ChemComm

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Journal:	*ChemComm*
Manuscript ID	CC-COM-01-2019-000287.R1
Article Type:	Communication

Journal Name

COMMUNICATION

Enhancing Selectivity of Cation Exchange with Anion Receptors

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

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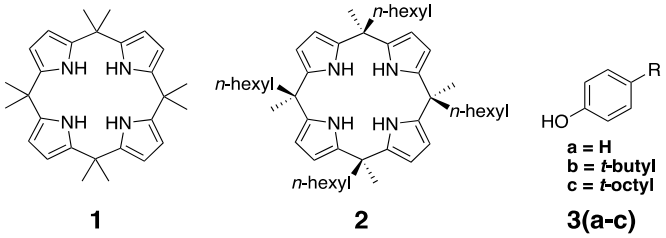
We introduce a new supramolecular strategy where an anion receptor modifies the selectivity ligands for cations. This is demonstrated by combining the classic anion receptor calix[4]pyrrole (C4P) and a phenolic ligand, which leads to remarkable enhancement in selectivity Cs^+ over Na^+. Crystal structures and molecular simulations confirmed the persistent formation of ion-pair C4P-Cs^+-phenolate complexes, while smaller Na^+ ion cannot efficiently interact.

Elucidating the intermolecular interactions that stabilize supramolecular assemblies is essential for controlling ion recognition to transcend selectivity based on classical coordination chemistry.[1] In this work, we ask the question as to whether an anion receptor can change by design the selectivity of cation exchange. If such a selectivity change is possible, it has wide-ranging ramifications for introducing a supramolecular dimension of control over the selectivity of extractive separations,[1] exploiting the wealth of knowledge available separately on the design of anion receptors[2a,b] and on the behavior of cation-exchange extractants[2c] that have hitherto helped to build the foundation of our metal-based economy.[2d]

For such a strategy, useful lipophilic organic acids that function by cation exchange based on a principle of pH swing include, for example, carboxylic acids, beta-diketones, phosphoric/phosphonic/phosphinic acids, phenols, hydroxyoximes, and sulfonic acids.[2c] By themselves, such groups possess their own native selectivity derived from the principles of classical coordination. In developing new anion receptors for selective anion separations, it occurred to us to ask whether

the rapidly developing field of anion recognition[2a,b] could be turned to the design of receptors that would bind to the anionic conjugate-base form of liquid-liquid cation exchangers in such a way as to impart a new cation selectivity. Provided that the resulting supramolecular entity is then structured so as to provide a new and hospitable coordination environment for a cation, it may be possible to bring about in a simple way cation-exchange selectivity that departs radically from the native selectivity of a cation exchanger used alone.



1 2 3(a-c)

Scheme 1. Structures of the anion receptors and cation exchange extractant used in this study. From left to right: *meso*-octamethyl-calix[4]pyrrole (**1**), α,α',α'',α'''-tetra-*n*-hexyl-calix[4]pyrrole (**2**), phenol (**3a**), 4-*t*-butylphenol (**3b**), and 4-*t*-octylphenol (**3c**).

While there are many ways to test this idea, calixpyrroles (C4P) proved expeditious in finding a first example. As we showed earlier, *meso*-octamethylcalix[4]pyrrole (**1**), can function as an ion-pair receptor in which the binding of an anion organizes the calixpyrrole into its cone conformation, opening up an electron-rich bowl that can accept a large cation such as Cs^+.[3] The α,α',α'',α'''-tetrahexyl analog **2** behaves similarly but is more organic-phase soluble and additionally provides a deep hydrophobic pocket for a narrow lipophilic anion.[3b] Because **1** in its cone conformation possesses spherical anion selectivity, the oxygen atom of a deprotonated lipophilic phenol emerges as an obvious choice of a conjugate-anion group. 4-Alkyl-substituted phenols in particular are well-known alkali metal extractants and provide the desired narrow linear structure.[4]

As a test of our hypothesis, we present the results of liquid-liquid extraction experiments that demonstrate a dramatic enhancement of Cs^+ selectivity from alkaline solution when both phenol cation exchanger **3c** and C4P **1** or **2** are present in a water-immiscible organic solvent. Based on structural analysis, we ascribe this effect to supramolecular organization of C4P with both Cs^+ cation and phenolate anion. Density functional theory (DFT)-based electronic structure calculations and *ab initio* molecular dynamics (AIMD)

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Electronic Supplementary Information (ESI) available: Experimental and computational details, including Figures S1–S4, Tables S1–S3, movies of MD trajectories, X-ray structures of Cs^+:**1**:**3b**, Cs^+:**2**:**3b**, and Cs^+:**2**:**3c**, and Cartesian coordinates and electronic energies of the complexes. . See DOI: 10.1039/x0xx00000x

simulations further support these findings, while showing poor structural organization of the binding site and low affinity for Na^+.

As shown in Figure 1, a synergistic effect is indeed observed in the extraction of cesium. Plotted is the cesium distribution ratio (D_{Cs} = $[Cs]_{org}/[Cs]_{aq}$) for C4P **1**, phenol **3a**, and their combination. Increasing alkalinity, needed for deprotonation of the weakly acidic phenol, clearly drives the extraction in the case of the synergistic system. The highest extraction is observed at 1 M NaOH, not yet arriving at the maximum that might be anticipated upon loading by Na^+ ions.[4b] A low background of cesium extraction by **1** used alone is not surprising in view of the ability of a strapped calixpyrrole to transport cesium hydroxide.[5] Phenol **3c** used alone produces a third phase at all of the NaOH concentrations tested. Simple lipophilic phenolic extractants used alone have long been associated with aggregation and third-phase behavior under alkaline conditions.[4b] Thus, one of the functions of the C4P is the solubilization of the alkali metal phenolate by the putative formation of the lipophilic supramolecular complex hypothesized above, at least in the case of the Cs^+ complex.

The continuous-variation experiment shown in Figure 2 reveals pronounced synergistic effects in combinations of phenol **3c** with either C4P **1** and **2**. Since sodium extraction into the bulk organic phase was not detected ($D_{Na} < 2 \times 10^{-6}$), the continuous-variation experiment (Fig. 2) implies a pronounced selective synergism for cesium. At the maximum in the curves, the separation factors ($SF_{Cs/Na} = D_{Cs}/D_{Na}$) are 11,200 for **1** and 95,500 for **2**. It is apparent that the deep-pocket C4P **2** effects a 10-fold greater enhancement vs the parent **1**. Both systems exhibit maxima at 0.5 mole fraction (see SI for additional plots). In a simple interpretation, a maximum at mole ratio 0.5 implies a 1:1:1 complex Cs^+:(**1** or **2**):**3**. However, given the proclivity of alkylphenols and their alkali salts to aggregate in organic solutions,[4a] a rigorous interpretation is not possible based on these limited data, and we in fact expect a more complicated situation, as discussed in the SI.

Solid-state structural analysis supports the hypothesis of cation-exchanger mediated supramolecular organization of C4P-phenolate with Cs^+. Single crystals of **1** and **2** with cesium salts of phenol (**3a**) and 4-*t*-butylphenol (**3b**) suitable for X-ray crystallography were obtained by slow evaporation of methanol and dichloromethane (1:1 v/v) solutions of receptors containing excess cesium salts. As shown in Figure 3, in both cases **1** and **2** adopted an anion-induced cone conformation, preorganizing the pyrrole rings in the bowl-shaped cavity for convergent N–H hydrogen bonding with phenoxide anions and π-donor interaction with the Cs^+ cation. One bonus feature of the ion-pair complexes with the lipophilic receptor **2** is the encapsulation of the phenolate anions within the deep hydrophobic cavity formed by the four alkyl chains located at the *meso* positions of C4P. Such interactions are likely to play a pivotal role in stabilizing the complex and enhancing the extraction efficiency of Cs^+.

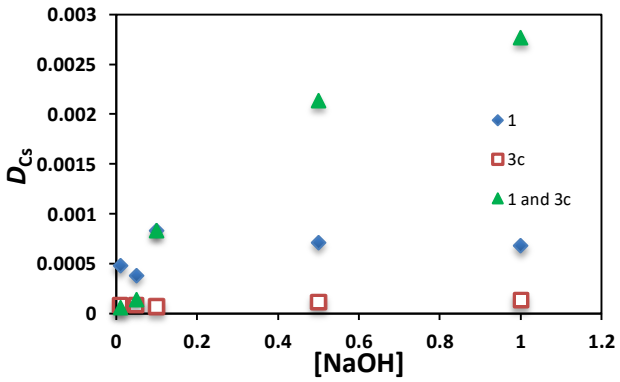

Figure 1. Effect of sodium hydroxide on extraction of cesium by C4P **2**, 4-*tert*-octylphenol **3c**, and their combination from aqueous solution to 1,2-DCE. Concentration of **1** and **3c** in 1,2-DCE are both 0.01 M. Aqueous solutions contain 0.0001 M CsOH with Cs-137 tracer and NaOH as noted.

To elucidate the structural and thermodynamic aspects of the hypothesized supramolecular organization, we conducted DFT calculations[6] on complexes with Cs^+ and Na^+ salts, including AIMD simulations for a periodic box filled with 1,2-DCE solvent molecules. The M06-2X[7] and PBE-D3[8,9] density functionals employed for molecular and periodic calculations, respectively, were validated against benchmark CCSD(T)/def2TZVPP //MP2/def2TZVPP calculations[10] for small model systems (Figure S1). PBE-D3 was further validated by providing accurate geometric parameters for Cs^+:**1**:**3c** in the solid state (Table S1).

The stabilization of ion-pairs of alkali metal ion M^+ and conjugate anion CE^- of the cation exchanger in 1,2-DCE by C4P can be expressed as the Gibbs free energy for

$$M^+(1,2\text{-DCE})_n{:}CE^- + C4P \rightarrow (1,2\text{-DCE})_n{:}C4P{:}CE^-,\ \Delta G_{r1} \qquad (1)$$

where M^+ = Na^+ or Cs^+, CE^- = p-tBu-PhO^-, and n = 0 or 2. The results given in Table 1 reveal much stronger solution-phase stabilization of ion-pair complexes with Cs^+ than with Na^+. Different treatment of solvation effects, including implicit solvation with and without optimization in the solvent reaction field, as well as explicit inclusion of two 1,2-DCE molecules (Figure S2) to complete the metal ion coordination sphere did not significantly affect the outcome of thermodynamic calculations. Since the degree of $M^+{:}CE^-$ dissociation in organic medium is expected to be larger for a more charge diffuse Cs^+ cation, we account for this effect using the following model reaction

$$Cs^+(1,2\text{-DCE})_3 + Na^+{:}CE^-(1,2\text{-DCE})_3 \rightarrow Na^+(1,2\text{-DCE})_3 + Cs^+{:}CE^-(1,2\text{-DCE})_3,\ \Delta G_{r2} \qquad (2)$$

Alternative reactions with different number of explicit solvent molecules were tested but produced similar results (Table S2). The corrected results, $\Delta G_{r1}+\Delta G_{r2}$, given in Table 1 for Cs^+ consistently show that the formation of ion-pair complexes is still much more

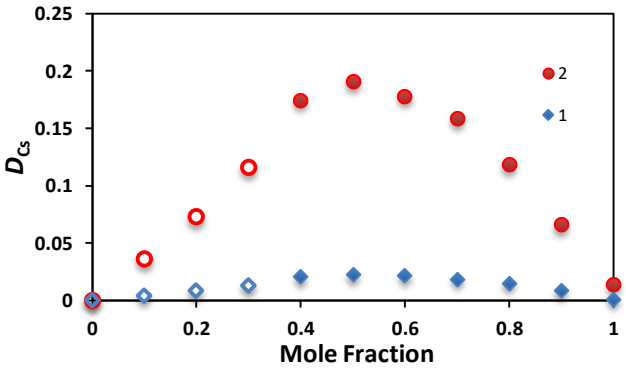

Figure 2. Continuous-variation experiments for cesium extraction from aqueous solution containing 1 M NaOH and 0.0001 M CsOH along with Cs-137 and Na-22 tracer into 1,2-DCE solutions of **3c** with **1** or **2**. The total concentration of **1** or **2** and **3** is 0.01 M. The mole fraction denoted the concentration of **1** or **2** with respect to total concentration in solution of **1** or **2** with **3**. The points that are unfilled denote the presence of a third phase in the solutions.

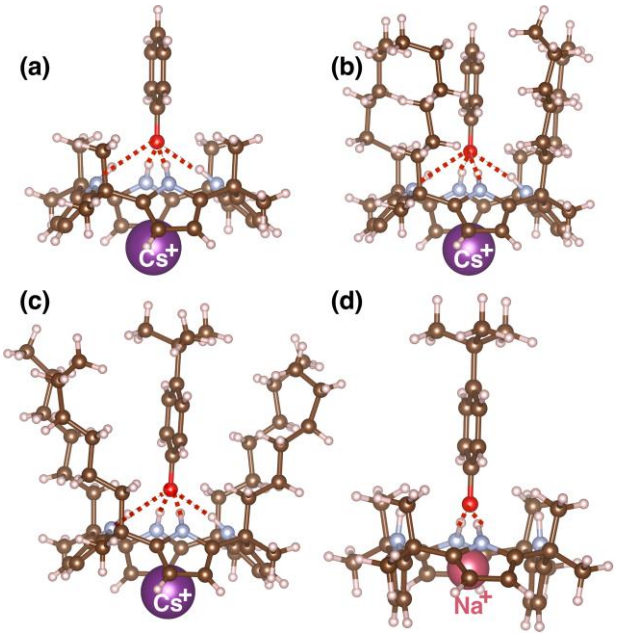

Figure 3. The X-ray crystal structures of a) Cs^+:**1**:**3a**, b) Cs^+:**2**:**3a**, and c) Cs^+:**2**:**3b**, showing a persistent formation ion-pair cesium-phenolate complexes with C4P. d) DFT-optimized structure of Na^+:**1**:**3b**, where Na^+ interacts with only two pyrrole rings, causing them to tilt and thus weaken the hydrogen bonding with the anion.

favorable with Cs^+ than with Na^+. Surprisingly weak affinity for the Na^+ salt is apparent from Figure 3d, reflecting the inability of a smaller Na^+ cation to effectively interact with all four pyrrole rings of C4P. The resulting global-minimum structure represents a compromise between stronger binding to two opposite C4P pyrrole rings and disruption of hydrogen bonding with the anion, while the symmetric complex similar to the one found for Cs^+ is significantly less stable (by 4.6–5.2 kcal/mol).

Consistent with the extraction results in Figure 2, the predicted solution-phase ion-pair complexation is stronger for the more liphophilic ligand **2** than for the unsubstituted ligand **1**. The calculations were carried out on isolated complexes taken from two crystal structures with **2** (Figure S3). In the most stable arrangement, a complex adopts a conformation with one gauche bond for each alkyl tail, giving rise to an asymmetric cleft for the lipophilic phenolate rather than a symmetric pocket, stabilized by dispersion

Table 1. Ion-pair stabilization free energies with C4P in 1,2-DCE computed for reactions 1 and 2 (kcal/mol)[a]

complex	Method I		Method II	
	ΔG_{r1}	ΔG_{r1}+ ΔG_{r2}	ΔG_{r1}	ΔG_{r1}+ ΔG_{r2}
Cs^+:**1**:**3b**	–14.6	–11.2	–12.9	–9.1
$Cs^+(DCE)_2$:**1**:**3b**	–13.4	–10.0	–11.9	–8.01
Cs^+:**2**:**3b**	–18.8	–15.4	–17.1	–13.2
$Na^+(DCE)_2$:**1**:**3b**	–7.6		–6.5	
Na^+:**1**:**3b**	–1.3		0.9	
Na^+:**2**:**3b**	–9.0		–7.8	

[a]Solvent effects were included employing single-point calculations (Method I) and geometry optimization in the SMD[11] solvent (Method II).

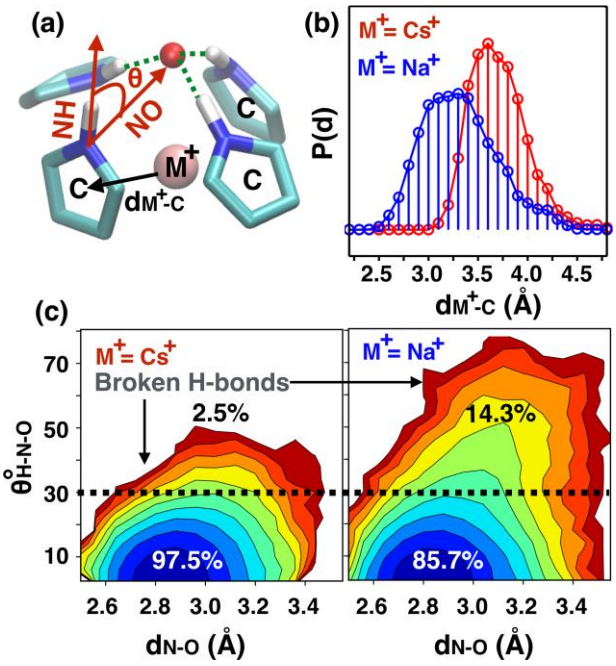

Figure 4. (a) Snapshot of the four rings (with centroid C) coordinating with the metal ion (M^+) and forming hydrogen bonds (H-bonds) with the oxygen atoms of the receptor. Here, we consider a standard definition of H-bond; it is formed when donor (N)-acceptor (O) distance (*d*) is less than 3.5Å and the H–N–O angle (θ) is less than 30°. (b) Distributions of C–M^+ distance for the Cs^+ and Na^+ cases; the broader distribution for the latter indicates greater structural disorder. (c) Such disorder is further observed on the 2D-free energy surface as a function of the H-bond parameters (*d* and θ); a significantly large fraction of the NH···O H-bonds are broken for the Na^+ case, whereas they remain mostly intact for the Cs^+ case.

and multiple CH/π hydrogen bonding interactions.[12] Decomposition of the ion-pair complexation energy into several elementary steps (Table S3) confirmed that higher binding affinity of **2** compared to **1** is 86% due to stronger interaction with the anion in the preorganized cone conformation and 14% is due to smaller energy penalty for a conformational change from the 1,3-alternate to the cone form. The latter effect is likely responsible for a slightly higher complex stability of **2** versus **1** with tributylmethylammonium chloride in chloroform.[3b]

To obtain better insights into solution structure, we analyzed 50 picosecond (ps) AIMD trajectories of **3b**:**1**:Cs^+ and **3b**:**1**:Na^+ solvated with 54 1,2-DCE molecules in canonical ensembles at 298 K (see the SI for details)[13]. While the average atomic distance in the Cs^+ coordination sphere in 1,2-DCE solvent are found to be slightly longer than those in the crystalline environment (Table S1), the complex geometry remains mostly intact, with Cs^+ 'snuggly' sitting in the C4P 'cup'. Conversely, a smaller Na^+ cation can effectively coordinate with only two or at most three pyrrole rings at a time, causing strong ring tilting and weakening or breaking hydrogen bonds with the anion. This is illustrated in Figure 4, showing greater degree of structural disorder illustrated by a broader Na^+-ring centroid distance distribution and a significant number of broken hydrogen bonds. Analysis of the structural correlations with the solvent (Figure S4) reveals that Na^+ and Cs^+ are on average additionally coordinated with two and four chlorine atoms of 1,2-DCE. This information enabled us to generate the representative structural models of ion-pair complexes with explicit solvent molecules (Figure S4) for predictive modeling of ion-pair complexation.

In conclusion, we demonstrated an as-yet unexplored strategy to manipulate cation-exchange selectivity in liquid-liquid separations via addition of an anion receptor. By binding the conjugate anion of the cation exchanger, the anion receptor thus can dramatically alter the selectivity of the cation-exchange process, which is otherwise governed by classical coordination chemistry. This supramolecular concept was structurally validated with crystal structures showing the expected role of C4P as ion-pair receptor. Extraction measurements demonstrated this effect in which a synergistic combination of C4P with an ordinary 4-alkylphenolic cation exchanger dramatically improves the extraction of Cs^+, while rejecting the extraction of Na^+. Theoretical calculations were employed to unravel structural and thermodynamic factors responsible for the shift in selectivity. This first demonstration illustrates a model combination of anion receptor that binds the anionic form of a cation exchanger, contrasting with known binary extractants[14] that are combinations of cation and anion exchangers. The generality of our concept to the large poll of known anion receptors with available liquid-liquid cation exchangers presents far-reaching and exciting new possibilities for introducing nonclassical selectivity in extractive separations.

Conflicts of interest

The authors declare no competing financial interests and no conflicts of interest.

Notes and references

‡ **Acknowledgment:** This research was supported by the U.S. Department of Energy, Office of Science, Basic Energy Sciences, Chemical Sciences, Geosciences, and Biosciences Division. This research used resources of the Oak Ridge Leadership Computing Facility and Data Environment for Science (CADES) at the Oak Ridge National Laboratory, supported by the Office of Science of the U.S. Department of Energy under contract No. DE-AC05-00OR22725.

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