** with sulfates combined with enhancement in anion binding promoted by cation assistance facilitated the selective extraction of potassium sulfate from aqueous into organic phase, overcoming the Hofmeister bias. The ability of receptor **2** not only to uptake but also to release salts was utilized, and U-tube transport experiments were conducted. We demonstrated for the first time that neutral receptor **2** is capable of transporting sulfates in the form of alkali metal salt without the presence of a bulky counterion. Both techniques (extraction and transport) were shown to be cooperative, and potassium sulfate was extracted or transported more effectively than tetrabutylammonium salt. By changing the extraction or transport technique or the composition of the receiving phase, it was possible to alter the selectivity and switch the depletion of the aqueous layer into extremely hydrophilic or less lipophilic salts.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.inorgchem.0c02114.

General information, synthetic details, ^{1}H NMR and UV–vis titration data, extraction experimental details, DOSY and DLS measurements (PDF)

Accession Codes

CCDC 1988974–1988976 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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https://dx.doi.org/10.1021/acs.inorgchem.0c02114
Inorg. Chem. XXXX, XXX, XXX–XXX

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by Grant no. 2018/30/E/ST5/00841 from the National Science Centre, Poland.

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https://dx.doi.org/10.1021/acs.inorgchem.0c02114
Inorg. Chem. XXXX, XXX, XXX−XXX