

# Strategies for Using Host-Guest Chemistry in the Extractive Separations of Ionic Guests

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Host-guest chemistry has led to a new paradigm in extractive separations, generating new possibilities for efficient separations of ionic species to meet the challenging needs of industry. This account describes the approach the authors have recently undertaken, recent results, and future directions toward highly selective separations of anions based on host-guest chemistry principles. The material presented deals mainly with the genesis and discovery of new extractive systems, illustrating the potential of particular chemical concepts with examples of practical application. Major questions of interest concern the role of anions in extractive processes and factors underlying the recognition and transport of anions. Theoretical efforts explore the technique of molecular-design itself as embodied in the evolving HostDesigner program. Design calculations are capable of generating ranked candidate multifunctional ion receptors based on hydrogen-bond-donor groups having O–H and N–H donor functionalities. Efforts to synthesize candidate receptors together with studies of molecular structure and the thermodynamics of binding and transport provide a complete picture for understanding structure-function relationships and feedback for further molecular modeling. Extraction data are evaluated in a thermochemical context in which the solvent matrix, including use of anion-solvating lipophilic alcohols, plays a pivotal role. Applications are envisioned for the solution of many types of separations needs, and examples are taken mainly from the authors' own research as applied to treatment of radioactive wastes for disposal.

Keywords: *Solvent extraction, ion exchange, molecular design, host-guest chemistry, nuclear waste, anion separations*

## Introduction

Separations constitute the dominant share of investment and cost in the chemical industry and thus have enormous economic impact.<sup>1–3</sup> They are essential to our quality of life, improving the quality of air we breathe, water that we drink, and food that we eat. They make it possible to produce energy, purify pharmaceuticals, and manufacture practically every product that we buy. As civilizations have become more technologically advanced and populations have grown, demands on separations processes have become more stringent. Raw materials for mining and manufacturing have become lower in grade as reserves are depleted and the need for recycling has increased. Technological advances in computers, electronics, and pharmaceuticals increasingly require ever higher-purity materials. Environmental regulations continue to reduce allowable limits of contaminants. All of these challenges make it necessary to continually improve the efficiency of chemical separations.

This review reports one group's efforts to address such challenges from mainly a fundamental point of view, making references to resulting applications that have emerged in the area of environmental cleanup and waste treatment. In general, a separation problem may be approached from fundamental considerations of physical and chemical for-

ces,<sup>4</sup> and corresponding techniques have been catalogued.<sup>1,4</sup> Improvements needed in separations technologies may come from innovations in devices or materials or a combination of both. Chemists naturally think in terms of devising new materials, that is, new separations agents. Thus arises the legitimate question of how one goes about devising new materials in the first place. Is there a structured, generic approach that might at the same time decrease the research effort required and increase the chances of a successful outcome? One may observe that advances in the field have historically occurred largely due to a combination of individual inspiration and empirical trials, there being practically as many routes to success as there are successful investigators. However, it is our belief that more rapid innovation could be fostered by developing new tools for the design of new separations agents and refining these tools through the synthesis of identified model compounds, characterization of their properties, and comparison of the predicted and actual behavior. In this account, we describe our own concepts, recent efforts, and future directions in launching such a structured approach to developing novel materials for extractive separations of ionic species, with special emphasis on anions and their role in extractive processes. The discussion and corresponding examples will primarily reflect our own interests and results, drawing in relevant literature where credit is due. No attempt is made

to be comprehensive in coverage, however, as selected examples cited are meant only to be illustrative. Most of the potential applications are intended for cleanup of radioactive wastes and environmental media, especially those endemic to the U. S. Department of Energy (USDOE) complex, but the principles used may be applied generically to related separations, such as those in hydrometallurgy.

## New directions in solvent extraction and ion exchange

As used here, the term “extractive separation” refers to a process in which an ionic or neutral solute species distributes from an aqueous phase to an immiscible liquid phase, a solid phase, or a pseudo phase (e.g., a micelle, bilayer, or interface). Among the many separation techniques that fall under this definition, solvent extraction and ion exchange are industrial methods of choice for separations of ionic species.<sup>1</sup> High selectivity and throughput have been signature advantages of solvent extraction, whereas ion exchange has been more attractive when the targeted solute ions are dilute. Primarily developed as off-shoots of the growth of coordination chemistry in the mid 1900s, both of these techniques have matured as critical technologies in nuclear<sup>5–9</sup> and hydrometallurgical<sup>10–15</sup> separations. Increasingly difficult separations problems, however, have recently challenged these technologies. Within the USDOE, for example, such challenges include cleaning up groundwater plumes containing nanomolar levels of technetium (or perchlorate at other sites),<sup>16,17</sup> reducing the cesium concentration in nuclear waste by a factor of more than ten thousand to nanomolar levels,<sup>18,19</sup> or developing the next generation of nuclear fuel cycles that generate negligible radioactive waste.<sup>20,21</sup> It is fair to say that such needs require no less than a paradigm shift within the fields of solvent extraction and ion exchange if these techniques will be ultimately applicable at all.

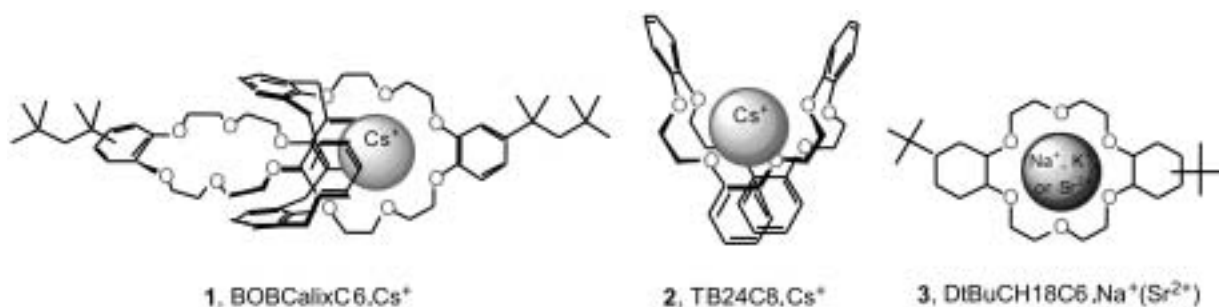
Fortunately, such a paradigm shift has indeed been well under way for at least a decade. As embodied in the field of supramolecular chemistry,<sup>22, 23</sup> the strategy of binding and extraction of ions by inclusion has re-energized progress in extractive systems. Extreme selectivity is now possible, at least in principle and as demonstrated in a limited number of practical examples, by design of molecules that possess preorganized functionalities directed to complement a target guest species. As just mentioned, the selectivity requirements of applications in radionuclide separations are often also extreme, making it difficult to turn to traditional separation agents. Understandably, significant applications of separations based on host-guest chemistry are to be found in

the nuclear industry, where high performance is required and where the peculiar economics of capital and operating investment in shielding and safety systems makes the cost of special materials such as crown ethers and calixarenes relatively affordable.

As an extension of coordination chemistry, initial developments in the supramolecular field sought understanding of how to arrange electron-donating groups in space for the recognition of cations. Crown ethers, cryptands, calixarenes, and other host compounds evolved over the course of three and a half decades,<sup>22–25</sup> resulting in solvent-extraction applications to radioactive waste treatment.<sup>19–21, 26–31</sup> Likewise, ion exchange of cations has also seen significant applications for cesium, technetium (as sodium pertechnetate), cobalt, and nickel based on host-guest principles.<sup>32–36</sup>

On a somewhat more recent timescale, investigators, including ourselves, have been asking the converse question dealing with arranging electron-accepting groups for recognition of anions.<sup>37</sup> This inquiry has initiated the development of coordination chemistry of anions and corresponding host-guest principles.<sup>22</sup> New possibilities for high-performance anion separations have therefore arisen,<sup>38</sup> with potential direct impact on problems in the USDOE complex.<sup>39,40</sup> Examples of such separation problems include separation of uranium and plutonium as nitrate anionic complexes from nitrate media, ion exchange of pertechnetate from groundwater, or removal of problem anions like pertechnetate, chromate, or sulfate from high-level waste. Although it is possible to point to some new technologies for separation of anions in this arena, specifically for pertechnetate,<sup>16,17,21,30,31,35</sup> use of anion receptors in process separations appears to be rare, if not altogether absent.

In recent years, efforts in our program have evolved from a focus on cation binding and extraction to a focus on understanding issues related to anion extraction, with regard both to the role of anions in cation extraction and to the use of anion receptors to control anion selectivity. More specifically, results have elucidated the chemical and structural principles of the binding, extraction, and transport of alkali cations as a series,<sup>41–45</sup> from lithium<sup>46</sup> at first and then up to cesium<sup>46–48</sup> and now even francium.<sup>49</sup> Cesium-selective extractants include calixcrown **1**, calix[4]arene-bis(*t*-octylbenzocrown-6) (BOBCalixC6),<sup>44</sup> and crown ether **2**, tetrabenzo-24-crown-8 (TB24C8),<sup>43</sup> shown bound to Cs<sup>+</sup> ion. Like other members of its class, calixcrown **1** extracts cesium with a selectivity factor in excess of 10<sup>4</sup> over sodium,<sup>44</sup> forming the basis of the Caustic-Side Solvent Extraction (CSSX) process,<sup>19,50–56</sup> scheduled to be implemented in a USDOE nuclear-waste treatment plant that will become



operational in 2010.<sup>57</sup> Crown ether **3**, di(*t*-butylcyclohexano)-18-crown-6, has application in the extraction of Sr<sup>2+</sup> from nuclear waste.<sup>20,21,29</sup> It also has strong affinity for K<sup>+</sup> ions and a lesser affinity for Na<sup>+</sup> ions and extracts sodium and potassium nitrate.<sup>42</sup> Our interest in questions regarding the anion in salt extraction began with the expectation that perchlorate should be extracted preferentially to nitrate,<sup>58</sup> as will be discussed later in this review. The finding that this was so,<sup>30,58</sup> led to the development and engineering demonstration of the SRTALK process for perchlorate separation from nuclear waste.<sup>31,58–61</sup> Successful resolution of anion issues were also critical in the development of the CSSX process.<sup>19,21,30,50</sup> Alcohol solvating agents (i.e., modifiers) were found to be necessary,<sup>51–53</sup> especially for the co-extracted nitrate anion,<sup>62</sup> and lipophilic anions interfered with reversibility.<sup>63</sup> In the remainder of this account, we will focus on the principles underlying such anion issues together with how one may approach the major question regarding whether one in the end may effect anion recognition by employing anion receptors in extractive processes.

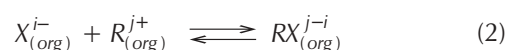
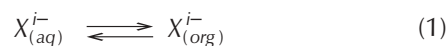
## Selectivity concepts regarding bias and recognition

The core question of separation science and technology concerns the means to achieve selectivity.<sup>4</sup> Given the increasingly challenging separations problems facing the chemical community, there in fact appears to be practically no limit to the degree of selectivity needed. Toward addressing this issue, research approaches may exploit virtually any chemical or physical phenomenon to achieve a chemical separation, where the object is to maximize differences between the affected property of the target species and those of all other matrix species. In general, selectivity arises from phenomena that induce bias or recognition.<sup>64</sup> Bias selectivity is characterized by a monotonic trend in which solute species are differentiated according to some uniformly varying property such as ion size, charge density, dipole moment, or lipophilicity parameter. One may manipulate the selectivity or steepness of a bias separation by changing the parameters of the physical phenomenon that induces the bias. As a prime example, for ion-partitioning processes in which an ion must be dehydrated and then resolvated in some new phase or pseudophase, inorganic ions are differentiated essentially according to charge density,<sup>41,64,65</sup> in view of the primarily electrostatic nature of solvation phenomena.<sup>66</sup> This bias may be quite steep and effective in ion discrimination, where the steepness of the bias may be manipulated by changing the solvating ability of the receiving phase. Such selectivity behavior characterizes a multitude of chromatographic and extractive systems, and the importance of understanding the underlying principles is indeed reflected in our recent studies on anion partitioning and recognition.<sup>67–69</sup> Although, bias selectivity has widespread use, its applicability in large-scale separations methods tends to be limited to situations where one desires to separate a species at the extremes of a trend.

To break away from the limitations of bias selectivity, it is desirable to achieve recognition, whereby the extractive material possesses a pronounced affinity for a particular target species based upon complementary binding inter-

actions (lock-and-key concept<sup>70</sup>). In such a case, one expects to see peak selectivity within a monotonic series. Well-known examples include the extraction of alkali, alkaline earth, and other metal cations by crown ethers.<sup>71–73</sup> Anion separation systems are less well developed, having been investigated more recently,<sup>37,38</sup> but some precedent now exists for escaping from simple monotonic selectivity trends.<sup>74,75</sup>

It is important to note that addition of a recognition element to a solvent-extraction system operates on top of whatever selectivity existed in its absence. If a steep bias already exists, then the recognition must be powerful if the target ion is otherwise weakly selected. (If the target ion is already selected by the strong bias of the background system, then the recognition element probably isn't needed!) Let us consider that an elementary extractive separation of an anion X<sup>i-</sup> of charge -i consists of at least two steps, an ion partitioning step (eq. 1) followed by a binding step (eq. 2). The partitioning will arbitrarily (though usefully) be written



here as taking place from an aqueous (aq) phase to an organic (org) one, and the binding will be assumed to involve the single anion receptor R<sup>j+</sup>, which for generality will be assumed to possess charge j+. As is typically the case in an extractive process, R<sup>j+</sup> resides in the organic phase, reflecting the lipophilicity built-in to prevent its loss to the aqueous phase. The issue of charge balance, as well as the effect of other interactions, will be dealt with later in this review. Together, equations 1 and 2 imply that the Gibbs energy  $\Delta C_{net}^{\circ}$  for the net extraction process is the sum of the individual Gibbs energies for the partitioning step  $\Delta C_p^{\circ}(X^{i-})$  and the organic-phase binding step  $\Delta C_{bind}^{\circ}(RX^{j-i})$ . That is, the recognition step (binding) is superimposed upon a partitioning step, the latter having its own independent selectivity that, in fact, operates according to the bias principle.<sup>64</sup> This superposition fundamentally distinguishes extraction from binding.

Based on reported standard Gibbs energies of transfer  $\Delta C_{tr}^{\circ}(X^{-})$  (approximating standard Gibbs energies of partitioning, where partitioning refers to the real situation in extraction in which the phases are mutually saturated) and ionic radii for univalent anions,<sup>64,65,76</sup> Figure 1 illustrates the importance of the bias selectivity imposed by the anion-partitioning process. The large organic anions tetraphenylborate and picrate are lipophilic, possessing negative values of  $\Delta C_p^{\circ}(X^{-})$ . Smaller inorganic anions are hydrophilic with positive values of  $\Delta C_p^{\circ}(X^{-})$ . In general, values of  $\Delta C_p^{\circ}(X^{-})$  increase essentially monotonically as ionic radius decreases, notwithstanding some minor reversals within series. The plots for three water-immiscible non-hydrogen-bond donor (non-HBD) solvents are not remarkably different, falling about a single, strongly biased trend. Alcohol solvents are much less biased and exhibit variability. The attenuated bias of alcohols follows from the ability of the alcohols to hydrogen-bond (H-bond) to anions, the strength of which increases with decreasing anion radius. The attenuation becomes more dramatic with increasing HBD ability of the alcohol, actually to the point of slightly reversing the trend with 1,1,1-trifluoroethanol (TFE). Among water-immiscible

solvents, however, such reversals are quite rare, though not unknown,<sup>77</sup> and the monotonic preference for anions of increasing size, or more generally decreasing charge-density, is ubiquitous.<sup>64</sup>

Over a hundred years ago, Hofmeister noted a relationship between the affinity of salts of a common anion for water and their ability to salt-out egg-white protein.<sup>78</sup> More hydrated anions salt-out proteins more efficiently. More hydrated anions also resist partitioning into immiscible organic solvents, which generally solvate anions more weakly than does water. That is, for small inorganic anions, the standard Gibbs energy of hydration is more negative than that of solvation in the organic phase, implying that anion partitioning is generally unfavorable. Thus,  $\Delta C_h^\circ(X^{i-}) < \Delta C_s^\circ(X^{i-})$ , and  $\Delta C_p^\circ(X^{i-}) = \Delta C_s^\circ(X^{i-}) - \Delta C_h^\circ(X^{i-}) > 0$ . Solvation and the special case of hydration of ions are electrostatically governed by their charge density,<sup>64</sup> and consequently, it happens that the difference  $\Delta C_s^\circ(X^{i-}) - \Delta C_h^\circ(X^{i-})$  increases with increasing ionic radius for a given charge type, giving rise to the trends shown in Fig. 1 (for all solvents but TFE). This trend is necessarily the reverse of what Hofmeister observed. To avoid a strict reference to the exact order that Hofmeister published, we have coined the term Hofmeister bias.<sup>68</sup> Since Hofmeister bias persists in the majority of anion separations, there has been considerable interest in finding recognition systems that can overcome it.<sup>74, 75</sup>

The trends shown in Fig. 1 clarify both the need for, and the challenge of, achieving recognition in extractive separations

of any two anions  $X^-$  and  $Y^-$ . One may appreciate that for many anion-separation problems, Hofmeister bias may be quite effective, permitting the use of inexpensive techniques, such as anion exchange with lipophilic quaternary ammonium salts or its resin analog (Type 1 anion-exchange resin) to achieve the desired result.<sup>64</sup> However, separating anions of similar thermochemical radius (e.g.,  $\text{NO}_3^-$  and  $\text{Br}^-$ , each with  $r^- = 0.196 \text{ nm}$ )<sup>64</sup> or extracting a charge-dense anion from more extractable one (e.g.,  $\text{F}^-$  from  $\text{NO}_3^-$ ) plainly cannot be achieved by exploiting Hofmeister bias. To apply recognition principles to such cases, binding selectivity must exceed partitioning selectivity.<sup>79</sup> To appreciate the magnitude of this challenge, consider the removal of  $\text{F}^-$  from  $\text{NO}_3^-$ , for example. For 1,2-DCE as the diluent,  $\Delta C_p^\circ(\text{F}^-) = 58 \text{ kJ mol}^{-1}$  and  $\Delta C_p^\circ(\text{NO}_3^-) = 34 \text{ kJ mol}^{-1}$ .<sup>80</sup> If the receptor has no affinity for  $\text{NO}_3^-$ , the binding strength ( $\Delta C_{\text{bind}}^\circ$ ) of a receptor for  $\text{F}^-$  must be more negative than  $-24 \text{ kJ mol}^{-1}$  ( $\log K_{\text{bind}} = 4.2$ ) to offset its unfavorable partitioning relative to  $\text{NO}_3^-$ . But since the receptor may be expected to bind both anions in general situations, the binding selectivity ( $\Delta \Delta C_{\text{bind}}^\circ$ ) of a receptor for  $\text{F}^-$  must be more negative than  $-24 \text{ kJ mol}^{-1}$  ( $\Delta \log K_{\text{bind}} = 4.2$ ) to offset its unfavorable partitioning relative to  $\text{NO}_3^-$ . More generally, in a competitive situation in which we desire to achieve selectivity for anion  $Y^-$  vs.  $X^-$  (both written as univalent for convenience), we require

$$\Delta C_p^\circ(Y^-) + \Delta C_{\text{bind}}^\circ(Y^-) < \Delta C_p^\circ(X^-) + \Delta C_{\text{bind}}^\circ(X^-) \quad (3)$$

or

$$\Delta \Delta C_{\text{bind}}^\circ(Y^- / X^-) < \Delta \Delta C_p^\circ(Y^- / X^-) \quad (4)$$

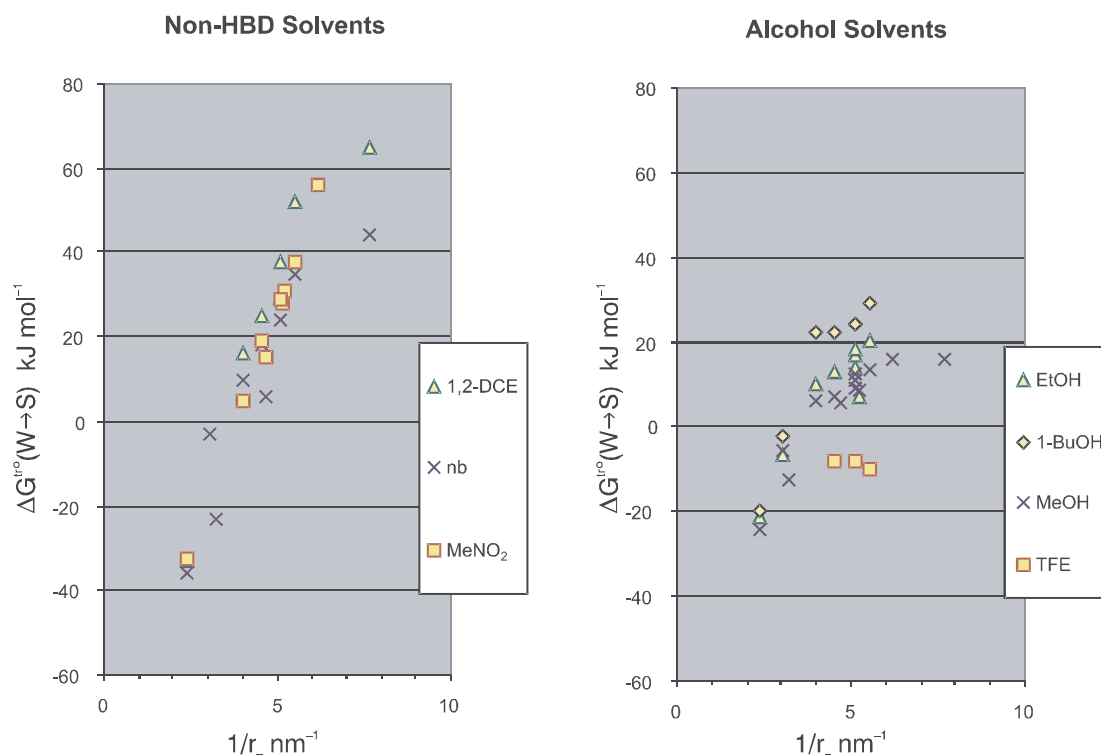


Fig. 1 – Standard Gibbs energies of transfer for univalent anions from water to organic solvents. Values are given in  $\text{kJ mol}^{-1}$  relative to the tetraphenylarsonium tetraphenylborate extrathermodynamic assumption at  $25^\circ\text{C}$ . Left: Non-hydrogen bonding donor (non-HBD) solvents. Right: Alcohol solvents. Abbreviations: 1,2-DCE, 1,2-dichloroethane; nb, nitrobenzene;  $\text{MeNO}_2$ , nitromethane; EtOH, ethanol; MeOH, methanol; BuOH, 1-butanol; TFE, 1,1,1-trifluoroethanol. In order of increasing reciprocal ionic radii, anions for which data are plotted are as follows (radii in nm in parentheses):  $\text{Ph}_4\text{B}^-$  (0.420),  $\text{Pic}^-$  (0.329),  $\text{I}_3^-$  (0.312),  $\text{ClO}_4^-$  (0.250),  $\text{F}^-$  (0.220),  $\text{SCN}^-$  (0.213),  $\text{Br}^-$  (0.196),  $\text{NO}_3^-$  (0.196),  $\text{N}_3^-$  (0.195),  $\text{CN}^-$  (0.191),  $\text{Cl}^-$  (0.181),  $\text{CH}_3\text{COO}^-$  (0.162), and  $\text{F}^-$  (0.130). Data taken from compilations.<sup>63, 64, 75</sup>

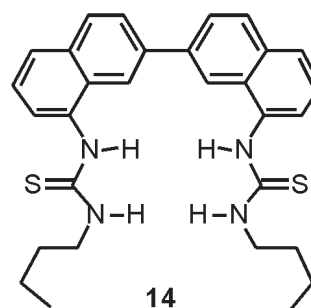
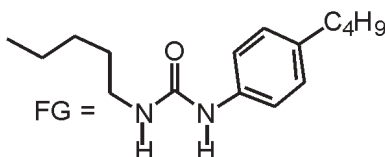
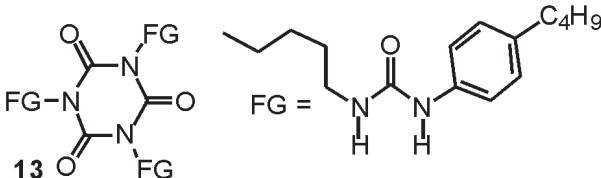
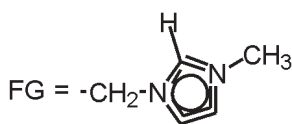
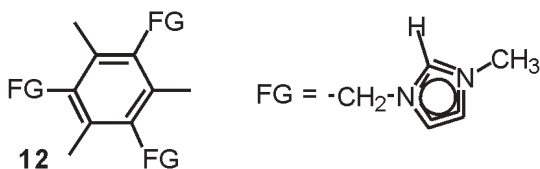
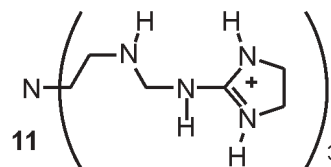
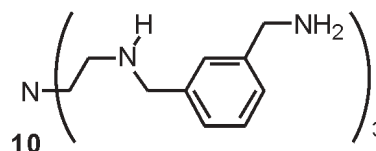
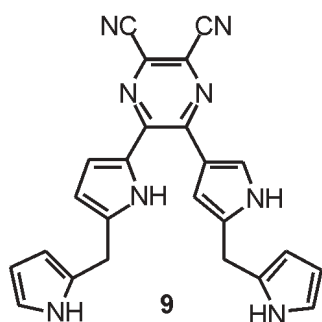
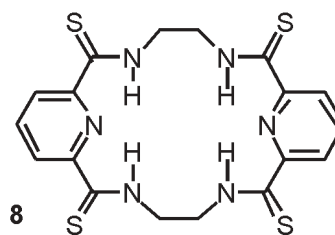
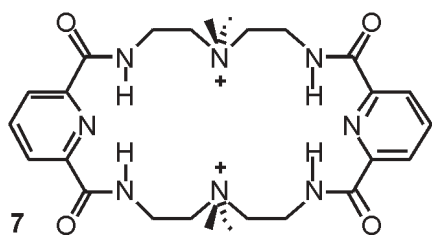
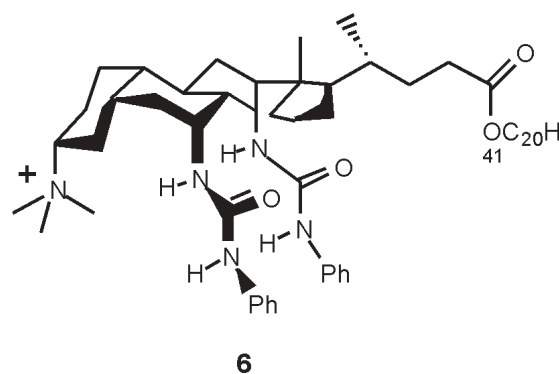
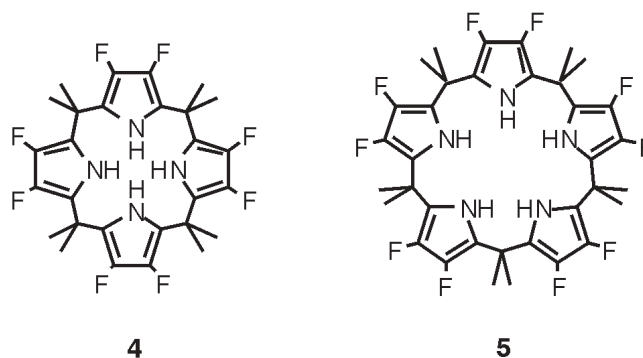
For negligible binding of  $X^-$ , the requirement is:

$$\Delta G_{\text{bind}}^{\circ}(Y^-) < \Delta \Delta G_{\text{p}}^{\circ}(Y^- / X^-) \quad (5)$$

If  $Y^-$  is understood to be the anion having the less favorable partitioning, equations 4 and 5 may be taken respectively as the fundamental requirements for binding *strength* and *selectivity* that must be simultaneously met to overcome the Hofmeister bias. Because of the steepness of the Hofmeister bias that may be encountered (viz. Fig. 1), it is plain that one must have both strong binding and very selective binding to achieve non-Hofmeister selectivity in extractive systems. We take it as our primary goal in anion-receptor design to find receptors that fulfill these two conditions.

## Design of anion receptors

Over the past decade, research directed toward the discovery of molecular receptors for anions has emerged as a key theme in the field of supramolecular chemistry.<sup>81–88</sup> Anion receptors may function as neutral electron-pair acceptors, either by Lewis acid-base interaction or by H-bonding; or they may bear a positive charge, either a permanent one, as characteristic of quaternary ammonium compounds, or a switchable one, as made possible by protonation or by oxidation of a metal center. Of greatest interest



here, one successful approach for preparing molecules that coordinate with anions has been to add HBD groups to an organic scaffold to yield charge-neutral receptors that only interact with anions through H-bonding. With a sufficient number of strong HBD groups around a guest anion, it should be possible to weaken or even reverse Hofmeister bias (*strength* criterion).<sup>64</sup> Because H-bonds are directional, it should also be possible to build hosts with shaped cavities that are capable of recognizing specific anion geometries, thereby overcoming the Hofmeister bias (*selectivity* criterion). These concepts have been demonstrated only recently. In collaboration with the Sessler group at the Univ. of Texas, Austin, we have shown that fluorinated calixpyrroles **4** and **5**, which respectively contain four or five strong HBD binding sites, do not follow the Hofmeister bias in the extraction of cesium salts from an aqueous phase into nitrobenzene.<sup>75</sup> A highly organized, singly charged cholapod receptor **6** has also been shown to perturb the Hofmeister series by transporting both bromide and iodide from an aqueous phase to chloroform more strongly than either perchlorate or hexafluorophosphate.<sup>74</sup>

Charge-neutral anion receptors are constructed by connecting two or more HBD groups with organic linkages. The choice of HBD group is based on properties such as their H-bonding strength, stability toward protonation/deprotonation, conformational rigidity, and ease of synthesis. HBD groups that recently have been used to construct anion receptors include amide<sup>89–95</sup> (e.g., **7**<sup>91</sup>), thioamide<sup>96,97</sup> (e.g., **8**<sup>96</sup>), pyrrole<sup>98–101</sup> (e.g., **9**<sup>100</sup>), amines<sup>102,103</sup> (e.g., **10**<sup>102</sup>), pyridine,<sup>104</sup> guanidinium<sup>105–108</sup> (e.g., **11**<sup>105</sup>), imidazolium **12**,<sup>109</sup> urea<sup>74,110–112</sup> (e.g., **6**<sup>74</sup> and **13**<sup>111</sup>), thiourea<sup>113,114</sup> (e.g., **14**<sup>113</sup>). These and even other HBD functionalities may be regarded as the active building blocks that one may use toward meeting the two criteria for extractive selectivity.

Deliberate host design requires knowledge of how structure impacts reactivity and the ability to distinguish a good architecture from a poor architecture. Extensive studies of host-guest chemistry have established that certain properties are needed in order to achieve more effective and more selective ion receptors.<sup>23,115–117</sup> These properties include (i) the presence of multiple binding sites,<sup>117</sup> (ii) the ability to adopt a conformation in which all binding sites are positioned to structurally complement the guest,<sup>118</sup> and (iii) a limited degree of conformational freedom.<sup>119–123</sup> It has long been recognized that increased binding affinities are obtained when the host is structurally constrained to the binding conformation, in other words, when the host is “preorganized”.<sup>124</sup>

With few exceptions,<sup>74,125,126</sup> the majority of anion-receptor development to date has remained largely Edisonian in nature, often based more on what can be readily synthesized rather than on a consideration of molecular geometry. The reason for this approach is understandable. In stark contrast to cation coordination chemistry, until recently, the coordination chemistry of anions has received sparse attention. Fundamental issues pertaining to the structural aspects of anion complexation remain to be clarified. Such issues include anion coordination number and coordination geometries, as well as the geometric features that define optimal interactions between an HBD and the anion.

Studies of H-bonding in a wide variety of systems suggest that certain structural features must be present to attain the optimal H-bonding interaction between D–H and the acceptor atom A of the anion.<sup>127,128</sup> First, for any given H-bond, there is a D–H•••A contact distance that will give the strongest interaction. This distance may show significant variation depending on the identity of the D–H, A pair, the presence of other H-bonding groups coordinated to the anion, and the influence of the surrounding medium. Second, H-bonds tend to be linear, that is, the D–H•••A angles are near 180°. Linear D–H•••A angles are expected for strong H-bonds and can be rationalized by the energetic stabilization that results from orienting the D–H dipole to point toward the acceptor atom.<sup>127</sup>

Complementary H-bonding is characterized by D–H•••A distance and D–H•••A angle alone when there is no significant directionality at the anion, as is the case with halide ions. This may not be true for anions containing two or more atoms. In a recent communication, we presented crystallographic evidence for the existence of distinct and general oxygen atom acceptor directionalities in both trigonal planar and tetrahedral oxyanions.<sup>129</sup> A survey of 2632 D–H•••O–X H-bonds in crystal structures where X is the central atom of a trigonal planar (X = C, N) or tetrahedral (X = P, S, Cl, As, Se, Cr, Mo) oxyanion, reveals that the spatial arrangement depends primarily on the geometry of the oxyanion. With the trigonal planar oxyanions the average H•••O–X angle is 115 ± 12°, and there is a clear preference for the hydrogen atom to lie within the plane of the anion. With the tetrahedral oxyanions the average H•••O–X angle is 122 ± 12°, and there is a weak preference for eclipsed H•••O–X–O dihedral angles. The observed directionality closely coincides with minima on electrostatic potential surfaces calculated for the anions. In addition, electronic structure calculations on isolated complexes corroborate the existence of the intrinsic directionality at the oxygen atom acceptors in oxyanion, yielding geometries with the same H-bonding geometries that are observed in the solid-state.<sup>130,131</sup> These observations, fully consistent with prior observations of oxygen atom acceptor directionality in weak-to-moderate H-bonds to ketones, aldehydes, ethers, epoxides, and alcohols,<sup>132–135</sup> establish that a third geometric feature must be considered in the design of receptors for oxyanions. This is the spatial arrangement of hydrogen atoms about the oxygen acceptor atoms.

Even after structural design criteria for anion receptors have been clarified, the deliberate design of host architectures by assembling sets of disconnected HBD groups in three dimensions remains a challenging task. In general, it is not readily obvious which linkage structures might be best used to connect HBD to yield a host cavity that is organized for coordination to a targeted anion. To address the problem of how to identify new host molecules that recognize and bind strongly to a guest ion, we have adopted a computational approach similar to that pioneered by the pharmaceutical industry.

Drug designers have developed methods to address the inverse of this problem, in other words, how to identify molecular structures (guests) that complement the binding site of a protein (host).<sup>136–138</sup> These approaches include *de novo* structure-based design strategies that couple molecule building algorithms with scoring functions used to prioritize

the candidate structures. The building algorithms assemble guest molecule structures that can physically interact with a known protein structure from pieces which are either atoms or larger, chemically reasonable fragments. The ability to generate large numbers of potential guest structures necessitates the use of simple scoring functions to prioritize the output. To this end, methods have been developed to estimate the binding free energy by summing free-energy increments for H-bond interactions, ionic interactions, lipophilic interactions, the number of rotatable bonds in the guest molecule, etc.<sup>139,140</sup>

The computer programs that have been developed to perform *de novo* structure-based drug design are, in general, not applicable for the design of host molecules. These programs require input of the atomic coordinates of a protein binding site, are highly specialized to address protein-organic interactions, and do not contain scoring functions to address the interactions that occur in other types of host-guest systems. To apply the powerful concepts embodied in *de novo* structure-based drug design to the design of ion receptors, we have developed a *de novo* structure-based design software, HostDesigner, that is specifically created for the discovery of host molecules for guest species.<sup>141,142</sup>

HostDesigner generates and evaluates millions of candidate structures in minutes on a desktop personal computer, and rapidly identifies three-dimensional architectures that position binding sites to provide an optimal interaction with a guest. The molecule-building algorithms combine user-input host fragments with linking fragments taken from a database. The user-input host fragments define the optimal geometry for one or more binding sites interacting with a guest. The current linking-fragment database used by HostDesigner contains over 10 000 structures composed of  $Csp^3$ ,  $Csp^2$ , and hydrogen atoms. The fragments consist of all connectivities and conformers that can be made from 0 to 6 carbons, excluding 3- and 4-membered rings. The fragments also include all dimethylated 5- and 6-membered rings and selected bicyclic structures. When using these fragments to build host molecules, all possible connectivities, stereochemistries, and conformations are constructed, which generates large numbers of structures. These structures are prioritized, based on how well the host binding sites converge at the metal ion guest. Cartesian coordinates for the top candidates are output to a file for subsequent viewing. The initial version of this software was created for use with single-atom guests.<sup>138</sup> We recently completed the next generation of this software, which has the ability to handle any guest, including multi-atom anions.<sup>139</sup>

### Categorization of separation systems employing host-guest chemistry

From a fundamental perspective, the study of host-guest chemistry in liquid-liquid systems facilitates the understanding of the origin of recognition in terms of the stoichiometry, structure, and function of discrete extraction complexes in controlled solvation environments.<sup>73</sup> We have found it useful to categorize separation systems that employ host-guest chemistry according to the eleven ways outlined in Table 1.<sup>143,144</sup> Although the categorization was devised in reference to liquid-liquid systems, analogies to solid-state

extractants can be made. The principle of charge neutrality in a separation process requires either counter-transport (exchange) of like-charged ions or co-transport of oppositely-charged ions. Hence, the eleven ways may be divided into three groups according to whether the mechanism is co-transport, cation exchange, or anion exchange. We consider that neutral hosts can facilitate salt extraction—commonly called ion-pair extraction—in five ways (Cases #1–#5; Case #1 is the null). Proton ionizable extractants or lipophilic salts with exchangeable cation may be used in three ways to extract via cation exchange (#6–#8), in which no anionic species are transferred. Likewise, lipophilic salts possessing a hydrophilic anion (#9–#11) may be used in three ways to extraction via anion exchange.

Table 1 – Eleven approaches to employ lipophilic host molecules in ion recognition and transport

Case	Name	Description
#1	No host	A polar solvent (e.g., 1-octanol) is used to solvate both cation and anion
#2	Cation host	A cation host (e.g., crown ether) binds the cation. Anion remains solvated
#3	Anion host	An anion host binds the anion. Cation remains solvated
#4	Dual hosts	Cation host and anion host are used in synergistic combination
#5	Ion-pair host	A single host binds both the cation and anion
#6	Cation exchange	A lipophilic organic acid or salt effects cation exchange. No hosts used
#7	Synergistic cation exchange	A cation host synergizes cation exchange by a lipophilic weak organic acid or salt
#8	Cation-exchange host	A proton-ionizable cation host effects recognition and cation exchange within the same molecule
#9	Anion exchange	A salt of a lipophilic cation effects anion exchange. No hosts used.
#10	Synergistic anion exchange	An anion host synergizes anion exchange by the lipophilic cation
#11	Anion-exchange host	An anion host with a positive charge effects recognition and anion exchange within the same molecule

Each of the different ways outlined in Table 1 may be represented by a series of Gibbs energy terms corresponding to individual steps in the overall extraction reaction. For example, Case #3 may be envisioned as taking place in a minimum of three steps corresponding to the partitioning of cation, partitioning of anion, and binding of the anion. In addition, one may need to include extra terms for such reactions as ion pairing or aggregation of extractant molecules. By breaking the extraction reactions down in this way, one can immediately identify those Gibbs energy terms that impact anion selectivity and whether the selectivity will be governed by Hofmeister bias or true recognition. Cases #1, #2, and #9 leave the extracted anion exposed to the solvation environment of the organic phase. These cases are thus expected to follow Hofmeister

bias,<sup>64,73</sup> as we have seen repeatedly.<sup>16,17,21,30,31,35,38,58–63,67–69,75</sup> Cases #3–5, #10, and #11 rely on anion coordination and therefore provide a means to achieve anion recognition through host design.

From a purely practical point of view, a preference for ion-pair extraction vs. cation exchange vs. anion exchange depends upon the particular separation problem being dealt with as defined by the type of starting (feed) matrix, desired product streams, constraints imposed, and processing goals. Outside the context of problem-defined criteria, any of the 11 ways given in Table 1 represent inherently useful and viable separation systems. Assuming that any of the 11 ways could meet one's processing goals and constraints, then economics would dictate that simple systems using inexpensive reagents would be preferred. Considering that synthetic hosts add cost, often considerably so, the order of preference would be systems that employ:

A) No extractant at all (Case #1). Simple water-immiscible diluents such as 1-octanol or tributylphosphate, are relatively inexpensive.

B) A simple cation exchanger (e.g., lipophilic carboxylic, sulfonic, or phosphoric acids) or anion exchanger (e.g., lipophilic quaternary ammonium salts) as commonly used in solvent-extraction practice<sup>5–15</sup> (Cases #6 and #9).

C) A single neutral host (Cases #2 and #3). Crown ethers and calixarenes are examples. Although not host compounds, simple monodentate (e.g., tributylphosphate) and bidentate (e.g., 1,10-phenanthroline) extractants might be considered primitive examples that are inexpensive yet possess some selectivity.

D) A single neutral host, such as a crown ether, mixed with an inexpensive ion exchanger (Cases #7 and #10).

E) Two neutral hosts mixed together (Case #4), the "dual-host" case, one for the cation and one for the anion.

F) Ditopic hosts that incorporate recognition and exchange capabilities (Cases #5, #8, and #11).

The above order follows the order of increasing sophistication of the host compound, presuming that cost follows this trend. Of course, extractant cost may not necessarily behave in this manner, and elegant selective hosts that are obtained via economical syntheses will ultimately find use. One should necessarily consider that, with the investment in sophisticated host compounds, one purchases high per-

formance to meet separation needs with high value (e.g., in nuclear-cleanup applications<sup>5–9,21,151</sup>). More on economics is included at the end of this article.

It is important to recognize that Table 1 represents a way to frame our thinking about how hosts can be used in a separation process. It is not meant to be a rigid or even complete classification. One must therefore exercise chemical judgment in associating an extraction system with one of the ways. Most of the time in dealing with receptors that truly function by inclusion, we find the distinctions quite approachable. However, some difficulty may be encountered in categorizing simple neutral extractants. For example, how do we treat some simple neutral extractants like tributylphosphate (TBP)? One might consider it a simple solvating agent (Case #1), certainly not a host at all. Yet it exhibits defined stoichiometry in coordination with metal cations and exhibits useful selectivity,<sup>145</sup> and thus one might consider it for some purposes a zeroth order Case #3 extractant. Likewise, carboxylic acid and dialkylphosphoric acid extractants may function as bidentate ligands in some cases. In other cases, they self-assemble around a metal cation in such a way as to resemble a host.<sup>46</sup> Are such examples to be ascribed to Case #6 or #8? Finally, one should note that exchange systems are actually derived from co-transport systems in a competitive situation, and this may cause some confusion that, again, requires chemical judgment. For example, a crown ether used to extract sodium pertechnetate from a sodium nitrate matrix may be envisioned as a simple example of Case #3. However, the crown ether is actually somewhat loaded with sodium nitrate in such systems, and it is often helpful to visualize the process as first an extraction of sodium nitrate (Case #3) followed by exchange for pertechnetate in the manner of Case #9.<sup>58–60</sup> This comparison of anion exchange is illustrated in Fig. 2.

In the following sections, we illustrate the 11 ways to use host-guest chemistry in ion separations, primarily based on our own recent results. The ways are divided according to mechanism. Emphasis is placed on anion effects, controlling Hofmeister bias, and building-in recognition for the anion. Certain sections, such as that for Case #3 employing crown ethers and calixarenes for cation separation, reflect a recent concentration of effort, though future results will see greater concentration in systems involving anion receptors. For simplicity, all chemical equilibria are written with univalent ions and with 1 : 1 binding stoichiometries, leaving it to the reader to adjust the equations appropriately for other charge types and stoichiometries.

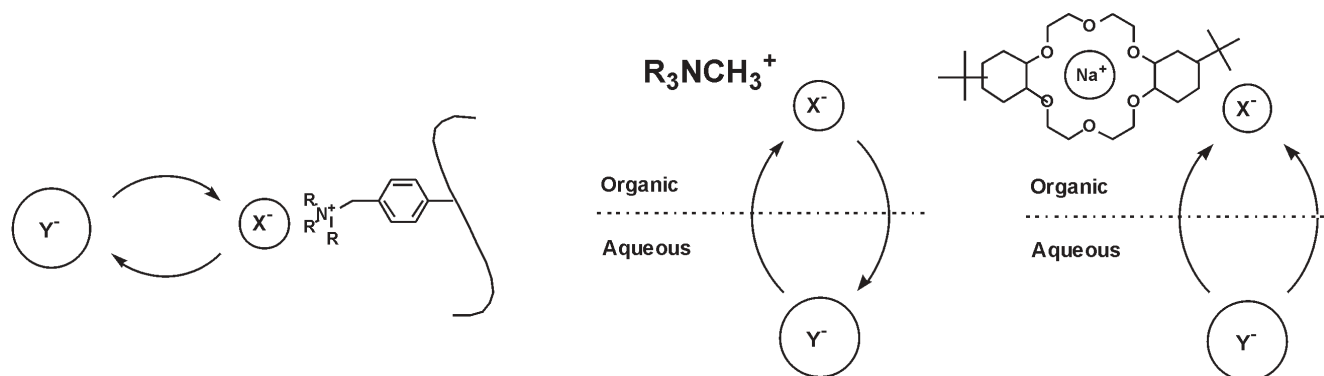


Fig. 2 – Three types of anion-exchange systems. At left is the traditional Type 1 anion-exchange resin.<sup>15</sup> In the middle is the liquid-liquid analog.<sup>64</sup> At right a complex of a crown ether with sodium ion provides an exchangeable anion.



## Extraction of salts

### General features

We have recently been attracted by the scientific challenge of direct ion-pair extraction (Cases #1–5), which in its more sophisticated forms means addressing the selectivity for both co-transported ions. Such systems offer the environmentally friendly (“green”) feature of allowing the extraction to be reversed by washing or stripping with water. Thus, in comparison with exchange systems, reversing the extraction need not necessarily consume reagents nor produce secondary waste. Generally for Cases #1–4, the Gibbs energy terms entail partitioning and, if applicable, binding of both ions. This relation is given in eq. 6, again written for convenience only with univalent ions. For Case #5, binding of the cation and anion is coupled.

$$\Delta C_{\text{ex}}^{\circ} = \Delta C_{\text{p}}^{\circ}(\text{M}^{+}) + \Delta C_{\text{bind}}^{\circ}(\text{M}^{+}) + \Delta C_{\text{p}}^{\circ}(\text{X}^{-}) + \Delta C_{\text{bind}}^{\circ}(\text{X}^{-}) \quad (6)$$

### Systems employing no hosts (Case #1)

In this primitive system, a water-immiscible diluent, perhaps with added solvating agents, is used without any host. Hence the coordination requirements of the cation and anion must be totally met by the solvent. We have reviewed such systems,<sup>41,64</sup> deriving much of our understanding from the comprehensive work of Marcus.<sup>65,66,76</sup> For extraction of small inorganic cations and anions, the solvent must supply respectively strong electron-pair-donor strength and electron-pair acceptor strength. Even with long-chain alcohols like 1-octanol, however, extraction is weak and probably not practical for most such salts.<sup>41</sup> There may be instances in which some salts with lipophilic ions may partition sufficiently strongly to be practical. For example, pure tributyl-phosphate is able to extract sodium pertechnetate from an aqueous nitrate matrix.<sup>146</sup> Even if extraction is in most cases weak, it may still be necessary for fundamental understanding of host systems to take into account the background extraction of a salt by the diluent when a host is being used. Hence, in the extraction of LiCl by nonamethyl-14-crown-4 in 1-octanol, the amount of LiCl taken up by the diluent

had to be considered to model quantitatively the extraction by the crown ether.<sup>147</sup> Likewise, in the use of receptors **1** and **2** in extracting cesium salts into nitrobenzene, the background extraction by the nitrobenzene was the reference point for comparison.<sup>75</sup>

### Systems employing cation hosts (Case #2)

In this case, a neutral cation receptor (B) is used to drive the extraction and to control cation selectivity. The seminal studies of Pedersen and Frensdorff on crown ethers as extractants<sup>148,149</sup> relied on this approach, where the binding and extraction of the cation requires co-extraction of an anion.<sup>71,73</sup> Without the presence of an anion host, solvation directs selectivity, giving rise to Hofmeister bias selectivity favoring low anion charge density.<sup>64</sup> Anions initially in aqueous solution must be dehydrated (at least partially) and are then resolvated in the solvent phase. Empirically, the HBD ability of the solvent medium is the single most important determinant of the solvation of small, inorganic anions.<sup>65</sup> For small anions, water molecules are extremely efficient solvating agents, being small, strong HBDs. Few organic solvent molecules can compete with water, and especially water-immiscible ones, as they generally do not possess as strong an HBD ability and cannot pack as efficiently around an anion. As illustrated in Fig. 1, organic solvents generally solvate common inorganic anions in organic solvents more weakly than water,<sup>64–66,76</sup> and this disparity increases as anion charge density increases, giving rise to the Hofmeister bias. Case #2 therefore suffers a thermodynamic penalty, resulting in extraction strength that is often weaker than desired.<sup>77,150</sup> At first, this penalty limited practical applications,<sup>151</sup> and it has therefore been regarded as a disadvantage of Case #2 approaches.<sup>72,152</sup> However, achieving good stripping efficiency generally requires an extraction that is not too strong, and perhaps the most successful applications of host-guest chemistry in metal-extraction processes utilize Case #2.<sup>19–21,26–31,50–61</sup>

By reference to eq. 6, where the fourth term is zero for Case #2, the two unfavorable partitioning terms may be overcome by use of a sufficiently strong cation host and

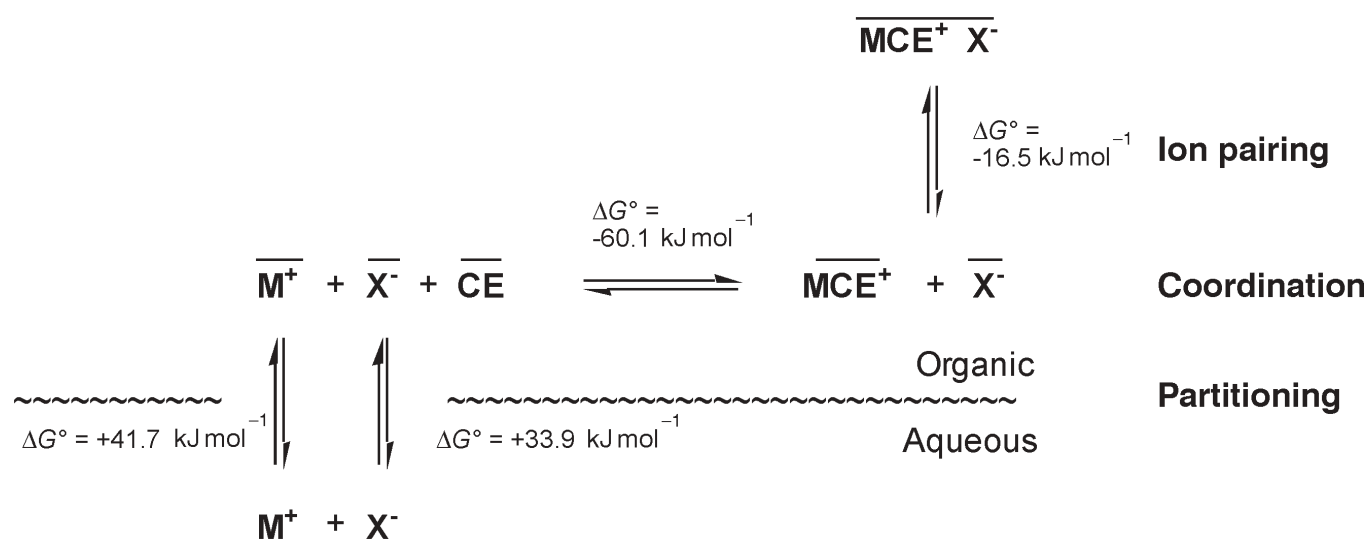
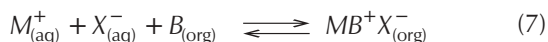


Fig. 3 – Thermochemical steps for Case #2, extraction of an alkali metal salt by a neutral host extractant. The Gibbs energy terms are evaluated for the example of CsNO<sub>3</sub> extraction by an alkylated tetrabenzo-24-crown-8 in 1,2-dichloroethane at 25 °C.<sup>47</sup>

judicious choice of solvent conditions. Fig. 3 illustrates the driving effect of the cation host, where the overall extraction is favorable as written:



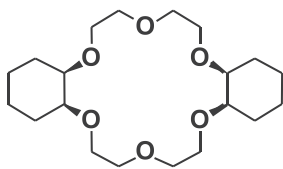
It may be seen that the overall extraction process possesses four terms:

$$\Delta C_{ex}^\circ = \Delta C_p^\circ(M^+) + \Delta C_{bind}^\circ(M^+) + \Delta C_p^\circ(X^-) + \Delta C_{ip}^\circ(MB^+X^-) \quad (8)$$

where the last term, that of ion pairing, contributes an additional boost to the net driving force. Note that for a given metal and cation host, the only terms affecting anion selectivity are the anion-partitioning term and the ion-pairing term. For a system in which ion pairing is negligible, the variation in  $\Delta C_{ex}^\circ$  depends only on the anion partitioning. We tested this expectation in a system in which the extraction was expected to conform to:



It was found that the cesium distribution ratio  $D_{Cs}$  varies linearly with  $\Delta C_p^\circ(X^-)$ , as shown in Fig. 4.<sup>68</sup> The slope of the plot with crown ether alone (no anion receptor) is  $-0.117$ , somewhat less than the theoretical slope of  $-1/(2.303RT) = -0.175$ . In a study of extraction of sodium salts by *cis-syn-cis*-dicyclohexano-18-crown-6 (**15**) in nitrobenzene, a diluent of much higher dielectric constant in which ion-pairing effects are less likely to interfere, we obtained the expected theoretical slope.<sup>144</sup> We shall return to the question of the effect of the sulfonamide anion receptors farther below.

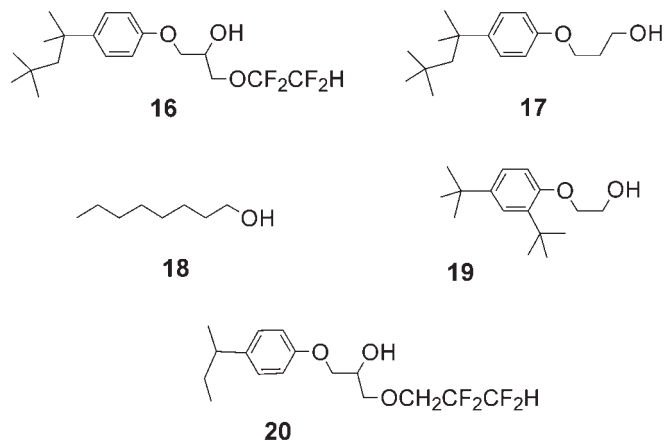


**15**

Given that conditions are found where eq. 7 is favorable, certain types of waste processing gain a considerable advantage by the ease with which the extraction is reversed to afford efficient solvent stripping. In most nuclear waste, the nitrate concentration is high, driving the extraction of, say, cesium or strontium traces, by Le Chatelier's principle. Or if it is the anion that is desired, as in the case of extraction of pertechnetate traces, it is the high sodium concentration in the waste that drives the extraction. Then it becomes possible to strip the solvent with water to recover and concentrate the extracted trace cationic or anionic contaminants with essentially no consumption of chemicals or generation of secondary waste in a complete cycle.<sup>31,54,55</sup> One should note that extremely strong extraction is undesirable in most extraction processes, in that the solvent then cannot be efficiently stripped. Successful processes generally achieve a mild, selective extraction that can be then reversed by a swing in some condition, such as nitrate or sodium concentration or pH. Thus, the fact that the typical extraction of a salt by a neutral host according to eq. (7), is only mildly favorable, is actually desirable, as opposed to being a disadvantage.

Based on the findings of Marcus,<sup>77,150</sup> we recognized that one must provide for good organic-phase solvation of the co-extracted anion by H-bonding if Case #2 is to achieve practicality for separation of  $CsNO_3$ . The value of this approach ultimately led to the successful spin-off of the CSSX process.<sup>50,51</sup> We have therefore been investigating issues of solvation and self-assembly (aggregation) involving a family of lipophilic alcohols activated by fluorination.<sup>51,62,153</sup> Understanding the role of lipophilic alcohols or "modifiers" in ion-pair extraction (Case #2) is of primary importance in the overall understanding of the behavior of an extraction system. Alcohols as modifiers can play the role of both donor and recipient of the hydrogen bonds, making a perfect scenario for aggregation of the modifier molecules with each other or with the other components of the solvent. Alcohol modifiers for hydroxyoxime extractants are a good example illustrating these behaviors.<sup>154,155</sup> Another example can be taken from our work with calixcrown **1** to extract  $CsNO_3$ . Mixing one of the different lipophilic alcohols (phenoxyalkanol, fluorinated or not), with a calixarene extractant in an aliphatic diluent provides for good solubility of the extractant and enhanced  $CsNO_3$  extraction through H-bonding.<sup>62</sup>

More recent results<sup>153</sup> show that, while the stoichiometry of complexes involved in the extraction of  $CsNO_3$  by **1** was fairly straightforward for the metal, anion, and calixarene, such was not the case for the alcohol-based modifiers. Three different alcohols, **16–18**, were investigated in depth in these studies. Two related modifiers, **19** and **20**, were included in the study for comparison purposes. Modifier concentrations below  $0.03 \text{ mol dm}^{-3}$  were not run, because of insolubility of **1**. One may see the net effect of the modifiers on extraction strength in Fig. 5. Addition of moderate concentrations of the modifiers dramatically increases extraction, and the order of modifier strength goes in the same order as expected H-bond acidity: **16** > **17** > **18**. By a mass-action analysis of extraction data including those shown in Fig. 5, it was deduced that the formation of 1 : 1 : 1 : *n* metal:anion:calixarene:modifier complex species occurs, together with aggregates of the modifier and of the modifier with the calixarene. Physical evidence confirmed the conclusion that modifiers of similar structures form aggregates, either in the solid state or liquid phase.<sup>153</sup> The crystal structure of 2,4-di-*t*-butylphenoxyethanol (**19**) revealed the formation of a cyclic hexamer. Electrospray mass



spectrometry showed the formation of modifier aggregates, modifier aggregates with nitrate, and modifier aggregates with nitrate and the calixarene. The results of vapor pressure osmometry experiments showed, that the aggregation number of these modifiers ranges from 3 to 5, usually in equilibrium with the monomer.<sup>156</sup> These results are in agreement with literature data that show unambiguously the formation of alcohol aggregates at moderate to high concentration.<sup>157–160</sup>

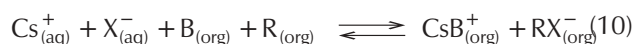
### Systems employing an anion receptor alone (Case #3)

Going a step further from H-bond donors as simple solvating agents, this case seeks non-Hofmeister anion selectivity via organizing H-bond donor groups in a single neutral anion receptor. With a strong enough anion receptor, one might actually obtain measurable salt extraction, which like Case #2, however, suffers the penalty of unfavorable partitioning of the unbound ion, this time the cation. Owing to the highly positive values of  $\Delta G_p^\circ(M^+)$  for the alkali metal cations, however, the binding strength of the anion receptors must be large indeed, and examples are rare. Using  $\text{Cs}^+$  as the alkali metal cation with the lowest value of  $\Delta G_p^\circ(M^+)$ , it was possible to demonstrate Case #3 for fluorinated calixpyrroles **4** and **5** as extractants for a range of cesium salts into nitrobenzene.<sup>75</sup> These calixpyrroles impart strong H-bonds owing to the inductive effect of their multiple fluorine atoms.<sup>161,162</sup> If these multi-point HBDs possess conformational constraints upon anion binding, some perturbation of the Hofmeister bias might be expected, as was observed. Smaller anions ( $\text{Br}^-$  and  $\text{Cl}^-$  for **1** and  $\text{NO}_3^-$  and  $\text{F}^-$  for **2**) were extracted as effectively as iodide into nitrobenzene.

### Dual-host systems (Case #4)

Much stronger extraction may be obtained through the dual-host concept, Case #4, in which the binding of the cation and anion by separate receptors compensates their unfavorable partitioning.<sup>68,163–167</sup> In addition to stronger extraction, the mix-and-match feature of Case #4 offers great flexibility in choice of receptors and in separate control of cation and anion selectivity. Thus, this case may be useful for situations where there is a desire to obtain a very specific salt from a mixture of electrolytes or where the enhanced extraction strength is needed to overcome an otherwise limited driving force.

As shown in Fig. 4, the addition of a sulfonamide H-bond donors to the calixcrown receptor **21** enhances  $\text{Cs}^+$  extraction into 1,2-dichloroethane.<sup>68</sup> Enhancement with the simple monosulfonamide **24** was weak, while the two potentially bidentate disulfonamides **22** and **23** yielded significantly stronger extraction, as one might expect. The sulfonamides used alone gave negligible extraction, and thus, the enhancement is said to be synergistic. That is, the two extractants acting together yield a stronger extraction than sum of the two extractants acting independently. For this to be true, there must exist a new reaction involving the two extractants. In this work, we deliberately chose conditions to favor dual 1 : 1 and 1 : 1 ion-binding stoichiometries, written as:



The 1 : 1 binding of cesium had been previously established.<sup>48</sup> NMR titrations of receptor solutions with tetrabutylammonium salts in dry 1,2-dichloroethane showed predominant 1 : 1 binding of the anions, plus a weak 1 : 2

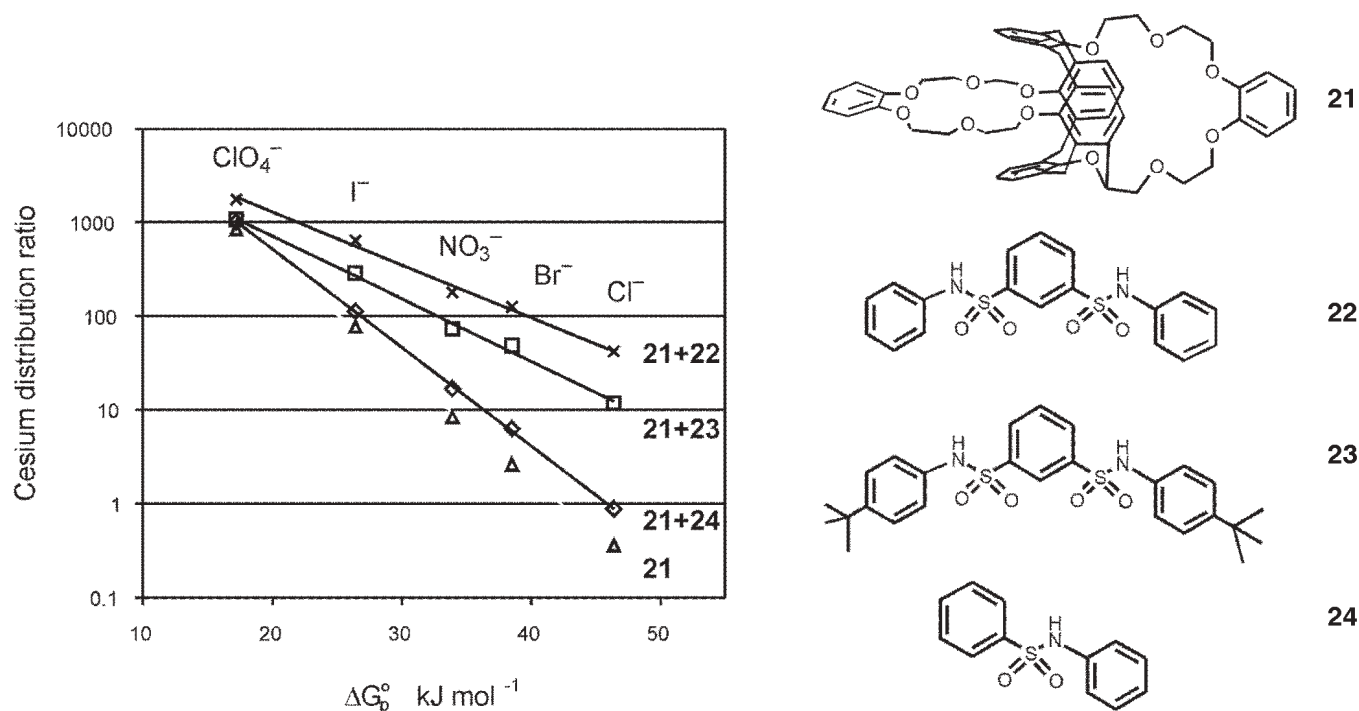


Fig. 4 – Effect of sulfonamide anion receptors on extraction of cesium salts by calixcrown **21** in 1,2-dichloroethane. In the experiment, equal volumes of the two phases were equilibrated at 25 °C, where the initial concentrations were as follows:  $[\text{CsX}]_{\text{aq}} = 5 \times 10^{-6} \text{ mol dm}^{-3}$ ,  $[\text{NaX}]_{\text{aq}} = 0.10 \text{ mol dm}^{-3}$ ,  $[\mathbf{21}]_{\text{org}} = 0.010 \text{ mol dm}^{-3}$ , and  $[\text{anion receptor}]_{\text{org}} = 0.035 \text{ mol dm}^{-3}$ . Data taken from ref. 68.

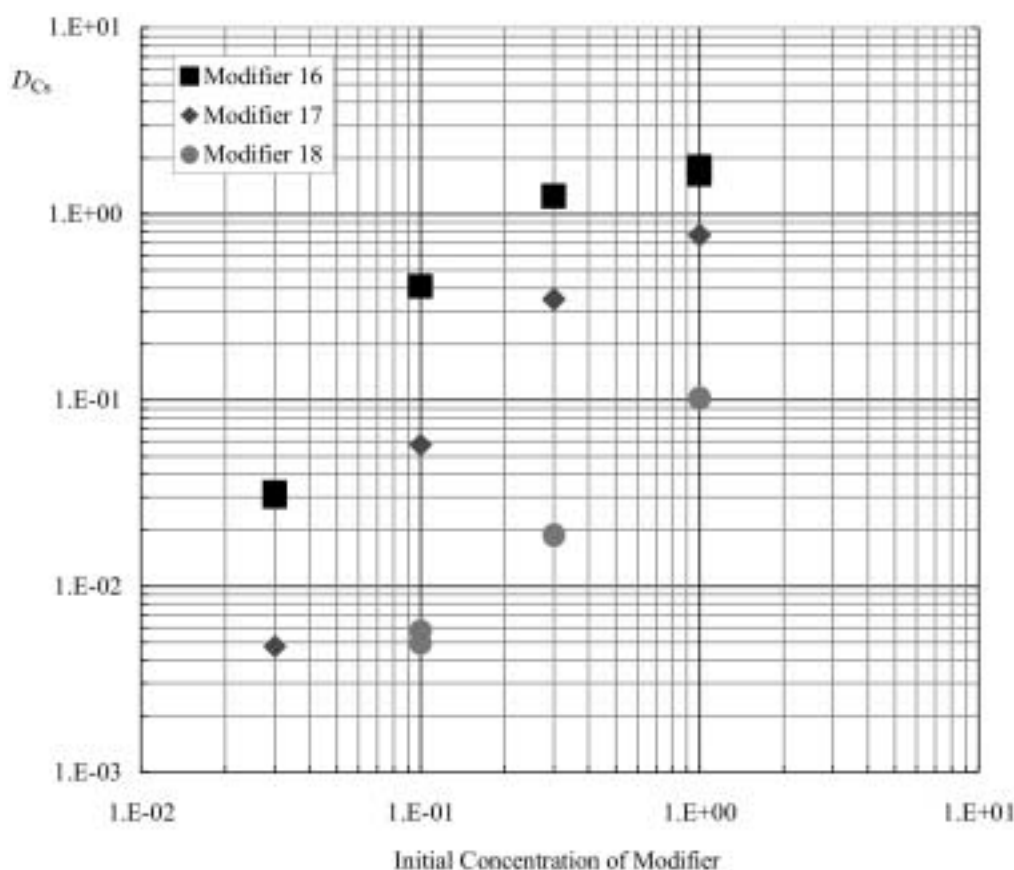


Fig. 5 – Effect of alcohol modifiers on  $CsNO_3$  extraction by BOBCalixC6 (**1**) in *n*-dodecane. In the experiment, equal volumes of the two phases were equilibrated at 25 °C, where the initial concentrations were as follows:  $[CsNO_3]_{aq} = 0.005 \text{ mol dm}^{-3}$ ,  $[NaNO_3]_{aq} = 0.10 \text{ mol dm}^{-3}$ , and  $[I]_{org} = 0.010 \text{ mol dm}^{-3}$ . Data taken from ref. 153.

anion-host interaction.<sup>68</sup> It was expected that the low organic-phase concentrations would disfavor ion pairing.

Equation 6 quantifies the enhanced extraction (vs Case #3) in terms of the added Gibbs energy term for anion binding. In principle, the synergistic enhancement upon adding an anion receptor to a given cation receptor may therefore be predicted from the anion-binding constant obtained under suitably analogous conditions. Based on 1 : 1 binding of the extracted ions according to eq. 10, an equation has been derived for conversion of the corresponding homogeneous anion-binding constants  $D_{cpX}$  to synergistic factors (SF) under the assumption that the anion host effects negligible extraction by itself.<sup>168</sup> Other key assumptions included low loading of the two hosts and negligible ion pairing. The relationship is:

$$\frac{D_{Cs \text{ syn}}^2}{D_{Cs \text{ B}}^2} = \quad (11)$$

$$\left( \frac{[Cs]_{(init)R=0}}{[Cs]_{(init)}} \right) \left( \frac{[NO_3^-]_{(aq)}}{[NO_3^-]_{(aq)R=0}} \right) \left( \frac{[B]}{[B]_{R=0}} \right) \left( \frac{\Phi D_{Cs \text{ syn}} + 1}{\Phi R=0 D_{Cs \text{ R=0}} + 1} \right) (1 + D_{cpX} [R]_{(org.)})$$

Here, the synergistic factor is given as  $SF = D_{Cs \text{ syn}} / D_{Cs \text{ B}}$ , the ratio of  $D_{Cs}$  obtained under synergistic conditions vs  $D_{Cs}$  obtained for the calixcrown alone. The variable  $\Phi$  is the organic-to-aqueous phase volume ratio. The absence of anion receptor is indicated by subscript "R = 0", and the

subscripts "init", "aq", and "org" refer to initial, aqueous, and organic.

A comparison of predicted and experimental synergistic factors SF for the experiment with calixcrown and sulfonamides given in Fig. 4 shows partial agreement (Table 2). It may be seen that adequate agreement was obtained for values of SF up to 33. High values of SF shown in the shaded area of the table are severely underpredicted. The reason for this disagreement is not understood, but we note that the NMR titration data were collected under conditions significantly different from the extraction conditions. In the NMR experiment, for example, the solvents are comparatively dry, and the receptors were titrated to saturation, conditions in which ion pairing and changing activity coefficients could play a significant role. Needless to say, we are seeking additional tests of eq. 11 under more ideal conditions.

Interestingly, the sulfonamide receptors did nothing to perturb the Hofmeister bias except to attenuate it.<sup>68</sup> Rather they acted more like HBD solvating agents than anion receptors, which tends to agree with structural results that show that the disulfonamides are not preorganized.<sup>169</sup> To reverse the Hofmeister bias, the thermochemical analysis (see above) requires that the anion binding more than compensates for the unfavorable anion partitioning, and to escape completely from any Hofmeister bias, highly com-

Table 2 – Comparison of experimental and predicted synergistic enhancements in dual-host extraction of cesium salts by calix-crown host **21** and sulfonamide receptors **22–24**\*

Anion X <sup>-</sup>	Synergistic factors		
	<b>22</b> + <b>21</b>	<b>23</b> + <b>21</b>	<b>24</b> + <b>21</b>
OAc <sup>-</sup> prediction	26.1	21.8	3.9
experiment	618	132.3	3.1
Cl <sup>-</sup> prediction	41.9	33.7	5.2
experiment	118	33.1	2.5
Br <sup>-</sup> prediction	19.3	17.7	2.5
experiment	47.3	18.4	2.4
NO <sub>3</sub> <sup>-</sup> prediction	12.4	8.0	1.7
experiment	21.3	8.6	2.0
I <sup>-</sup> prediction	7.1	5.0	1.3
experiment	8.3	3.7	1.5
ClO <sub>4</sub> <sup>-</sup> prediction	2.0	1.6	1.0
experiment	2.1	1.3	1.2

\* Extraction conditions are the same as given in Fig. 4. Predicted enhancement factors (see text) were obtained from eq. 11 using NMR binding constants obtained by titrating the sulfonamides with tetrabutyl ammonium salts in 1,2-dichloroethane-*d*<sub>4</sub> at 22 °C. Data taken from ref. 68.

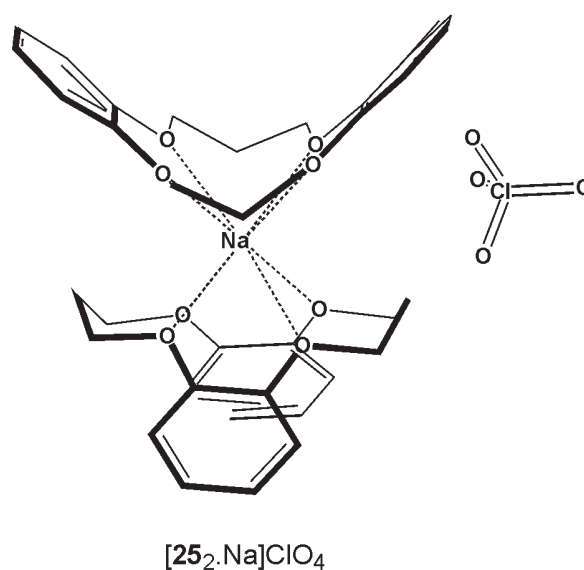
plementary and net strong interactions with selected anions must take place. We have therefore begun an investigation of calixpyrroles, noting that the fluorinated analogs do perturb the Hofmeister bias when used alone (Case #3).<sup>75</sup> Experiments with dual-host systems are in progress.

### Ditopic salt receptors (Case #5)

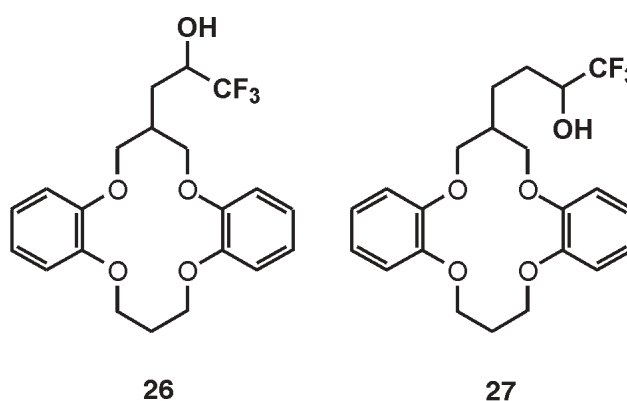
The more sophisticated Case #5 combines cation and anion binding into a single ditopic ion-pair receptor, a theme that has been gaining increasing attention.<sup>170,171</sup> Ditopic salt-receptor design strategies utilize Lewis Acid sites (non-H bonding)<sup>172</sup> or H-bond donor functionalities<sup>173</sup> like amido groups for anion binding. Despite the elegance of this approach, the question remains as to whether the synthetic investment yields significantly enhanced properties that cannot be gained via the mix-and-match dual-host paradigm, Case #4. One synthetically easy approach has been to append H-bond donor sites to the periphery of a cation receptor so as to form a ligand-separated ion-pair, as in the substitution of a thiourea group on the benzo group of a benzo-15-crown-5 ether.<sup>174</sup> However, when the cooperativity of the two binding sites is limited, the dual-host approach is preferable. Indeed, a direct comparison of salt transport by a ditopic salt receptor prepared by the substitution of thiourea groups onto the ends of the propoxy tails of dipropoxycalix[4]arene-crown-6 and its dual-host analog showed faster transport with the latter.<sup>164</sup> On the other hand, cooperativity via inductive effects<sup>171</sup> or by allosteric effects<sup>175</sup> enhances the ditopic approach. Smith maximizes cooperativity in macrobicyclic salt receptors by enforcing contact ion pairing in the complex.<sup>176–178</sup> In his designs, the binding site is electronically and sterically complementary for given ion pairs, and true salt selectivity appears to be demonstrated. Although such progress has been promising, especially in Smith's systems, the question of whether the ditopic case (Case #4) confers a compelling advantage vs.

Case #5 remains an open one generally, and more research is needed.

Another way to achieve cooperativity in a salt-binding receptor may be to self-assemble potential anion-binding HBD units. We have initiated such an approach using ditopic cation-anion host molecules whereby the cation serves to assemble the scaffold from which the HBD for anion interaction elements are attached. It has been found from structural studies and consistent extraction results (Case #2) that dibenzo-14-crown-4 (**25**) forms a sandwich complex with sodium ions under certain conditions.<sup>179,180</sup> The formation of this bimolecular sandwich (with the crowns rotated 90° to each other) forces the accompanying anion to reside outside of the complex.<sup>180,181</sup>



It was hypothesized that if a fluoro-alcohol lariat arm is attached to the center carbon of one of the propyl ether linkages of the crown, upon self-assembly of the sandwich, the two lariat arms (one from each crown) might be oriented in a manner so that the hydroxyl groups could interact with the anion. Thus, the salt receptor functioning as Case #5 might exhibit a true salt selectivity unobtainable via a dual-host (Case #4) strategy. Two such DB14C4 ethers with fluoro-alcohol lariat arms, –CH<sub>2</sub>CH(CF<sub>3</sub>)–OH (**26**) and –CH<sub>2</sub>CH<sub>2</sub>CH(CF<sub>3</sub>)–OH (**27**), have been prepared, and these are now being evaluated in extraction experiments.<sup>182</sup>



## Cation exchange systems

### Simple cation exchange

#### (Pseudo hydroxide extraction, Case #6)

Simple cation exchange is a major area of solvent extraction covered in standard texts on solvent extraction and ion exchange.<sup>10,11,15,145,183,184</sup> Its only application to anion separation is for the specific case of hydroxide. Focusing on univalent ions and neglecting aggregation, cation exchange as driven by neutralization of the released hydrogen ion by hydroxide may be written most simply as:

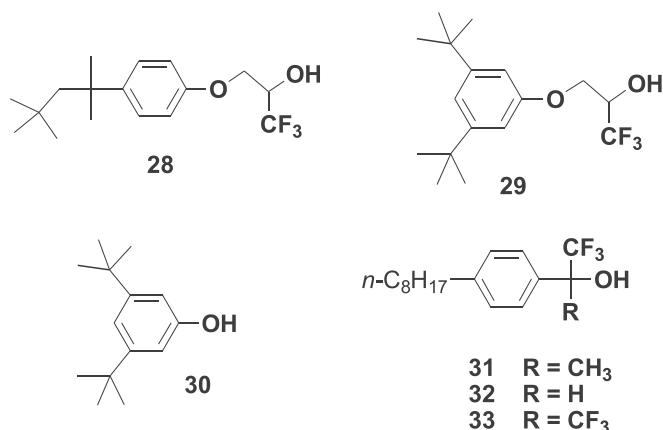


The reverse reaction affords recovery of sodium hydroxide upon stripping with water, whereby the alcohol returns to its protonated form in the organic phase. When used in tandem, the forward and reverse steps constitute a cyclic process affording the transfer of alkali metal hydroxide from an aqueous mixture into water. Because only hydroxide equivalents rather than actual hydroxide ions are transferred, this approach has been termed pseudo hydroxide extraction (PHE, Case #6).<sup>143,185</sup> Surprisingly, a single study involving phenols represents the only citation of such a process in the literature prior to our work.<sup>186,187</sup>

PHE has been found to be a highly promising approach to NaOH separation from alkaline salt solutions.<sup>41, 143, 185–190</sup> Not only has the principle been shown to be sound, but the reagents may be very economical for process use. A series of lipophilic phenols and fluorinated alcohols, typified by **28–33**, has been tested<sup>143,185,188,189</sup> in the well-studied water-immiscible alcohol 1-octanol, chosen to provide a suitable solvation environment<sup>41</sup> for organic-phase sodium salts. The fluorine substituents inductively increase the acidity of the –OH groups, and depending on the type and location of the fluorines relative to the hydroxy group, the acidity is tunable. Most of the tested proton-ionizable compounds significantly enhanced the extraction of sodium from aqueous NaOH over that which is extracted by 1-octanol alone. The extraction qualitatively increases with the acidity of the extractants. In contrast, little or no enhancement of sodium extraction from aqueous NaNO<sub>3</sub> solution by the same compounds has been observed, an encouraging demonstration of the specificity of the tested compounds toward hydroxide. This specificity was successfully challenged in complex simulants of radioactive waste, from which it may be useful to recycle the recovered NaOH. It was further established that the extracted sodium is quantitatively recoverable as NaOH by stripping the loaded solvent with water. Results have been found to be quantitatively consistent with a predominant mechanism given by eq. 12 with minor background NaOH extraction by 1-octanol.<sup>190</sup> Regarding the practicality of fluorinated alcohols vs. phenols, increased cost for the former are offset by their increased stability to oxidation. Whereas one may seek lower costs in phenols, certain applications may require greater robustness, whence the fluorinated alcohols may be preferred.

### Synergistic cation exchange (Synergistic PHE, Case #7)

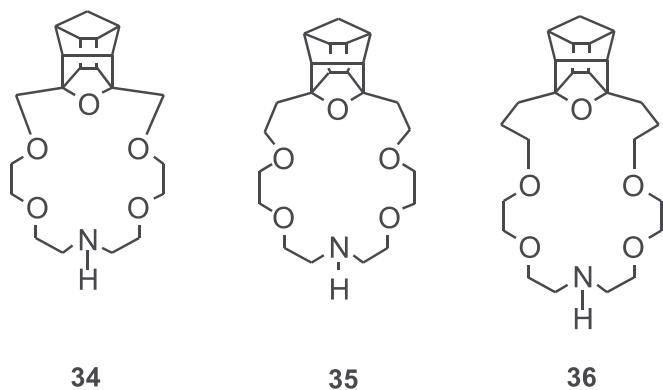
Synergistic combinations of cation hosts and cation exchangers were introduced<sup>191</sup> based on the desire to move away from the anion limitations of ion-pair extraction sys-



tems targeting metal cations. A recent review describes the variety of systems that have since been characterized and the depth of understanding that has emerged.<sup>192</sup> Very early papers from our own research applied crown ethers as synergists to cation-exchangers such as lipophilic sulfonic acids, dialkylphosphoric acids, and carboxylic acids (Case #7), wherein cation exchange obviated the co-extraction of an anion with the cation.<sup>72,193</sup> Because of the great variety of combinations of hosts and cation exchangers that may be tested and studied quickly, this type of system has obvious utility for the design of cation-selective extraction systems for many purposes, such as the separation of radio-cesium<sup>194</sup> or alkaline earth metals.<sup>195</sup> The hydrogen-ion transfer that accompanies cation extraction implies that one effects extraction-stripping cycles by pH swing, stripping at a lower pH than extraction.

Despite the appeal of synergistic cation exchange, these systems present two disadvantages. First, attempts to understand the equilibria in such systems have revealed complicated behavior that entails aggregation of the cation exchanger and formation of competing complexes between the cation exchanger and the crown ether.<sup>196–198</sup> This problem makes fundamental study more difficult. It also means that one cannot readily predict the outcome of mixing a given crown ether and a given cation exchanger. In fact, the competing interaction of the two extractants can actually depress extraction, a phenomenon referred to as antagonism. Second, the desired synergistic effect must be strong enough to overcome the background additive selectivity imposed by the two types of extractants acting independently. Cation exchange in particular often exhibits a strong size bias. Sulfonic acid extractants are exceptional, as their relative nonselectivity for metal cations of a given charge type make them ideal for this application.<sup>193,197,198</sup>

By extension of the PHE concept for sodium hydroxide separation, we have by contrast suggested the use of very weak acids like **25–30** for synergized cation exchange, so that the exchange would occur only at very high alkalinity.<sup>69,144</sup> Such systems would selectively respond to hydroxide anion and allow control of the cation selectivity as well. The expected synergism was demonstrated with crown ether **15**<sup>69</sup> and the novel lipophilic cage-annulated crown ethers **34–36** in nitrobenzene.<sup>144</sup> It was found that the strength of the effect increased with increasing acidity of the organic acid that was used with the cation host. As in PHE, regeneration of the solvent may be accomplished by contact with water, releasing sodium hydroxide.<sup>144</sup>



It is instructive to note the contrasting role that the acidic hydroxy compound may have in combination with a neutral cation host. In the first case discussed (Case #2), the acidic compounds (e.g., **16–20**) are designed to function by H-bond donation to the anion to boost the extractability of the salt by the host. In this function, the alcohol may be considered a solvating agent. We have seen that the effect increases with acidity of the alcohols tested.<sup>62,144</sup> By contrast, if the acidity of the alcohol is increased sufficiently, the cation-exchange mechanism may be accessed at high alkalinity, giving synergized cation exchange (Case #7). Thus, the mechanism of extraction may be controlled by the acidity of the alcohol or by manipulation of the aqueous pH.

#### Cation-exchange host (Case #8)

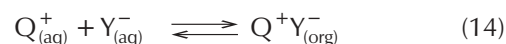
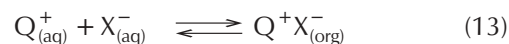
Proton-ionizable cation hosts have been intensively studied since the early 1980s as the next level of sophistication over synergistic combinations of neutral hosts and cation exchangers.<sup>199</sup> This strategy again avoids a dependence on the anion and allows control by pH change. Where this approach differs from the less sophisticated, though easy, synergized cation exchange, lies in the potential for cooperativity between the recognition and cation-exchange functions. To the degree that it may be achieved, this forced cooperativity potentially means better selectivity, because one at the same time enhances the synergy exclusively for the target ion while sterically hindering the abilities of the individual functionalities to act independently in extracting other ions. Among the many examples that may be cited are those of *Bartsch*, who has pioneered this concept with a great many proton-ionizable lariat ethers each possessing an ionizable sidearm appended to a carbon pivot atom on a crown ether.<sup>200–202</sup> The intended forced cooperativity was demonstrated when quaternary carbon pivot atoms were employed in which the extra substituent on the carbon pivot was a bulky alkyl group that serves to preorganize the proton-ionizable group relative to the crown cavity. More recently, *Bartsch* has reported cesium-selective calixcrowns bearing an ionizable group on one of the calixarene aromatic groups.<sup>203</sup> *Bradshaw and co-workers* at Brigham Young University have developed many proton-ionizable crowns by appending the ionizable groups to aza pivot atoms.<sup>204</sup> *Gloe and co-workers* demonstrated effective alkaline earth metal extraction by crown ethers bearing intra-annular carboxylic acid groups.<sup>205,206</sup>

In our own work in collaboration with *A. P. Marchand*, the approach has been to attach very weakly proton-ionizable

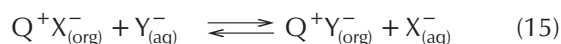
groups to the aza pivot atom of lipophilic cage-annulated azacrown ethers like **34–36**.<sup>207</sup> First-generation molecules with long ionizable sidearms exhibit behavior much like that of independent crown ether and fluorinated alcohol molecules. Such predictable results point to second-generation designs that possess forced cooperativity through strategies such as intra-annular ionizable groups or use of quaternary carbon pivot atoms bearing a bulky alkyl group.

#### Anion-exchange systems

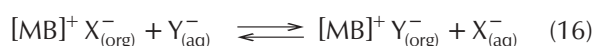
The area of anion exchange offers some exciting possibilities for expression of anion recognition. The baseline case of simple anion exchange (Case #9) has been reviewed.<sup>64</sup> In classical systems, bulky cations such as alkyl quaternary ammoniums are employed. If the quaternary ammonium cation is small (e.g., tetramethyl), the salts of small inorganic anions are water soluble with minor partitioning to the organic phase. As the alkyl groups become larger, the partitioning of these salts increases until finally the salt is for practical purposes completely distributed to the solvent phase, where it may then function as an anion exchanger. One may therefore view anion exchange as a case of competitive simple ion-pair extraction (Case #1). Consider the competitive extraction of salts  $Q^+X^-$  and  $Q^+Y^-$ :



The net reaction is exchange (Case #9):



Thus, it makes sense to refer to anion exchange rather than ion-pair extraction when the cation  $Q^+$  is highly lipophilic. The cation can, of course, be a complex as noted earlier (see Fig. 2), where the net reaction relates to competitive Case #2 with cation host B:



It follows that the anion selectivity of such systems as represented by eqs. 15 and 16 should exhibit Hofmeister bias, which is well known to be the case.<sup>64</sup>

An advantage of categorizing host-guest extraction chemistry as in Table 1 is that it allows one to see additional possibilities. Accordingly, anion extraction via an anion-exchange approach has also emerged as possible via Cases #10 and #11. If an anion receptor is combined with a quaternary ammonium extractant, one derives from competitive Case #3 synergized anion exchange (Case #10):



Case #11 involves a positively charged anion host, whose stoichiometry then would follow eq. 15. Other charge types may be involved, of course, and the applicable equilibria may be obtained easily by analogy to the above equations.

Although simple anion exchange is a standard technique, a glance at the literature reveals that anion-exchange extraction systems involving recognition are not common. Case #10 in fact appears to have no precedent in terms of ex-

traction, though there do seem to be a number of examples of combinations of anion receptors with lipophilic quaternary ammonium salts in the liquid membranes of potentiometric anion sensors.<sup>208, 209</sup> The presence of the quaternary ammonium salt is necessary for proper function of the sensors and is thought to ensure response to anions vs. cations, charge balance for the anion-receptor complex in the membrane phase or interface, and reduced electrical resistance. It would appear likely that the role of the quaternary ammonium salt in these systems would involve reactions such as eq. 17. Like Cases #4 and Cases #7, synergized anion exchange (Case #10) offers the attraction of mixing and matching two extractants. Another advantage of Case #10 arises in that it is a truly competitive technique, as it pits the initial anion of the receptor against the aqueous one being exchanged for it. We have begun investigating this case and are continuing this line of investigation, especially in regards to understanding the speciation and selectivity as fundamentally related to binding of the individual anions by the receptor.

Case #11 has some literature precedent in, for example, bisguanidinium extractants.<sup>210</sup> The cholopod anion-exchange receptor **6** was recently shown to extract anions according to non-Hofmeister bias.<sup>74</sup> Quite a few guanidinium and quaternary ammonium receptors are known,<sup>37</sup> but most studies limit themselves to binding in homogeneous solution rather than extraction.

## Design of solid-phase anion exchangers

Solid-phase separation materials offer the means to study and control selectivity at binding sites fixed in space.<sup>211</sup> It may be considered that liquid- and solid-phase extraction materials share common design elements in that, that both entail questions of positioning and connecting individual binding groups.

Anion recognition, binding, and separation in the solid state are far less understood, in comparison with the equivalent processes in solution. While polymeric resins have long been utilized for the separation of anions, the fundamental understanding of the principles governing the binding of anions with these materials is still limited, due, in part, to their amorphous nature, which precludes detailed structural characterization. The chemical separation of anions using ion-exchange resins is based on the electrostatic interaction between the anion and the quaternary ammonium groups grafted on the polymeric resin. Although, the anion selectivity can be modulated to some extent by changing the organic substituents on the quaternary ammonium centers, the separation process involves little or no recognition, and is essentially governed by Hofmeister bias.<sup>64</sup> The introduction of HBD groups (i.e. hydroxyethyl) in these anion-exchange resins has been shown to lead to selectivity reversals as a result of stronger H-bonding to the more basic anions, which can be considered a crude form of molecular recognition. Inorganic anion exchangers<sup>212</sup> such as layered double hydroxides<sup>213,214</sup> have been developed as an alternative to the organic resins. While they have the advantage of crystallinity and chemical and thermal inertness, it has been more difficult to achieve the structural diversity, kinetics, and reversibility characteristic of organic materials,

making thus the incorporation of desired functionalities for chemical recognition problematic.

It appears therefore desirable to combine the properties of inorganic networks, such as crystallinity and chemical and thermal stability, with the versatility and functionality of organic structures for the rational design of anion exchangers. Recently, the syntheses of mesoporous organic-inorganic hybrid materials with anion exchange abilities have been reported.<sup>215–217</sup> These materials are typically synthesized by the hydrolytic polycondensation of silica or organosilica precursors, in the presence of surfactant templates. The anion-exchange capability comes from the incorporation of ammonium groups in the inorganic frames by either grafting or co-condensation with appropriate quaternary ammonium precursors. Alternatively, cationic aluminophosphate or titanium phosphate mesoporous networks have been synthesized in the presence of anionic surfactants, which could be subsequently exchanged with various anions.<sup>211,218,219</sup> However, these empirical approaches, based on the systematic variation of reactants, stoichiometry, reaction conditions, and templates, offer limited predictability and control over the 3D architecture of these materials, particularly the arrangement of the organic functionalities. Another impediment for a more rational approach to the synthesis of these materials is their poor crystallinity, which prevents their detailed structural characterization.

Another class of materials that has recently found applications in anion exchange is metal-organic frameworks (also called coordination polymers). These crystalline solids have become a major area of research,<sup>220–230</sup> starting with the pioneering work of *Robson* and *Hoskins* in the early 1990s.<sup>231</sup> This approach, based on the self-assembly of transition metal cations (nodes) with various organic ligands (spacers) with multiple, divergent coordinating groups, gives easy access to a wide variety of crystalline materials with topologies that may be controlled to a great extent by the coordination geometry and symmetry of the selected transition metal and organic ligand. These coordination polymers are typically synthesized by slow evaporation of a solution containing the transition metal salt and the organic ligand, layering of separate metal salt and ligand solutions, or hydrothermal synthesis. The resulting materials are often obtained in single-crystalline form and are usually insoluble in water or organic solvents. An attractive feature present in many of these materials is their porosity, conferred by the large cavities or channels contained in their frameworks. These channels are mostly occupied by the solvent used for crystallization, which, in favorable cases, can be removed with the retention of framework crystallinity and porosity. This behavior earned these materials the name of “organic zeolites”, and indeed, it has been demonstrated that some of them can supersede traditional zeolites in porosity and inclusion and exchange abilities.<sup>232</sup> The advantage over the inorganic zeolites is that the pore size and functionality can be systematically and predictably adjusted by simply modifying the organic ligand.<sup>233</sup>

When neutral ligands are used, the resulting metal-organic frameworks are cationic, with the counteranions either coordinating the metal, or occupying random positions in the network. Fig. 6 shows a few examples of such metal-organic frameworks assembled from the 4,4'-bypyridine ligand and



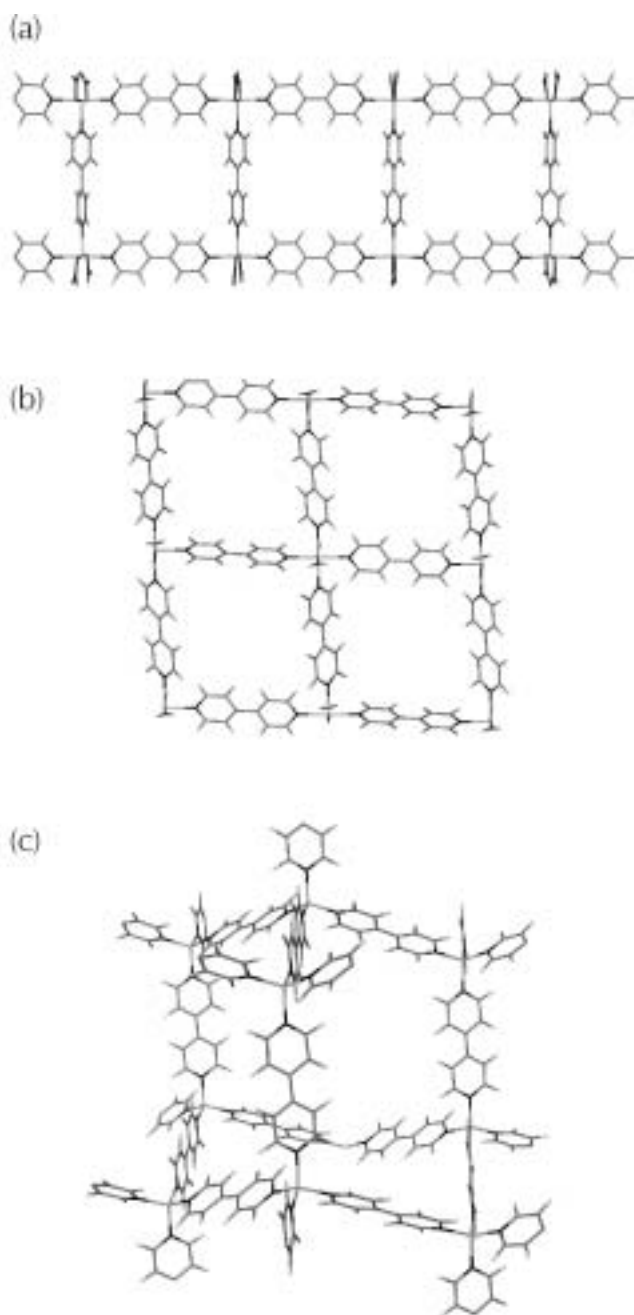


Fig. 6 – X-Ray crystal structures of selected coordination frameworks from the 4,4'-bipy ligand. (a) 1D ladder structure of  $\text{Co}(4,4'\text{-bipy})_2(\text{NO}_3)_2(\text{naphthalene})$ .<sup>228</sup> The  $\text{NO}_3^-$  anions coordinate the  $\text{Co}^{2+}$  centers. The disordered naphthalene guest is not shown. (b) 2D square-grid structure of  $\text{Zn}(4,4'\text{-bipy})_2(\text{H}_2\text{O})_2(\text{SiF}_6)$ .<sup>229</sup> The  $\text{SiF}_6^{2-}$  anions are not shown. (c) 3D diamondoid structure of  $\text{Cu}(4,4'\text{-bipy})_2(\text{PF}_6)$ .<sup>230</sup> The  $\text{PF}_6^-$  anions are not shown. Interpenetration of identical networks is present in (b) and (c).

different late transition metal salts. Some of these materials have been reported<sup>234–245</sup> to undergo anion exchange when immersed in aqueous or organic solutions containing salts of various anions such as  $\text{NO}_3^-$ ,  $\text{SO}_4^{2-}$ ,  $\text{ClO}_4^-$ ,  $\text{CF}_3\text{SO}_3^-$ ,  $\text{MoO}_4^{2-}$ ,  $\text{F}^-$ ,  $\text{I}^-$ ,  $\text{BF}_4^-$ ,  $\text{PF}_6^-$ ,  $\text{SiF}_6^{2-}$ ,  $\text{GeF}_6^{2-}$ . The exchange may be reversible, and the exchange times vary from minutes to hours. The cationic networks either remain intact or may undergo structural reorganization upon anion exchange. A major gap in understanding arises in the lack of

competition experiments or exchange isotherms to assess selectivity and thermodynamics. In one particular study, though, on a silver-polynitrile network, the order of affinity was found to be:  $\text{ClO}_4^- > \text{NO}_3^- > \text{CF}_3\text{SO}_3^- > \text{Cl}^-$ ,<sup>237</sup> which coincides with Hofmeister bias. However, unlike in the liquid-liquid or anion-resin exchange, other factors are likely to be important for the anion-exchange selectivity in these metal-coordination networks, such as packing effects, and the dimension, position, and order of anion in the network.

## Conclusions

Sophisticated host compounds may be expected to have application in meeting very high-performance needs with high value. Nuclear cleanup applications represent a prime example.<sup>5–9,21,151</sup> For such critical uses, investment in more sophisticated extractants buys performance that cannot otherwise be obtained. Use of high-throughput devices (e.g., centrifugal contactors<sup>31,54–56,246</sup>) maximize reagent turnover and minimize reagent inventory, thereby making the most efficient use of the reagent possible. One should take note, however, that the reagent cost in operating extractive separation processes is primarily felt through attrition, which includes loss to the aqueous phase, decomposition, or fouling.<sup>10,11</sup> Such losses can be mitigated by optimal extractant design (e.g., building in lipophilicity, minimal interfacial activity, and robustness<sup>19,50,51</sup>) and employing recovery methods (e.g. solvent coalescers<sup>247</sup>). Even so, it may be desirable to fix host compounds to solid supports so that reagent losses to the aqueous phase are practically eliminated.<sup>32,36,248,249</sup> This approach has indeed proven successful and applies well to dilute feeds. However, it must be noted that attrition due to decomposition<sup>249</sup> and fouling still must be reckoned with, just as for liquid-liquid systems.

Toward obtaining the desired high performance for critical separations needs, we have outlined a fundamental approach that relies on deliberate receptor design. The design methodology employs computational combinatorial algorithms to link donor atoms in such a way that they will be preorganized and complementary for targeted guest species. Once synthesized, newly designed materials may be employed in the context of liquid-liquid or solid-phase separation systems. A hierarchical categorization of 11 charge-balanced approaches to employing host-guest chemistry in separations has been helpful in both understanding host function and in choosing appropriate systems for a given need. As the area of anion binding and separation is still very young, we envision a blossoming of the field as the basis of recognition is gradually understood and applied to the development of increasingly more effective materials.

## ACKNOWLEDGMENTS

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## SAŽETAK

### Strategije za upotrebu kemije domaćin-gost u ekstrakcijskom odvajanju ionskih gostiju

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Kemija domaćin-gost dovela je do nove paradigme u ekstrakcijskim odvajanjima, rađajući nove mogućnosti za učinkovita odvajanja ionskih vrsta da bi se zadovoljile potrebe industrije. U ovom radu opisuje se pristup koji su autori poduzeli nedavno, svježi rezultati i budući smjerovi prema vrlo selektivnim razlučivanjima aniona temeljenih na principima kemije domaćin-gost. U predočenom materijalu radi se o genezi i otkriću novih ekstrakcijskih sustava, ilustrira se potencijal pojedinih kemijskih koncepata s primjerima praktične primjene. Glavna pitanja tiču se uloge aniona u ekstrakcijskim procesima i čimbenika koji leže u temeljima prepoznavanja i prijenosa aniona. Teoretski naponi istražuju tehnike molekularnog dizajniranja utjelovljenog u razvijanju programa HostDesigner. Dizajnerski proračuni sposobni su generirati slojevite multifunkcionalne kandidate za svrhe ionskih receptora koji se temelje na vodikovoj vezi kao donorskoj grupi koji imaju O-H i N-H donorske skupine. Napori za sintetiziranjem receptora zajedno sa studijama molekularne strukture i termodinamike vezanja i prijenosa daju cjelovitu sliku razumijevanja odnosa strukture i funkcije i povratne sprege za daljnje molekularno modeliranje. Podaci o ekstrakcijama vrednovani su u termokemijskom kontekstu u kojem matrično otapalo, uključujući upotrebu anionsko-otapajućeg lipofilnog alkohola, igra glavnu ulogu. Primjene su zamišljene za rješavanje mnogih tipova razdvajanja, a primjeri su uzeti uglavnom iz vlastitih istraživanja autora primijenjenih na obradu odlažućeg radioaktivnog otpada.

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