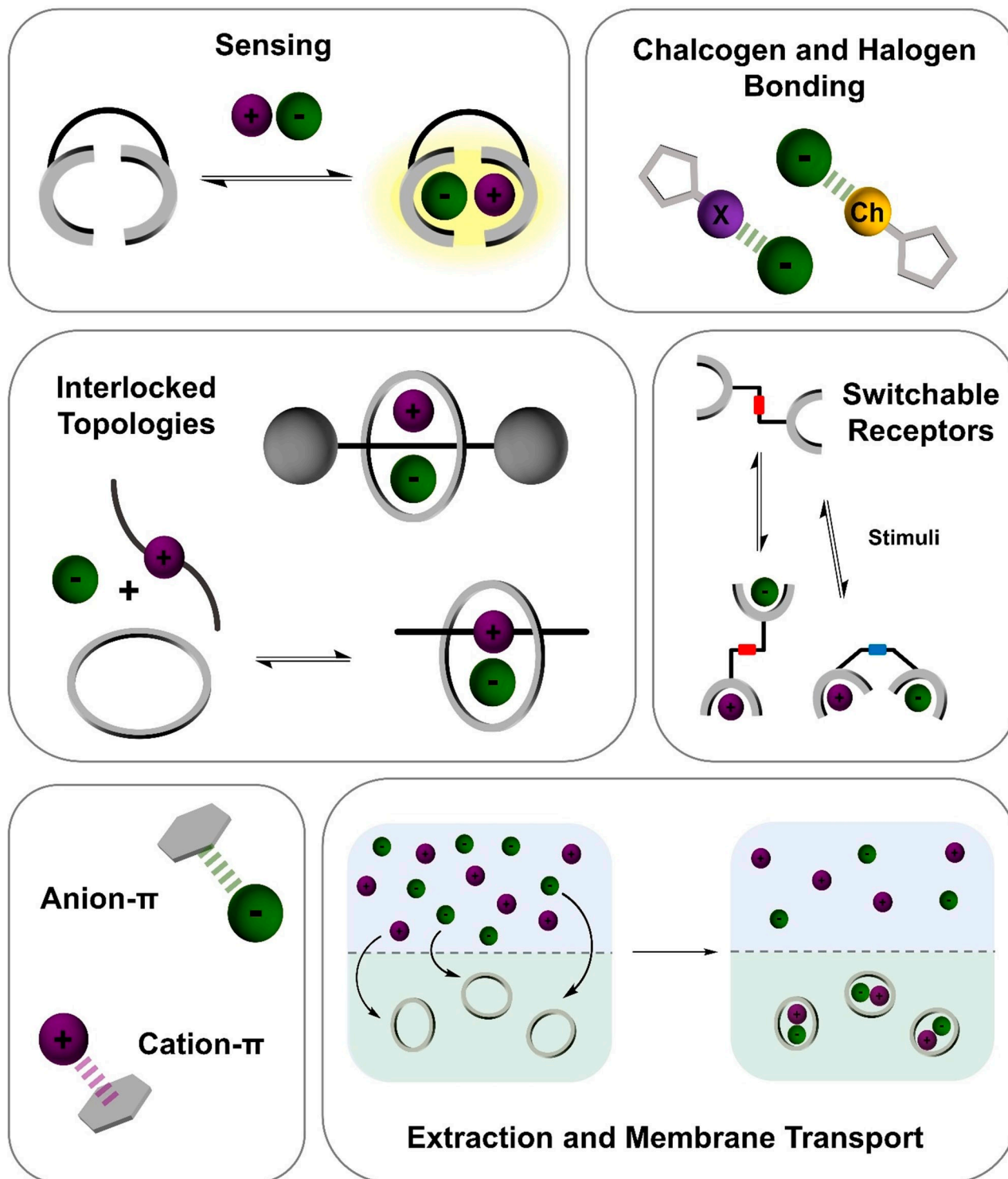


VIP Very Important Paper

From Heteroditopic to Multitopic Receptors for Ion-Pair Recognition: Advances in Receptor Design and Applications

Anna J. McConnell,^{*,[a]} Andrew Docker,^[b] and Paul D. Beer^{*,[b]}

Ion-pair recognition has emerged from cation and anion recognition and become a diverse and active field in its own right. The last decade has seen significant advances in receptor design in terms of the types of binding motifs, understanding of cooperativity and increase in complexity from heteroditopic to multitopic receptors. As a result, attention has turned to

applying this knowledge to the rational design of ion-pair receptors for applications in salt solubilisation and extraction, membrane transport and sensing. This Review highlights recent progress and developments in the design and applications of heteroditopic and multitopic receptors for ion-pair recognition.

1. Introduction

Charged species play a crucial role in many processes from the regulation of homeostasis in the body to the storage of energy in lithium-ion batteries. As a result, dysfunction of these processes is implicated in wide-ranging global challenges from diseases to environmental issues, such as pollution and eutrophication. Supramolecular chemistry offers the opportunity to solve these problems through the design of synthetic receptors that bind charged species selectively and with high affinity. While the design of cation and anion receptors has been studied for many decades, these monotopic receptors have the disadvantage that ion-pairing between the ion and its counterion can inhibit binding of the individual ion, since there is an energetic cost to separating the ions. The design of heteroditopic ion-pair receptors with a binding site for both the cation and anion offers a solution to overcome this problem and also introduces the opportunity to exploit cooperativity in ion-pair binding. Consequently, ion-pair recognition has grown from cation and anion recognition over the last several decades into an established field of its own.

This Review is not intended to be a comprehensive review on the history of ion-pair recognition, but instead serves as an update to our previous review from 2012.^[1] Examples are chosen to highlight progress, new developments and challenges in the design as well as applications of ion-pair receptors. For more detailed treatments of particular classes of ion-pair receptors, the reader's attention is drawn to many excellent recent reviews on calix[4]pyrrole,^[2] macrocyclic,^[3] organotin,^[4] metal-salophen and -salen,^[5] pyrrole,^[6] imidazole^[6] and triazole^[6] ion-pair receptors.

As an introduction to the topic, this Review will start with an overview of the different binding modes for ion-pair

recognition, as exemplified by heteroditopic ion-pair receptors, before discussing the role of cooperativity in ion-pair recognition. Recent advances in receptor design, from unusual binding motifs for the cation and anion guest species to interlocked receptors and multitopic receptors with multiple binding sites for the cation and/or anion are discussed. The final section focuses on applications of heteroditopic and multitopic receptors in salt extraction and solubilisation, membrane transport and sensing.

1.1. Binding Modes and Cooperativity

The spatial relationship of co-bound ions in a heteroditopic receptor, or *binding mode*, serves as a useful criterion to categorise ion-pair host structures. These may conveniently be divided into *contact ion-pair* and *separated ion-pair* receptors. In the former, ions are said to be in direct contact with their counterion. When the bound ion-pair is inorganic there is little ambiguity in this classification, as inspection of solid-state structures and comparison between known ionic radii reveal their proximity to each other (Figure 1a). Organic ions, however, possess a wider range of geometries and are less easily defined in terms of radii. In this case, whilst the extent of 'contact' maybe less obvious, the observation of non-covalent interactions between the ions (e.g. hydrogen bonding) is often sufficient to classify the ion-pair as a *contact ion-pair*. Bound ion-pairs not exhibiting contacts between each other are termed *separated ion-pairs*. Receptors displaying this binding mode are, in general, a consequence of either: (i) cation and anion recognition sites being situated at sufficient distance apart such that mutual ion-pair contact is not feasible, often called *host-separated* (Figure 1b) and (ii) another chemical entity, normally solvent, coordinates to one or both of the ions in the space between the two, referred to as *solvent-separated* (Figure 1c).

Whilst the binding mode may vary, one feature common to heteroditopic systems is *cooperativity*; the interplay between how co-bound ions influence host-guest ion-pair recognition

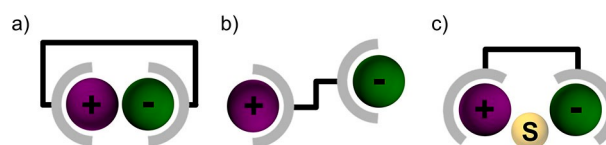


Figure 1. Cartoon representations of the recognition mode of ion-pairs in heteroditopic receptors: a) contact ion-pair b) host-separated c) solvent-separated.

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behaviour. This cooperative ion-pair binding effect is usually attributed to two factors: electrostatic interactions between the complexed ions and/or allosteric conformational changes induced by a binding event.^[1,3,7] In either case, when a binding event causes an enhancement or inhibition of counterion association, the cooperativity is referred to as positive or negative, respectively. Attempts to quantify and delineate mechanisms of cooperativity are notoriously challenging and fraught with experimental difficulties due to the numerous and complex equilibria implicated with ion-pair binding.^[8] The majority of reports characterise cooperativity by so-called 'turn-on' or cooperativity factors, usually the ratio of a receptor's affinity for a given ion, in the presence and absence of a counterion. For example, Martinez's heteroditopic hemicryptophane **1** (Figure 2a) was found to bind Br⁻ with an association constant of $1.05 \times 10^3 \text{ M}^{-1}$ in CDCl₃.^[9] However, upon pre-complexation with tetramethylammonium picrate the bromide affinity increases to $13.5 \times 10^3 \text{ M}^{-1}$, indicating the presence of NMe₄⁺; presumably, favourable electrostatic interactions enhances Br⁻ affinity giving a cooperativity factor of 13.

Flood *et al.* reported a quantitative analysis of cooperativity in ion-pair binding using macrocyclic receptor **2** (Figure 2b).^[10] Utilising extensive cation, anion and ion-pair affinity measurements, supplemented with computational studies, the authors were able to ascribe thermodynamic parameters to cooperativity and relative contributions of electrostatic and allosteric effects. For example, these studies determined NaI and NaClO₄ ion-pairs are bound cooperatively in CD₂Cl₂/CD₃CN (4:1), wherein the electrostatic contribution to cooperativity dominates and

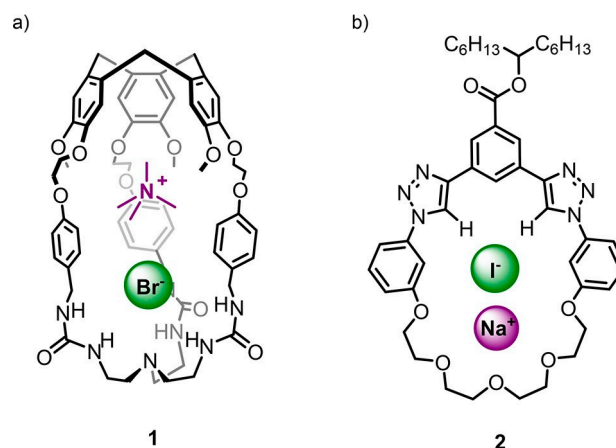
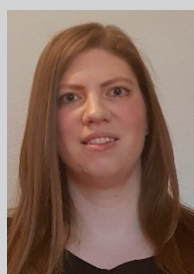


Figure 2. a) Martinez's hemicryptophane receptor for ammonium halides b) Flood's macrocyclic contact ion-pair host.

is dictated by ionic size, explaining the larger cooperativity observed for NaI relative to NaClO₄.

Aside from detailed analysis,^[11] it is the judicious exploitation of positive cooperativity in heteroditopic receptor design that has produced remarkable improvements in the recognition of charged species in both binding strength and selectivity, that continues to stimulate intense interest in the field.



Anna McConnell obtained a D.Phil. under the supervision of Prof. Paul Beer at the University of Oxford. Following postdoctoral research stays at the California Institute of Technology and the University of Cambridge in the groups of Prof. Jacqueline Barton and Prof. Jonathan Nitschke, respectively, she became a Junior Professor at Christian-Albrechts-Universität zu Kiel in November 2016. Her research focuses on stimuli-responsive metal-organic cages, dynamic covalent chemistry and luminescent complexes. I am very grateful to Paul for his mentorship and support during not only my D.Phil. but also in my subsequent scientific career. This contribution updates our review on ion-pair recognition from my D.Phil. studies and I have enjoyed working with Paul and Andrew discussing the latest progress in the field.



Andrew Docker obtained his undergraduate degree from the University of Oxford. He is currently working towards a D.Phil. degree under the supervision of Prof. Paul Beer, with research into the field of halogen and chalcogen bonding mediated anion and ion-pair recognition and extraction.



Paul Beer obtained a PhD from King's College London in 1982 with Dr C. Dennis Hall. After a Royal Society European Postdoctoral Fellowship with Professor J.-M. Lehn and a Demonstratorship at the University of Exeter, he was awarded a Lectureship at the University of Birmingham in 1984. In 1990, he moved to the University of Oxford where he was made a University Lecturer and Fellow at Wadham College, and became a Professor in 1998. His research interests focus on supramolecular host-guest chemistry and coordination chemistry.

2. From Macrocyclic to Interlocked Heteroditopic Ion-Pair Receptors

Recent decades have shown enormous progression in the development of receptors for ion-pairs capable of eliciting high levels of affinity and selectivity for a range of charged species. However, the variety of recognition motifs and receptor topologies employed has been somewhat less diverse, with the vast majority of heteroditopic receptors reported to date relying on crown ether-based cation binding sites appended with acidic hydrogen bond (HB) donors to achieve anion complexation. This section will discuss recent reports of new strategies utilised in heteroditopic receptor design, focusing first on the use of unusual non-covalent interactions in macrocycles before discussing complex molecular topologies.

2.1. Binding Motifs

Hydrogen bond (HB) donors have been extensively employed as anion binding components in ion-pair host design. Over the last decade, however, sigma hole bonding interactions such as halogen bonding (XB) have risen to prominence in the field of anion recognition, frequently displaying enhanced affinity and unique selectivity properties relative to HB analogues.^[12] Despite this, the incorporation of sigma-hole interactions in heteroditopic host systems is rare. Whilst an early report by Resnati and Metrangolo demonstrated the potential of XB mediated ion-pair recognition,^[13] it was over a decade later before another example appeared.^[14] In this study, Schubert described an iodo-triazole motif embedded in a triethylene glycol containing macrocycle **3** (Figure 3a). It was envisioned that the Lewis-basic nitrogen atoms of the triazole would, in concert with the polyether backbone, complex alkali metal cations. Indeed, X-ray crystallographic analysis of **3**·NaBPh₄ revealed participation of triazole N-ligation generating a six-coordinate Na⁺ environment and solution phase ¹H NMR titration experiments demonstrated **3** was capable of binding Na⁺ ($K_a(\text{Na}^+) = 434 \text{ M}^{-1}$) in CD₂Cl₂/CD₃CN (3:1) mixtures. Practical considerations necessitated the use of ¹³C NMR titration experiments to determine anion affinities in the same solvent system and although **3** exhibited moderate iodide affinity $K_a(\text{I}^-) = 4.7 \text{ M}^{-1}$, upon complexation with NaBPh₄ this was dramatically improved, $K_a(\text{I}^-) = 135 \text{ M}^{-1}$. The cooperative ion-pair recognition

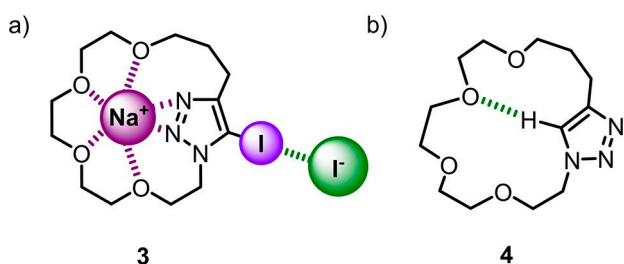


Figure 3. Schubert's XB/HB-based crown ether receptors: a) schematic view of NaI binding by **3** b) Intramolecular HB formation in **4**.

behaviour was attributed to a combination of favourable electrostatic interactions and improved XB donor potency by cation induced C–I bond polarisation. Interestingly, the HB analogue **4** demonstrated no significant cooperative ion-pair binding, as ROESY NMR and X-ray crystallographic analysis revealed intramolecular HB formation (Figure 3b), which negated HB formation with anionic guests and attenuated cation binding $K_a(\text{Na}^+) = 126 \text{ M}^{-1}$.

Chalcogen bonding (ChB), a sister interaction to XB, has recently been incorporated into anion receptor frameworks demonstrating improved enantioselectivity, sensory outputs and unique selectivity behaviour relative to XB and HB systems.^[15] While these relatively rare examples demonstrate notable promise, ChB mediated recognition is still very much in its infancy and key fundamental characteristics regarding the nature of chalcogen bonding still remain to be elucidated. A very recent report this year, 2020, by Beer *et al.* describes a direct comparison of unprecedented ChB ion-pair recognition with XB and HB using a series of structurally homologous heteroditopic receptors **5a–c** incorporating XB, chalcogen bonding (ChB) and HB donor groups covalently linked with benzo-15-crown-5 ether motifs (Figure 4).^[16] Extensive ¹H NMR titration experiments in 10% d₆-DMSO/CDCl₃ solution with TBABr and TBAI, in the presence and absence of sodium cations determined $K_a(\text{Na}^+)/K_a(\text{None})$ cooperativity factors (α) for each receptor, summarised in Table 1. All receptors demonstrated positive cooperativity ($\alpha > 1$), consistent with favourable electrostatic interactions. Most importantly, the XB and ChB analogues displayed remarkable 100- and 200-fold enhancements in halide affinity, respectively, while only modest cooperativity factors were observed with the HB receptor **5c**.

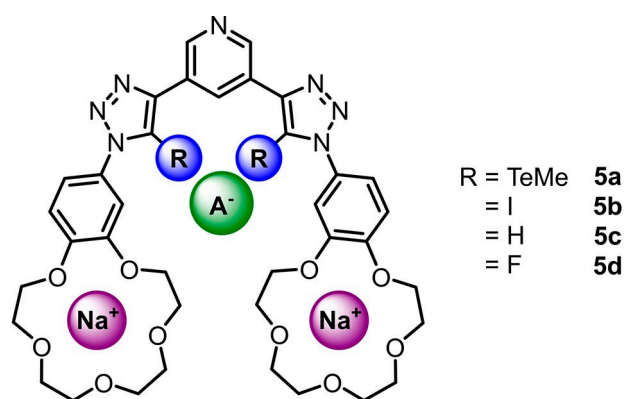


Figure 4. Heteroditopic receptors containing ChB, XB and HB donors **5a–c** and non-bonding fluorotriazole analogue **5d**.

Table 1. Summary of cooperativity factors for heteroditopic receptors **5a–c** calculated from ¹H NMR titration experiments for bromide and iodide

Anion ^[a]	Cooperativity Factor (α) ^[b]		
	5a	5b	5c
Br [−]	280	127	21
I [−]	216	162	23

[a] Anions added as their TBA salts [b] The cooperativity factor (α) is given by $\alpha = \{K_a(\text{Na}^+)/K_a(\text{None})\}$.

Control experiments with the fluorine substituted system **5d** and DFT calculations suggest the substantial α values for **5a** and **5b** are attributable to a sodium cation-crown ether bound induced polarisation of the respective receptor's XB and ChB donor atoms, providing a unique mechanism of cooperativity.

Borne out of theoretical studies, the association of anions to electron-deficient aromatic systems, known as anion- π interactions, is perhaps the least common non-covalent interaction employed in ion-pair host design. One rare example reported by Wang *et al.* is macrocyclic host **6a**, consisting of a pentaethylene glycol chain linked to two electron deficient chlorotriazine units (Figure 5a).^[17] Upon complexation with equimolar $\text{Ca}(\text{ClO}_4)_2$ the resulting $[\mathbf{6a}\cdot\text{Ca}^{2+}]$ complex bound halides in a 1:2 host-guest stoichiometry with association constants of 5508 M^{-2} and 477 M^{-2} for I^- and Br^- , respectively, in CD_3CN solution (Figure 5b). Saliiently, the role of anion- π interactions in the ion-pair binding event was confirmed by analogous anion titration experiments conducted with electron rich diethylamino

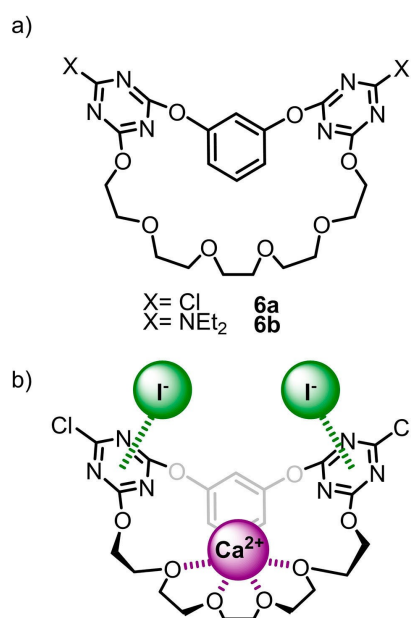


Figure 5. a) Wang's triazine-based macrocyclic receptor binding calcium halide ion-pairs b) schematic view of $\text{CaI}_2\cdot\mathbf{6a}$ binding mode.

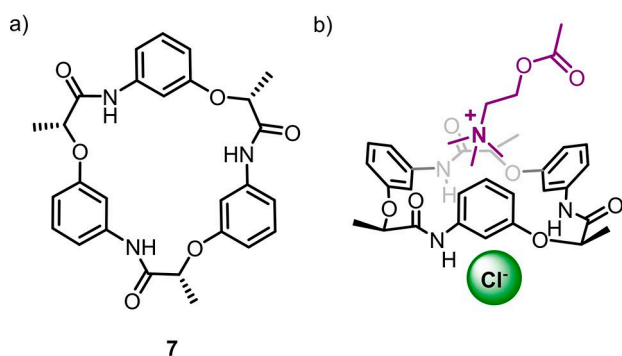


Figure 6. Akazome's peptidomimetic receptor **7** a) molecular structure b) schematic view of the acetylcholine chloride binding mode.

triazine analogue **6b**, which exhibited no measurable halide affinity upon complexation with $\text{Ca}(\text{ClO}_4)_2$.

The attractive interaction between positively charged species and an electron dense aromatic- π system, referred to as *cation- π* interactions, has long been known to profoundly influence biological systems, especially fundamental aspects of protein structure^[18] and enzymatic catalysis. In biotic systems, this interaction is typically observed between a quaternary ammonium compound and electron rich aromatic side chains of amino acids.^[19] Taking inspiration from this, a library of synthetic macrocyclic hosts were developed in which cyclic arrays of aromatic panels bind a range of ammonium, pyridinium and metal cations.^[20] In a biomimetic approach, Akazome and co-workers reported a novel tripeptide bowl-like receptor, **7** (Figure 6a), for the neurotransmitter acetylcholine chloride ($\text{ACh}\cdot\text{Cl}$).^[21] Preliminary ^1H NMR titration experiments in CDCl_3 revealed **7** was capable of binding $\text{ACh}\cdot\text{Cl}$ with strong affinity $K_a = 1640\text{ M}^{-1}$; in contrast, TBACl was bound much less strongly $K_a = 252\text{ M}^{-1}$. Further studies including X-ray crystallography, ^1H - ^1H NOE NMR spectroscopy, and MD simulations demonstrated that Cl^- complexation by **7** was accompanied by a flipping of amide HB donors to convergently bind the halide. This anion-induced conformational change preorganised the orientation of the aminophenol linkers in the macrocycle, favouring the binding of the $-\text{NMe}_3^+$ group of acetylcholine via multiple cation- π interactions, stabilising the ion-pair complex (Figure 6b). The TBA^+ cation was deemed too large to enter the concave interior of **7**.

In 2008, Ogoshi *et al.* reported the synthesis of a series of novel macrocyclic structures, coined pillar[n]arenes, consisting of methylene linked dialkylated hydroquinone panels. This family of macrocycles constitutes a readily accessible and highly functionalisable addition to the cache of supramolecular building blocks.^[22] As a consequence of the structurally well-defined electron rich interior of these macrocycles, in particular pillar[5]arene, facilitating the formation of strong inclusion complexes with a series of cationic aromatic and aliphatic molecules, pillar[5]arenes have found extensive application in the development of novel host frameworks for organic cation recognition.^[23] In general, these have been limited to monotopic receptor systems, however, more recently Huang has exploited rim-functionalised pillar[5]arene derivatives to provide recognition environments for ion-pairs. In a 2019 report, Huang investigated a series of peralkylated pillar[5]arenes **8a-c** as hosts for the complexation of silver trifluoroacetate (Figure 7a).^[24] X-ray structures of $\mathbf{8b}\cdot[\text{Ag}(\text{CF}_3\text{CO}_2)]_2$ and $\mathbf{8c}\cdot[\text{Ag}(\text{CF}_3\text{CO}_2)]_2$ revealed the nature of this host-guest interaction as an encapsulation of a silver trifluoroacetate dimer stabilised by a series of multiple bifurcated $\text{Ag}^+\cdots\pi$ interactions and $\text{C-H}\cdots\text{O}$ and $\text{C-H}\cdots\text{F}$ contacts to the CF_3CO_2^- counterions bridging the dinuclear silver unit (Figure 7b). Quantitative ^1H NMR experiments in CDCl_3/d_6 -acetone (1:1) determined **8b** to bind $\text{Ag}(\text{CF}_3\text{CO}_2)$ with the highest affinity relative to **8a** and **8c**, in which **8b** was deemed to maximise stability by size complementarity. Subsequently, **8b** was used as a solid absorbent material for the extraction of $\text{Ag}(\text{CF}_3\text{CO}_2)$ from methanol solutions. It appears that the unique nature of the

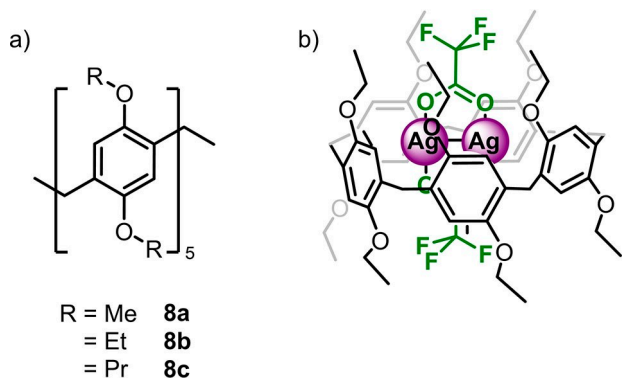


Figure 7. a) Huang's pillar[5]arene silver ion-pair receptors **8a–c** b) Representation of dimeric $\text{Ag}(\text{CF}_3\text{CO}_2)_2$ complex encapsulated in **8b**.

$\text{Ag}^+\cdots\pi$ interactions was a significant contribution to the stability of this complex, as other trifluoroacetate salts with Cu^{2+} , Na^+ or K^+ counteranions showed negligible extraction from MeOH solution.

2.2. From Pseudorotaxanes to Rotaxanes

Organic alkyl ammonium cation – halide anion ion pair species have been demonstrated to assemble interpenetrated and interlocked structures, in which the cooperative binding of the ion-pair is crucial to the formation of the molecular ensembles. In addition, examples of rotaxane architectures in which their macrocycle and axle components generate unique three-dimensional cavities for ion-pairs are also summarised.

Recent studies by Huang have demonstrated that simultaneous cation and anion recognition can also influence the stability of [2]pseudorotaxanes formed between pillar[5]arene-based receptors and triethyloctylammonium salts **9**⁺ (Figure 8a).^[25] ¹H NMR titration experiments in CDCl_3 solution showed that urea functionalised pillar[5]arene **10** was able to form moderately stable interpenetrated assemblies between **9·Br** and **9·PF₆** with association constants of 522 M^{-1} and 232 M^{-1} , respectively (Figure 8b). In an attempt to delineate the relative contributions of cation and anion derived association, affinity measurements between the quaternary ammonium salts and monotopic receptors **11** and **12** were also investigated (Figure 8c). Interestingly, 1,4-dimethoxypillar[5]arene **12** displayed no evidence of binding **9·Br** and **9·PF₆**, and the simple anion-binding urea receptor **11** exhibited only a modest affinity for **9·Br** and **9·PF₆** with K_a values of 121 M^{-1} and 107 M^{-1} , respectively. All these observations suggested **10** was capable of binding ammonium ion-pairs in a cooperative fashion, and importantly, that its heteroditopic nature was crucial for pseudorotaxane formation.

Reports in 2014 from Yuan *et al.* also detail the role of the counteranion in [2]pseudorotaxane formation with heteroditopic macrocyclic cyclo[6]aramide **13** and a series of dibutylammonium halide salts (Figure 9).^[26] ¹H NMR studies in CDCl_3 solution indicate **13** binds **14·Cl**, **14·Br** and **14·I**, with

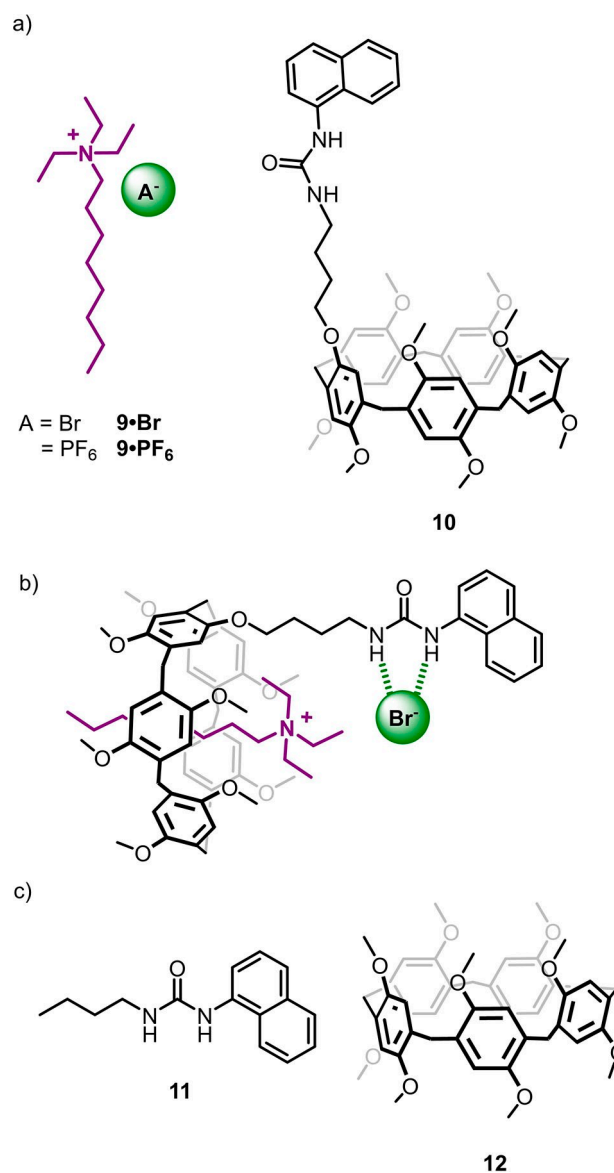


Figure 8. a) Huang's urea appended pillar[5]arene **10** b) proposed [2]pseudorotaxane binding mode and c) corresponding monotopic analogues.

considerable affinities $1.8 \times 10^5 \text{ M}^{-1}$, $1.2 \times 10^4 \text{ M}^{-1}$ and $5.5 \times 10^3 \text{ M}^{-1}$, respectively. The role of the counteranion was elucidated by inspection of the X-ray crystal structure of **13** complexed with **14·Cl**, showing the inclusion of the ammonium cation and chloride anion as an intimate ion-pair, engaged with multiple hydrogen bonding interactions between themselves in addition to the macrocyclic host. The preference exhibited for the chloride salt of **14**⁺ was rationalised on the basis of size complementarity wherein the ion-pair is able to maintain a compact salt-bridge like relationship in the aperture of macrocycle **13** while simultaneously interacting with HB donors and acceptors of the macrocycle interior.

Smith *et al.* have also investigated the influence of ion-pairing on quaternary ammonium chloride salt recognition by tetralactam macrocycle **15** (Figure 10).^[27] Through ¹H NMR titration experiments it was discovered that Cl^- salts of smaller

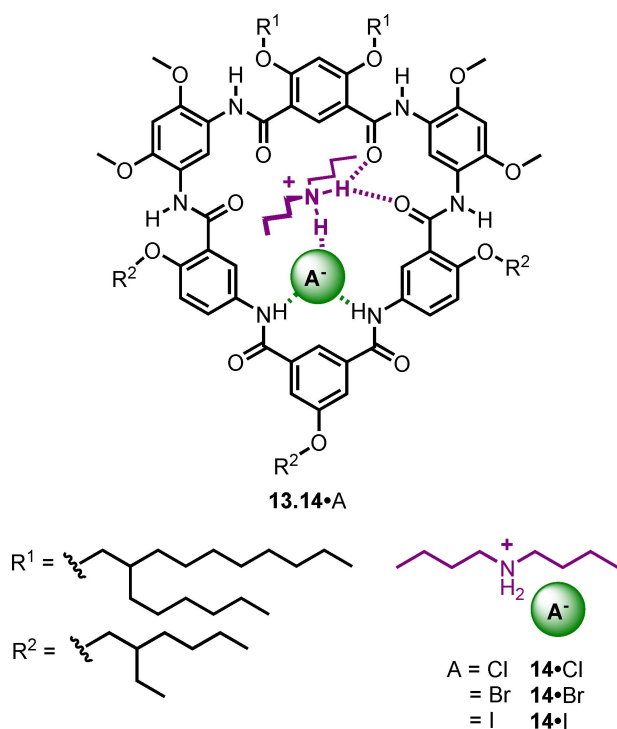


Figure 9. Yuan's cyclo[6]aramide **13** and observed binding mode of contact ion-pairs of dibutylammonium salts.

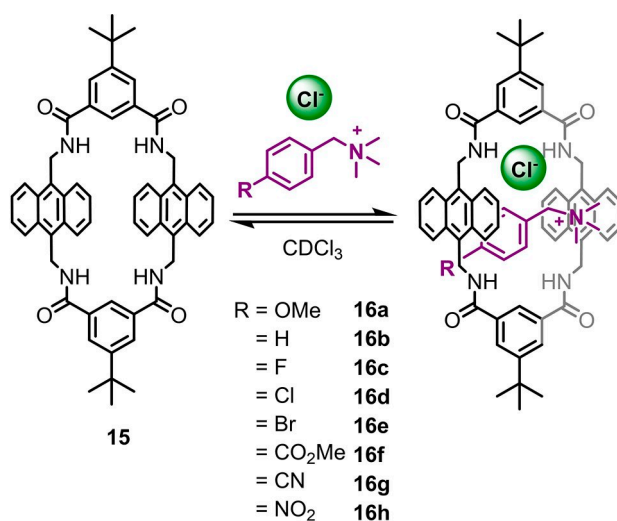


Figure 10. Smith's tetralactam macrocycle **15** for quaternary ammonium chloride salt recognition.

alkylammonium compounds, such as acetylcholine (ACh), were bound with considerably increased affinities relative to bulkier tetrabutylammonium cations, e.g. $K_a(\text{ACh}\cdot\text{Cl})/K_a(\text{TBACl})=19$. The authors rationalised this enhancement in binding constant to the formation of contact ion-pairs endotopically bound by **15**, stabilised by cation- π , $\text{NH}\cdots\text{Cl}^-$ and internal hydrogen bonding between an intimately associated ion-pair. In order to elucidate the role of cation-anion hydrogen bonding interactions between macrocycle-bound ion-pairs, the authors also investigated a series benzyl trimethylammonium chloride salts

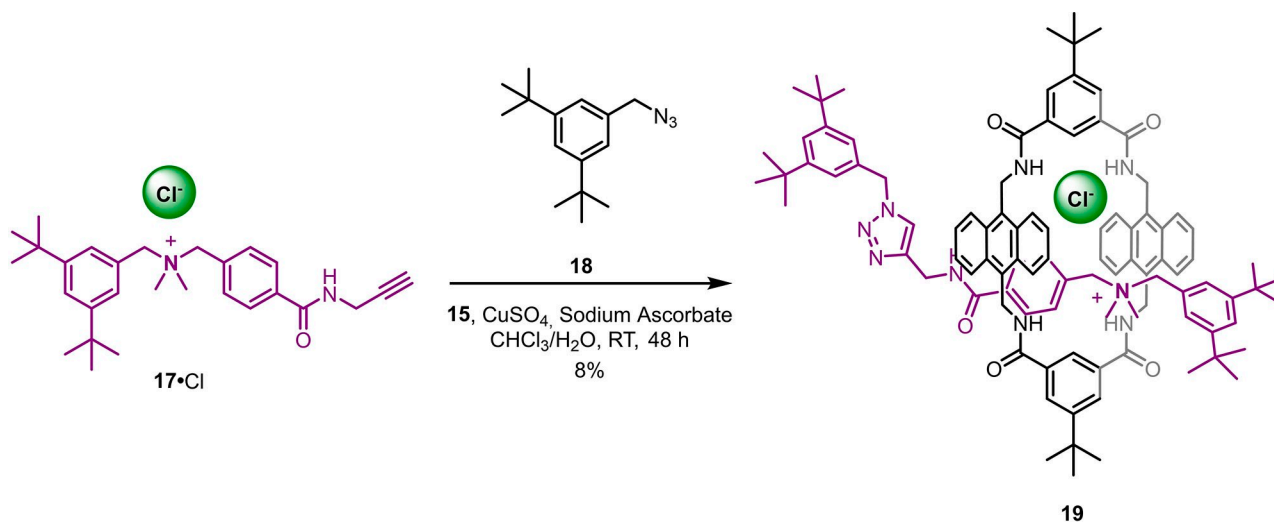
16a-h with various *para* substituents. Increasing the electron withdrawing nature of R resulted in the K_a value for ion-pair binding to **15** to also increase e.g. $K_a(\mathbf{16g})/K_a(\mathbf{16a})=4$. In addition to other factors such as improved π - π interactions, this was attributed to more acidic C-H HB donors strengthening ion-pairing between **16**⁺ and Cl^- .

Building on this work, these tightly associated ion-pairs were used as functional templates for the synthesis of interlocked structures. A 'stopping' copper(I) azide-alkyne cycloaddition reaction between axle precursors **17**-Cl and **18** in the presence of macrocycle **15** afforded [2]rotaxane **19** in a modest yield of 8% (Scheme 1).

Although acyclic and macrocyclic receptors dominate the literature, mechanically interlocked molecules (MIMs) have also been investigated as novel heteroditopic ligands. The first example in 2014 by Beer *et al.* used a neutral [2]rotaxane, **20**, to bind 'axle-separated' alkali-metal halides (Figure 11).^[28] The ability of **20** to bind ion-pairs was dependent on an alkali metal cation induced pirouetting behaviour of the interlocked components, in which the calix[4]diquinone containing macrocycle and pyridine N-oxide functionalised axle coordinate either Li^+ , Na^+ or K^+ , considerably improving the anion recognition properties of **20** through preorganisation of hydrogen bond donors on both components. Quantitative investigations revealed sodium cations generated the largest enhancements in halide affinities relative to lithium and potassium, in particular complexation with Na^+ demonstrated a considerable 15-fold enhancement for chloride in $\text{CDCl}_3/\text{CD}_3\text{OD}$ (4:1) solvent mixtures.

Ballester *et al.* reported the stability of a [2]pseudorotaxane assembly formed between a bis-calix[4]pyrrole macrocycle **21** and pyridine N-oxide **22** was significantly increased upon the addition of tetrabutylammonium (TBA) salts of various polyatomic anions (Figure 12).^[11c] In particular, TBANCO proved a powerful template quantitatively forming pseudorotaxane complexes ($K_a=9.1\times 10^{10}\text{ M}^{-2}$) in CDCl_3 solution. The remarkable fidelity of the four-component assembly was determined to originate from the linear geometry of NCO^- which was able to engage six NH hydrogen bond donors from both the macrocycle **21** and thread **22** in the cavity of the interpenetrated assembly. Furthermore, X-ray crystallographic and NMR evidence confirmed the simultaneous binding of the quaternary ammonium counteranion which is situated in the convex electron rich π surface of the calix[4]pyrrole moiety.

Later reports also by Ballester detailed the exploration of [2]rotaxane **23** (Figure 13) for binding tetraalkylammonium salts with structurally diverse anions including Cl^- , OCN^- and NO_3^- .^[29] ITC titration experiments in CDCl_3 reveal interlocked host **23** displays a preference for TBANCO over TBANO_3 and TBACl with association constants of $7.9\times 10^5\text{ M}^{-1}$, $4\times 10^4\text{ M}^{-1}$ and $5\times 10^4\text{ M}^{-1}$, respectively, rationalised by host-guest shape complementarity between NCO^- and the cylindrical cavity of **23**. In addition, the significant influence of cation recognition by the macrocycle component in **23** was also demonstrated, as methyltrioctylammonium chloride (MTOCl), an organic cation better encapsulated by the cone conformation of calix[4]



Scheme 1. Synthesis of [2]rotaxane **19** via an ion-pair templated CuAAC stopping reaction.

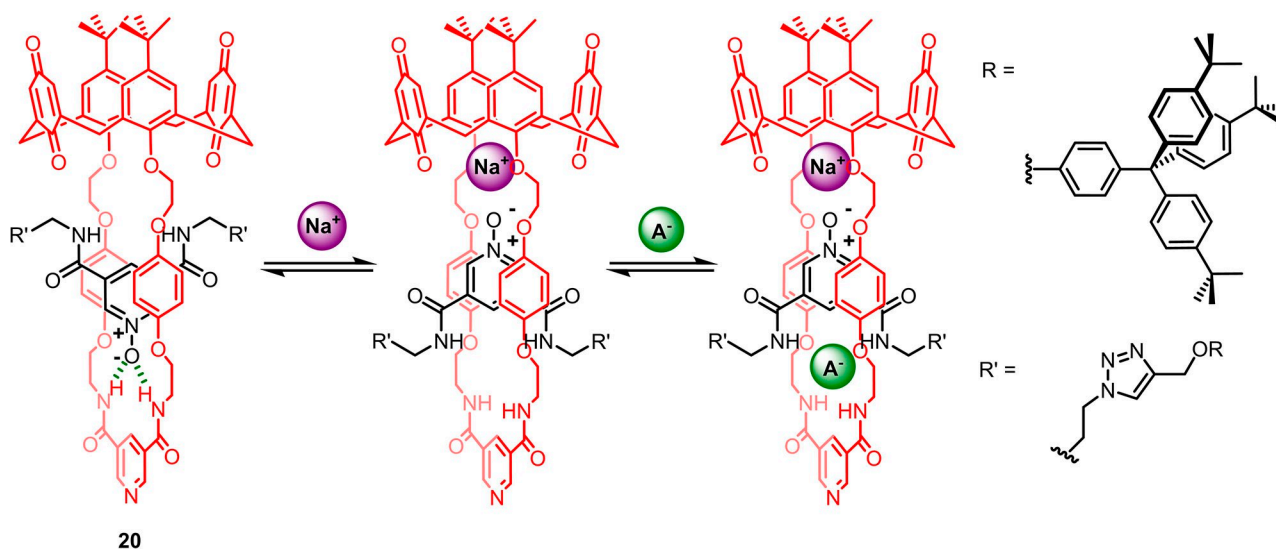


Figure 11. Beer's calix[4]diquinone based [2]rotaxane exhibiting Na^+ induced pirouetting behaviour.

pyrroles, was found to exhibit a K_a value of $1.58 \times 10^7 \text{ M}^{-1}$, a twenty-fold enhancement relative to TBANCO.

Transition metal cation ion-pair recognition is less common, however, in 2017 Beer reported a series of [2]rotaxanes **24**, **25 a** and **25 b** capable of cooperatively binding halides and nitrate anions in the presence of ligated Zn(II) cations (Figure 14).^[30] Strong coordination of Zn^{2+} was achieved by a mechanically bonded array of chelating ligands derived from a tris-amine-functionalised macrocycle and either a bipyridine or pyridine 2,6-dicarboxamide containing axle. ^1H NMR anion titration experiments with **24**· $\text{Zn}(\text{ClO}_4)_2$ revealed moderate Cl^- and Br^- selectivity over I^- and NO_3^- in $\text{CDCl}_3/\text{CD}_3\text{OD}$ (1:1) mixtures. The effect of XB donor incorporation into the anion binding cavity was also investigated with the zinc complexes of **25 a** and **25 b** in a more competitive $\text{CDCl}_3/\text{CD}_3\text{OD}/\text{D}_2\text{O}$ (45:45:10) solvent medium. Interestingly, only a minor difference in association constant values was observed for the halides and nitrate,

suggesting that the isophthalamide containing macrocycle component and favourable Coulombic interactions dominate the anion recognition process.

Goldup and co-workers have reported a [2]rotaxane which employs conformational control of ion-pair recognition behaviour (Figure 15).^[31] The interlocked structure **26** consists of a bipyridine containing macrocycle and a urea moiety integrated into the axle component where ^1H NMR and the X-ray crystal structural analysis revealed the formation of intercomponent hydrogen bonding interactions between the macrocycle bipyridine nitrogen atoms and HB donor urea, locking its conformation. Protonation of the bipyridine using HBF_4 resulted in a translocation of the macrocycle component to the triazole station of the axle, exposing the urea motif. This pH stimulus effectively switched on the anion recognition properties of the interlocked host demonstrating strong affinities for a range of anions including $K_a(\text{Cl}^-) > 10^4 \text{ M}^{-1}$, $K_a(\text{Br}^-) = 4.7 \times 10^3 \text{ M}^{-1}$ and K_a

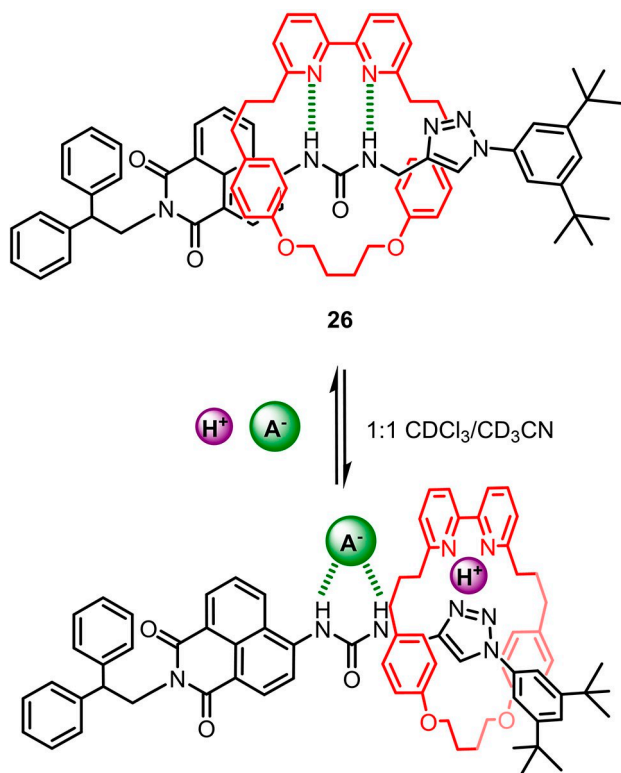


Figure 15. Goldup's allosterically regulated [2]rotaxane ion-pair receptor.

Calix[4]pyrrole functions as a heteroditopic receptor for ion-pairs,^[11a,36] and has recently been exploited by Bryantsev and Moyer in a supramolecular approach to modulate the selectivity of a cation exchanger, a lipophilic phenolate.^[37] The enhanced selectivity for caesium over sodium was attributed to the cation exchanger binding to the calix[4]pyrrole, preorganising the receptor into the cone conformation for binding caesium. Several groups have developed calix[4]pyrrole based multitopic receptors by incorporating additional cation binding sites on the upper rim.^[11b,33,34b,38] The binding modes of calix[4]crown strapped calix[4]pyrrole^[11b,33c,d] and hemispherand strapped calix[4]pyrrole^[34b,38a] multitopic receptors will be discussed in Section 4.1 with regard to salt extraction and solubilisation applications. The multitopic bis- and tetraphosphonate calix[4]pyrrole cavitand receptors of Ballester *et al.* have two possible binding modes for MX-type ion-pairs: a receptor-separated and contact ion-pair binding mode (Figure 16).^[33a,b]

Interestingly, the subtle difference in the orientation of a single phosphonate group (ie pointing towards or away from the cavity) on the upper rim in diastereomeric receptors can result in different binding modes for the same ion-pair in some cases; while diastereomers **27** and **28** both bound tetramethylphosphonium chloride as a receptor-separated ion-pair, octylammonium chloride was bound as a receptor-separated and contact ion-pair by diastereomers **27** and **28**, respectively (Figure 16).^[33a] The phosphonate orientation influenced not only the binding mode but also the binding affinity; diastereomer **27** bound tetramethylphosphonium chloride four times more strongly than diastereomer **28**, attributed to the electrostatic

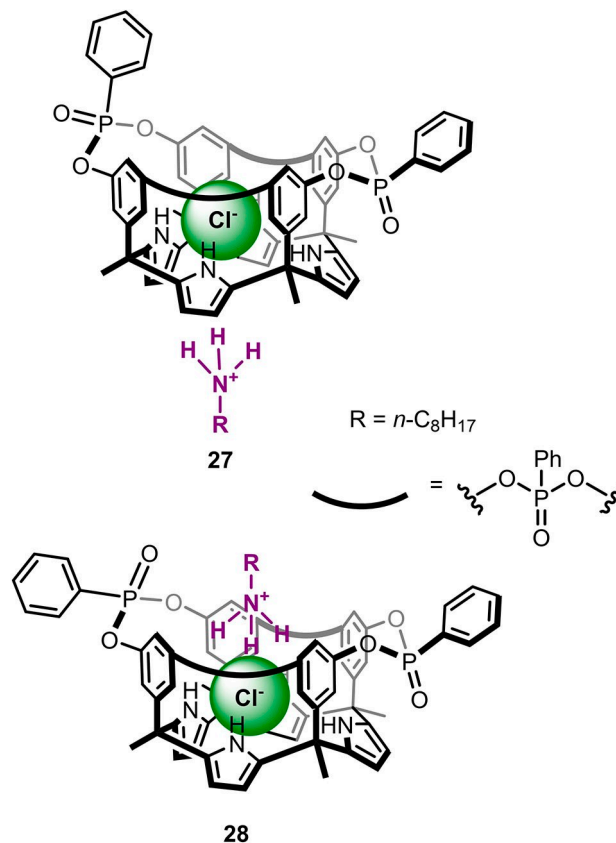


Figure 16. Ballester's diastereomeric multitopic receptors **27** and **28** showing the receptor-separated and contact binding modes for binding octylammonium chloride ion-pairs.

repulsion between the anion and negative end of the phosphonate dipole pointing inwards. In contrast, diastereomer **28** bound octylammonium chloride as a contact ion-pair two times more strongly than as a solvent-separated ion-pair to diastereomer **27**.

Following the initial reports of tritopic receptors by Lünig^[32b] and Jabin,^[32c] the number of tritopic receptors has increased to include those that bind: calcium chloride and strontium chloride;^[39] calcium bromide and calcium iodide (receptor **6a** in Figure 5, Section 2.1);^[17] alkylammonium sulfates,^[34a] and caesium carbonate.^[34b] The tritopic receptor for caesium carbonate also functions as a multitopic receptor for the recognition and extraction of MX-type ion-pairs^[34b,38] and is discussed in this context in Section 4.1.

Although rare, tetratopic hosts for binding two ion-pairs are of interest for providing insight into the rational design of complex cooperative systems. Despite the challenges associated with the numerous binding equilibria, tetratopic receptors have been the subject of detailed binding studies to determine binding modes and the role of cooperativity in ion-pair recognition. Thordarson's^[35b,c] tetratopic receptor design was based upon Lünig's^[32b] tritopic receptor using isophthalamide anion binding sites but replacing the cation binding crown-4 units with crown-6 units for binding multiple cations (Figure 17). Binding studies in organic solvent mixtures of different

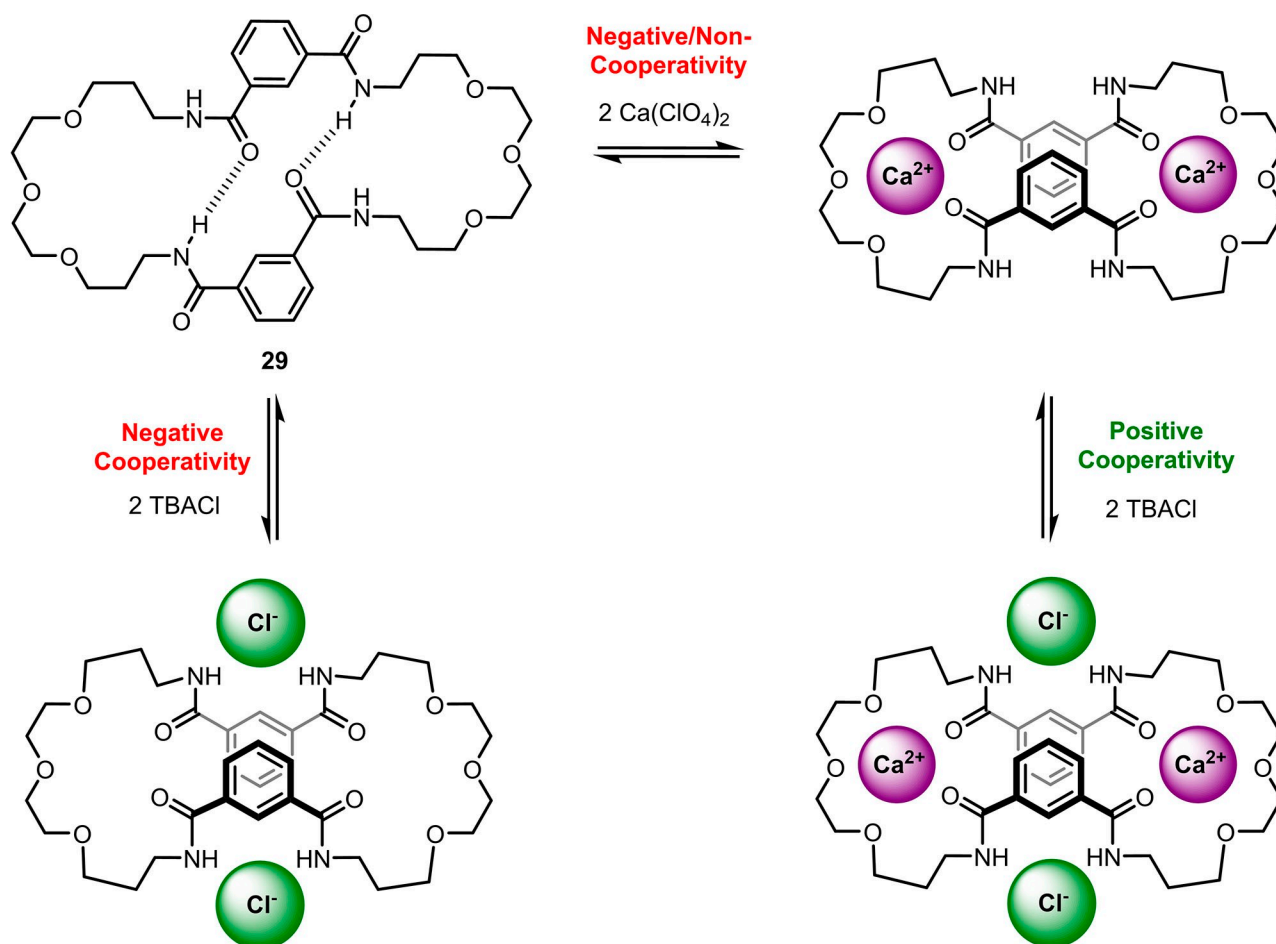


Figure 17. Thordarson's tetratopic receptor that binds anions with negative cooperativity, cations with negative or non-cooperativity but calcium chloride ion-pairs with positive cooperativity.

polarities revealed receptor **29** bound two chloride anions (with non-coordinating TBA counterions) with negative cooperativity, attributed to electrostatic repulsion inhibiting binding of the second anion. Cation binding was more complicated, with ¹H NMR titrations suggesting that two calcium cations bound to the receptor with negative/non-cooperativity. The authors proposed a conformational change from a folded-closed to an open conformation upon the binding of two calcium cations based on a comparison of the X-ray crystal structures of the receptor in the absence and presence of bound metal cations, NOESY NMR spectroscopy and computational studies (Figure 17). Unlike anion binding, the negative/non-cooperativity was unlikely to be due to electrostatic repulsion, given the large distance between calcium binding sites. Despite these negative or non-cooperative binding effects, chloride binding was switched on when two calcium ions were bound to the receptor, even in the competitive solvent system (9:1 CDCl₃/CD₃OD). This positive cooperativity was attributed to the conformational change resulting from cation binding which preorganises the receptor for anion binding.

Ballester and co-workers investigated the bis(calix[4]pyrrole) macrocycles **21** (see also Section 2.2 for its use as the macrocycle component in rotaxane **23**) and **30** as tetratopic receptors

for binding dimers of ion-pairs (Figure 18).^[35a,d] The cation controlled both the mode and cooperativity of binding; receptor **21** bound two tetrabutylammonium chloride ion-pairs with positive cooperativity in the cascade binding mode (Figure 18a) but methyl trioctylammonium chloride ion-pairs bound as receptor separated ion-pairs with no cooperativity (Figure 18b).^[35a] When both tetrabutylammonium and methyl trioctylammonium chloride were present, hetero ion-pair dimers were bound with positive cooperativity as cascade complexes with the methyl trioctylammonium cation bound to the external calix[4]pyrrole binding site. The shape and size of the receptor's cavity also influenced the cooperativity since bent receptor **30** with a smaller cavity bound tetrabutylammonium chloride with no cooperativity as a cascade complex and methyl trioctylammonium chloride with negative cooperativity as receptor separated ion-pairs.^[35d]

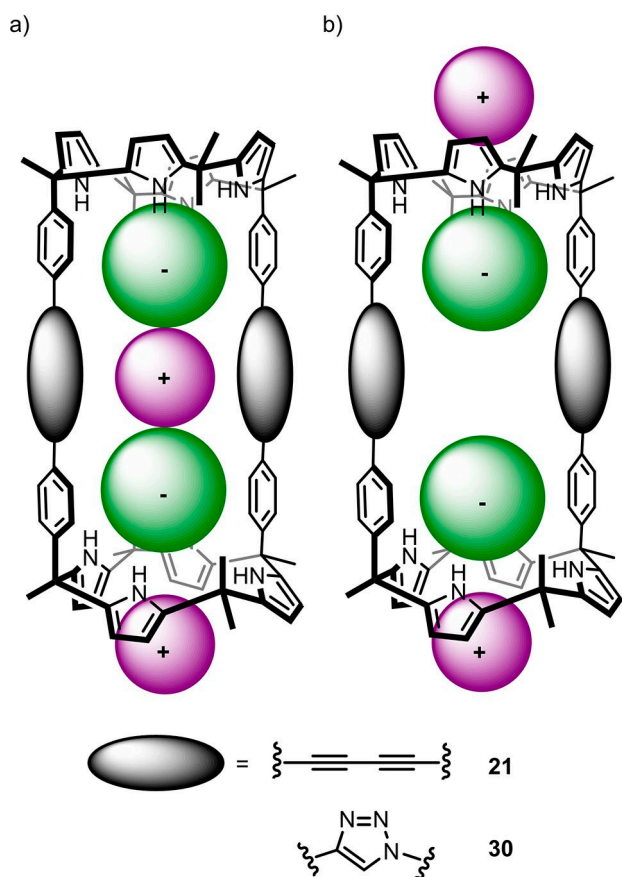


Figure 18. The a) cascade and b) receptor-separated binding modes in Ballester's tetratopic receptors 21 and 30.

4. Applications of Heteroditopic and Multitopic Receptors

Heteroditopic and multitopic receptors have several advantages over cation and anion monotopic receptors in applications. Firstly, cooperativity can be exploited to tune the ion-pair recognition properties for improved selectivity and secondly, the formation of an electrically neutral host-guest complex is advantageous for applications, such as solvent extraction and membrane transport.^[40] The ultimate goal is the rational design of a selective ion-pair receptor for a particular function in systems where other ions are present, often in large excess to the target ion-pair. This section will discuss progress and challenges associated with the translation of ion-pair recognition to applications.

4.1. Salt Extraction/Solubilisation Agents

During the last decade significant advances have been made in the application of ion-pair receptors as salt extraction and solubilisation agents. Importantly, the lattice energy of the target ion-pair is a determining factor in solid-liquid extraction, whereas receptor-ion-pair binding competes with hydration energies in aqueous liquid-organic phase liquid extraction.^[41]

The rational design of a salt extraction/solubilisation agent for a target ion-pair is challenging since the ion-pair binding affinity alone cannot be used to predict the extraction efficiency. For example, Romański and Piatek reported receptor 31 (Figure 19) extracts sodium nitrate in solid-liquid extraction experiments more efficiently than sodium acetate and chloride even though this ion-pair was bound the most weakly of the sodium salts in ion-pair binding studies.^[42] Furthermore, the extraction ability of the receptor was enhanced with a copolymer material 32 based on poly(butyl methacrylate); while the ion-pair receptor 31 alone could not extract sodium nitrate in liquid-liquid extraction studies, the increased lipophilicity of copolymer 32 strengthened ion-pair binding enabling extraction.^[42] Thus, not only the affinity of ion-pair binding but also the lipophilicity of the ion-pair/receptor complex and other

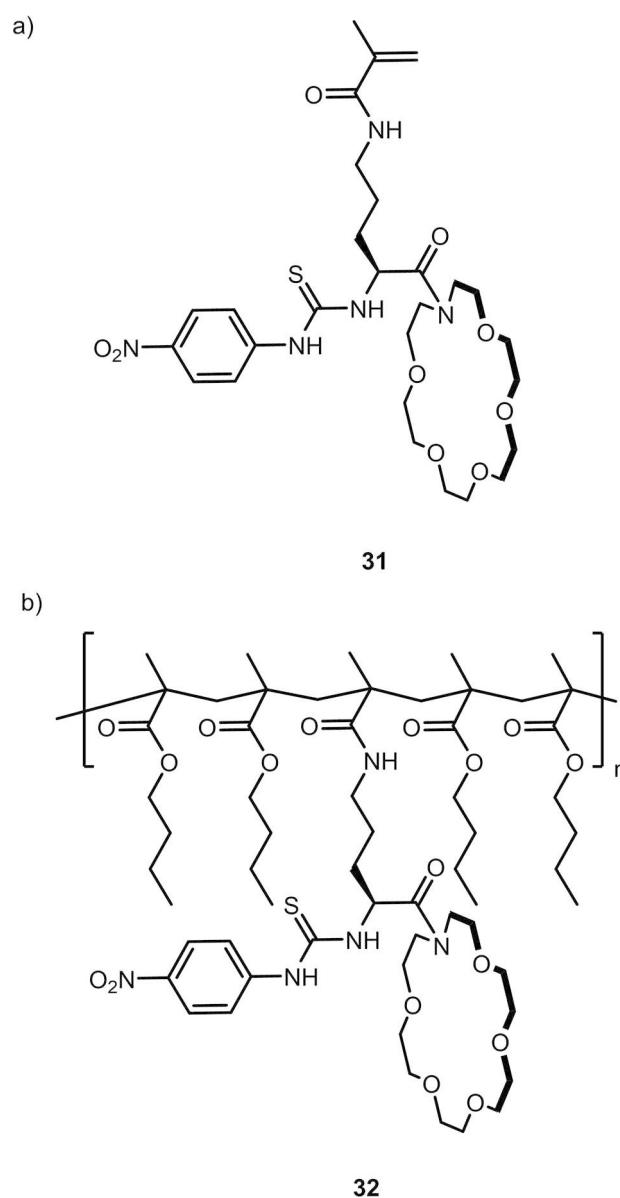


Figure 19. Romański and Piatek's a) ion-pair receptor 31 and b) copolymer 32 for the extraction of sodium nitrate.

factors like binding kinetics need to be taken into consideration in the design of a salt solubilisation/extraction agent.^[43]

A number of ion-pair receptors have been developed for the solid-liquid extraction^[38b,41] and liquid-liquid extraction^[11b,38,40,44] of alkali metal salts in particular. Lithium salts are important components in batteries, however, the world's lithium reserves are limited. The current major source of lithium is Bolivian salt flats where sodium and potassium salts are also present.^[38] Kim, Moyer, Sessler *et al.* reported a series of hemispherand calix[4]pyrrole based ion-pair receptors (Figure 20) where subtle changes to the hemispherand unit significantly altered extraction efficiency and selectivity.^[38] Receptor **33**, which also functions as a tritopic receptor for caesium carbonate (Section 3), extracted lithium nitrite selectively under both solid-liquid and liquid-liquid conditions in the presence of sodium and potassium nitrite.^[38a] However, it did not extract lithium chloride under liquid-liquid conditions,^[38b] attributed to a host-ion-pair guest size mismatch, as evidenced by X-ray crystal structures revealing lithium nitrite associated as a contact-ion-pair, whereas lithium chloride was bound as a water-bridged ion-pair.^[38] Reducing the cavity size with receptors **34** and **35** led to selective lithium chloride extraction over sodium and potassium chloride in solid-liquid extraction studies. Receptor **35** exhibited a relatively higher degree of selectivity in comparison to receptor **34**, enabling extraction of 200 ppm (by mass) lithium chloride in the presence of a large excess of sodium and potassium chloride.^[38b] In liquid-liquid

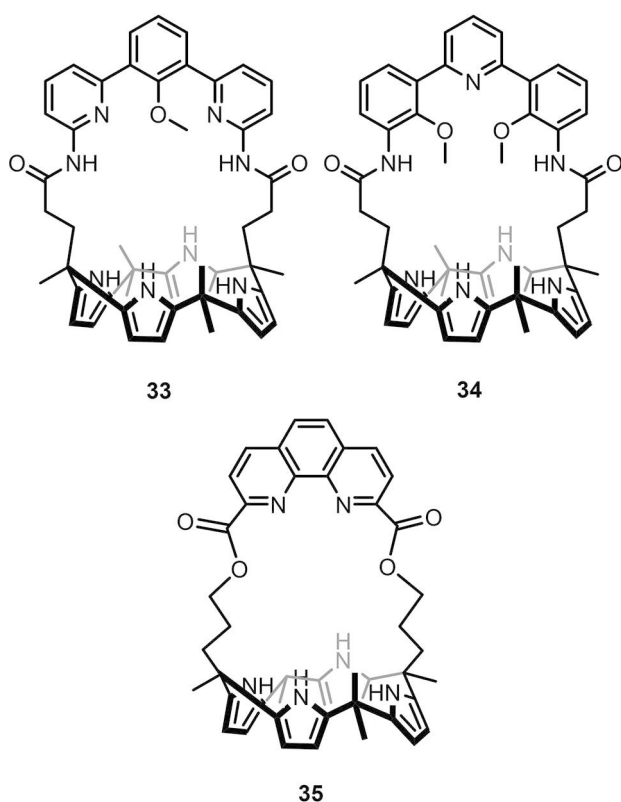


Figure 20. Kim, Moyer and Sessler's series of hemispherand calix[4]pyrrole based ion-pair receptors for the extraction of lithium salts under solid-liquid and liquid-liquid conditions.

extractions, **35** extracted lithium chloride with greater selectivity but lower efficiency than **34**.

The hierarchical self-assembly of ion-pair receptors into larger supramolecular architectures upon ion-pair binding can also influence extraction efficiencies and selectivities. An amphiphilic block copolymer appended with calix[4]pyrrole ion-pair receptors self-assembled into reverse micelles in dichloromethane and extracted ion-pairs such as caesium halide ion-pairs from the aqueous to the organic phase more effectively than the ion-pair receptor alone.^[45] Upon increasing amounts of the ion-pair, the amphiphilicity of the polymer increased and DLS confirmed the formation of larger aggregates.

Romański and co-workers reported receptor **36a** selectively extracts potassium sulfate from the aqueous phase into an organic phase, even when lipophilic anions such as nitrate are present (Figure 21).^[31] The selectivity was attributed to the formation of an organic soluble 4:1 receptor/ion-pair self-assembly in the presence of potassium sulfate as evidenced by ¹H NMR titrations, the crystal structure of the sodium sulfate analogue, DOSY NMR and DLS experiments. In contrast, other potassium salts with monovalent anions formed insoluble 1:1 complexes. Application as a potential sulfate anion transporter was proposed since the ion-pair was released following back extraction of a chloroform solution with water. Receptor **36b** with a nitro group proved to be an optical sensor for potassium sulfate where a naked eye colorimetric response was attributed to deprotonation of the squaramide by sulfate (Figure 21).

For recycling extraction applications, the functionalisation of polymeric beads with ion-pair receptors^[43] and cation^{[11b,33c]/ion-pair^[33d] metathesis have been investigated. The metathesis strategy exploits the presence of multiple binding sites with different affinities to exchange the cation or ion-pairs. For example, Hay, Kim, Moyer, Sessler *et al.* reported calix[4]crown strapped calix[4]pyrrole multitopic receptor **37** binds potassium nitrate as a contact ion-pair enabling extraction of this hydrophilic salt from D₂O into C₆D₅NO₂ (Scheme 2).^[33d] Potassium nitrate can be recovered by addition of a D₂O phase containing caesium perchlorate due to ion-pair metathesis; the caesium ion binds strongly to the crown-6 site with the perchlorate weakly associated and the displaced potassium nitrate partitions back into the aqueous phase. Similarly, replacement of the crown-6 with a crown-5 binding site changed the cation binding affinity so that extraction and recovery of caesium nitrate was driven by metathesis with potassium perchlorate.^[33c]}

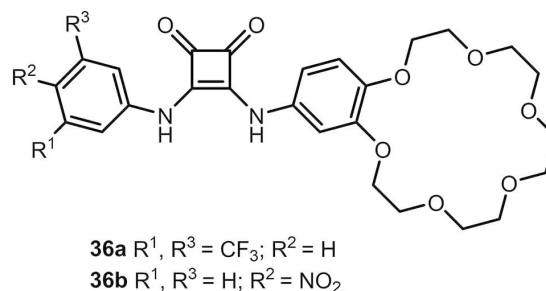
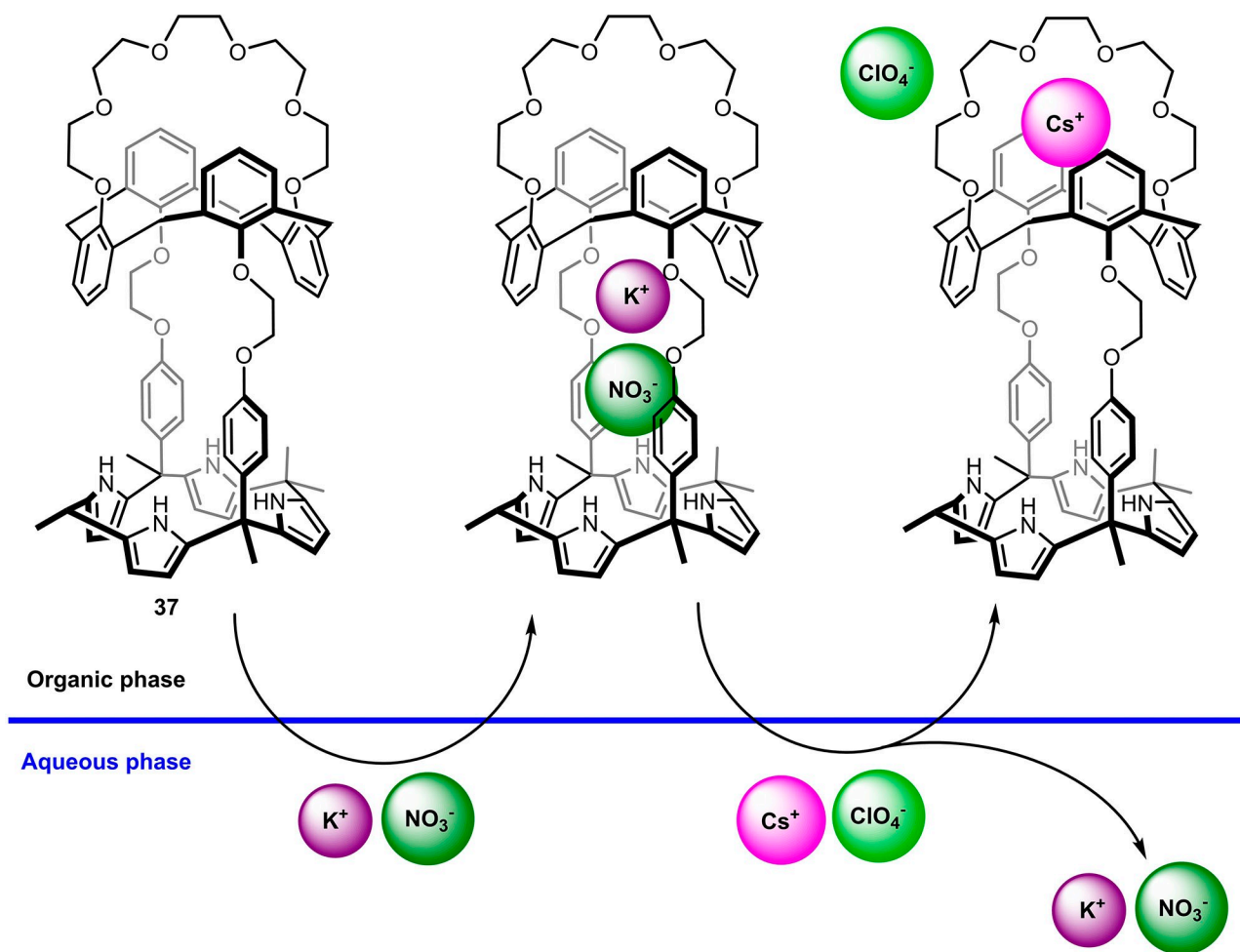


Figure 21. Romański's receptors for the extraction and sensing of potassium sulfate.

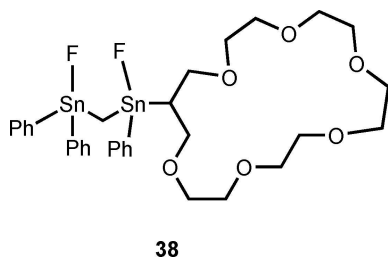


Scheme 2. Ion-pair metathesis reported by Hay, Kim, Moyer and Sessler for the extraction and release of potassium nitrate by receptor **37**.

4.2. Membrane Transport

Ion-pair receptors that function as salt extraction agents have also been investigated in membrane transport across lipid membranes^[46] or bulk liquid membranes in U-tube experiments.^[44,46d,47] For example, an analogue of receptor **31** in Figure 19 (Section 4.1) transported NaNO_2 between aqueous phases in a U-tube experiment through a liquid membrane of CHCl_3 .^[47]

Jurkschat *et al.* reported that organotin-based receptor **38** extracted and transported the highly hydrophilic KF salt through a CH_2Cl_2 bulk liquid membrane (Figure 22).^[44] At both



38

Figure 22. Jurkschat's organotin membrane transporter.

low and high concentrations of KF (0.37 M and 8.0 M, respectively), receptor **38** was a more efficient membrane transporter than a 1:1 mixture of the organotin and 18-crown-6 monotopic receptors; with an 8.0 M salt concentration in the source phase, 22.5% KF was transferred by the heteroditopic receptor **38** compared to only 8.7% for the mixture of the monotopic receptors.

Valkenier, Jabin and Bartik recently demonstrated the potential of calix[4]arene-based receptors to transport ion-pairs composed of biologically relevant cations like catecholamines and lysine; receptor **39** (Figure 23) transported primary ammonium chloride ion-pairs, such as PrNH_3Cl , into vesicles and across a bulk chloroform liquid membrane in a U-tube experiment.^[46d] Although membrane transport was driven by anion binding and occurred in the absence of a co-complexed cation, transport efficiency was demonstrated to be improved with the bound ion-pair.

4.3. Sensing

The development of chemosensors for ion-pairs necessitates the incorporation of a reporter group into the receptor design

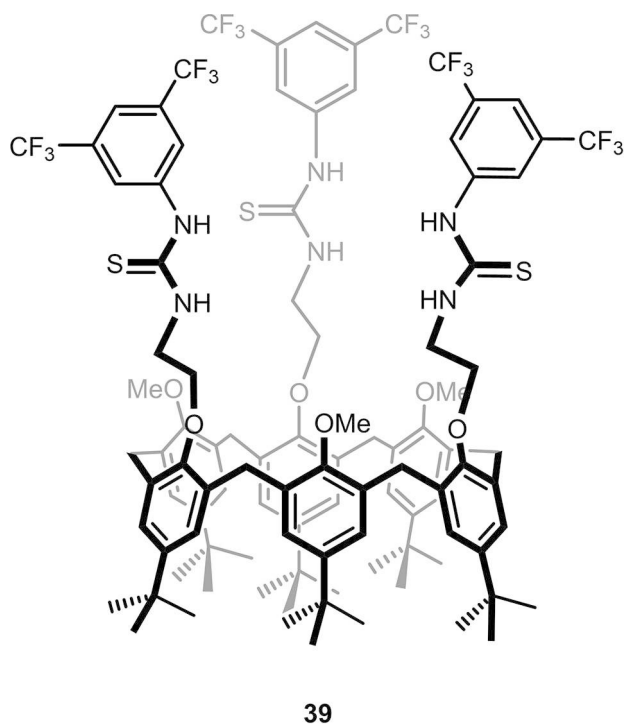


Figure 23. Valkenier, Jabin and Bartik's calix[6]arene tris(thio)urea based ion-pair receptor for membrane transport.

that changes its properties (e.g. optical or electrochemical) upon ion-pair binding. Ideally, such a chemosensor would display different responses for cation, anion and ion-pair binding. Ion-pair receptors functionalised with reporter groups such as BODIPY,^[48] pyrene,^[49] imidazoquinoxaline,^[50] and imidazobenzothiadiazole^[51] have been exploited for fluorescent sensing.

Solvent-free ion-pair recognition resulted from grinding receptor **40** (Figure 24a) as a solid with solid $\text{Zn}(\text{OAc})_2$ or $\text{Cd}(\text{OAc})_2$; ion-pair recognition was not only sensed by a 30–52 nm red-shift of the emission band but the two host-guest complexes could also be discriminated on the basis of their solid-state fluorescence.^[51] Furthermore, ion-pair binding solubilised the insoluble inorganic salts in organic solvents and $\text{Zn}(\text{OAc})_2$ could be selectively extracted into chloroform or diethyl ether in the presence of $\text{Cd}(\text{OAc})_2$. This was attributed to the higher affinity of the receptor for $\text{Zn}(\text{OAc})_2$ and the insolubility of the host-guest complex with $\text{Cd}(\text{OAc})_2$ in these organic solvents.

By combining multiple reporter groups into a single receptor, Tárraga and Molina reported a series of multichannel ion-pair receptors^[52] with redox-active ferrocene and fluorescent reporter groups for the electro-optical sensing of ion-pairs. Receptor **41** sensed the binding of Pb^{2+} and $\text{HP}_2\text{O}_7^{3-}$ through shifts of the receptor's Fc/Fc^+ redox couple, a naked-eye detectable colour change from yellow to green and quenching of the excimer emission band of the receptor/anion complex upon addition of the cation (Figure 24b).^[49b] Cooperative ion-pair recognition was observed for some multichannel receptors^[49c,d,50] and with some, demonstration of BOOLEAN

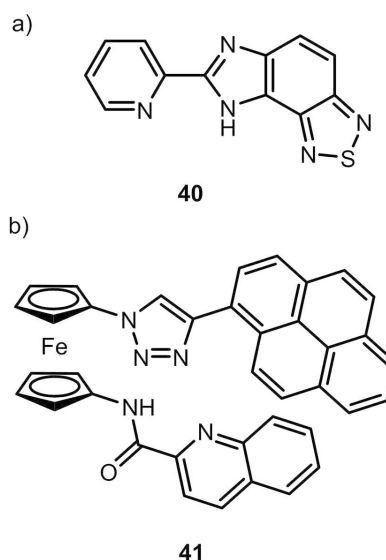


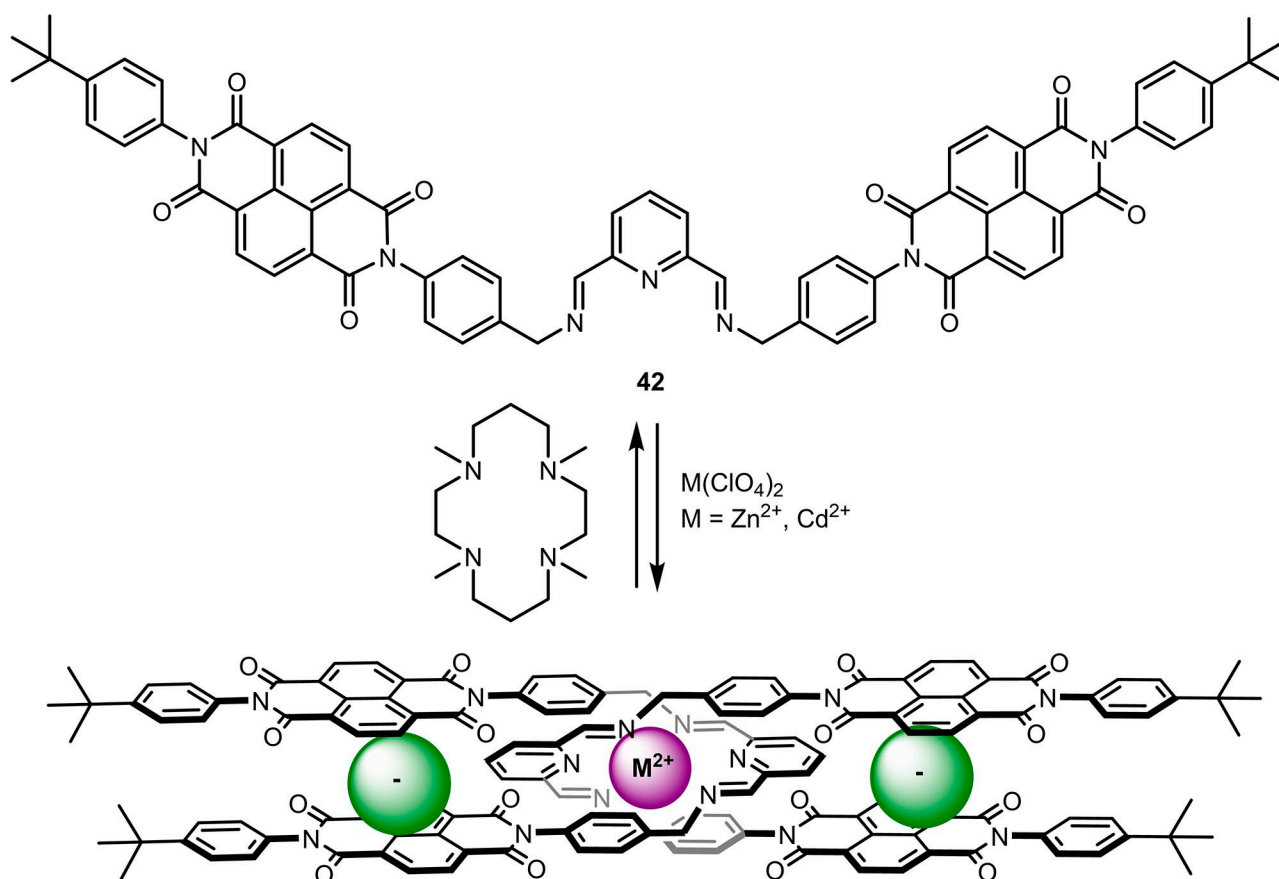
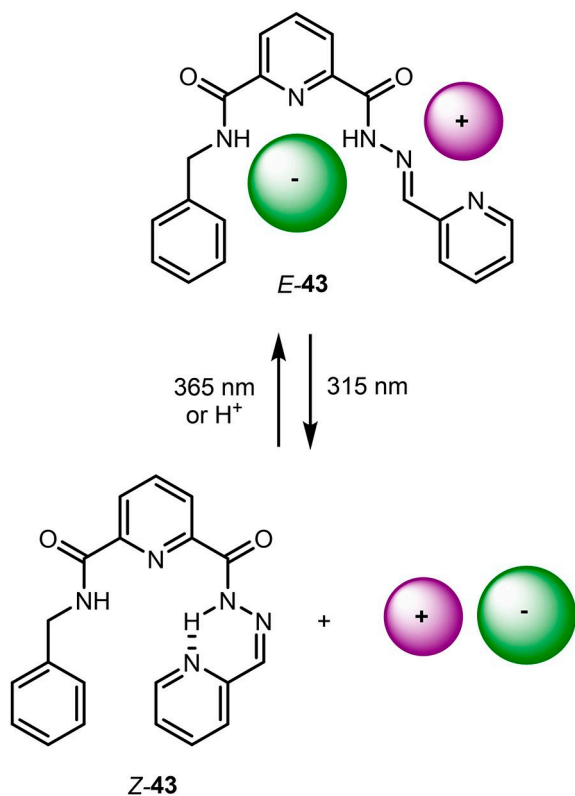
Figure 24. Tárraga and Molina's a) imidazobenzothiadiazole-based receptor **40** and b) multichannel ion-pair receptor **41**.

cooperative AND logic, where the receptor does not bind the "free" cation or anion but only binds the ion-pair when both the cation AND anion are present.^[50b,c]

4.4. Switchable Receptors

While strategies like cation/ion-pair metathesis (Section 4.1) have been developed to control ion-pair uptake, switchable receptors are appealing for the potential to reversibly turn ion-pair binding on and off. In one approach, Saha and co-workers exploited the relative binding affinities of ligands to reversibly bind MX_2 ($\text{M}=\text{Zn}^{\text{II}}$, Cd^{II} ; $\text{X}=\text{BF}_4^-$, OTf^- , ClO_4^-) ion-pairs with tridentate pyridyl imine Schiff base linked naphthalenediimide-based receptor **42** (Scheme 3).^[53] Satisfying the transition metal octahedral coordination requirements, two receptors complexed the metal cation guest which enabled two charge-diffuse anion to be sandwiched between the naphthalenediimide arms. Exploiting the macrocyclic effect, switching was achieved by addition of 1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecane (TACT) which released the free receptor.

Ion-pair binding and release can also be achieved through incorporation of a photoswitchable unit, however, this poses a design challenge since both binding sites for the cation and anion need to be simultaneously switched on or off. The first example of a photoswitchable ion-pair receptor was recently reported by Chmielewski *et al.* using acylhydrazone photo-switch receptor **43** (Scheme 4); in the *E*-configuration, the anion binds to the 2,6-pyridine bis-amide in the *syn-syn* conformation and the cation (alkali metal or ammonium cation) coordinates or hydrogen bonds to the 2-pyridyl acylhydrazone.^[54] Photoisomerisation with 315 nm light to the receptor *Z*-configuration renders the anion binding site inaccessible and weakens cation binding. Reversible but incomplete switching was observed upon irradiation with 365 nm light. Complete back-isomer-

Scheme 3. Saha's switchable receptor for MX_2 ion-pairs.

Scheme 4. Chmielewski's photoswitchable heteroditopic ion-pair receptor.

isation could be achieved, however, upon addition of acid. Although the field of photoswitchable ion-pair receptors is still very much in its infancy, this initial report demonstrates the proof-of-principle and paves the way for the design of new photoswitchable receptors.

5. Summary and Outlook

Evolving from the fields of cation and anion recognition, ion-pair recognition has become an established and highly active field in the last decade. The sophistication of receptor design has increased with the first examples of ion-pair receptors exploiting halogen and chalcogen bonding motifs, reports of mechanically bonded hosts and the extension from heteroditopic to multitopic binding. As the complexity of ion-pair receptors increases, so too does the difficulty of elucidating the contributions of the various equilibria involved in the overall recognition process, in terms of quantifying cooperativity and rationalising observed selectivity trends. Nevertheless, detailed binding studies of tetratopic receptors have already provided some insight towards the rational design of more complex cooperative ion-pair binding systems. Thus, the study of multitopic ion-pair receptors could also provide a greater understanding of cooperativity in not only synthetic but also natural systems.

Heteroditopic and multitopic receptors have been exploited in applications from salt solubilisation and extraction to sensing. There has already been early success in the development of receptors for the extraction of highly hydrophilic salts, solubilisation of salts with high lattice energies and membrane transport of ion-pairs with biological relevance. Furthermore, strategies like ion-pair metathesis and incorporation of photo-switchable motifs have been developed for releasing the bound ion-pairs to regenerate the free receptor. While significant progress has already been made, the challenge of the rational design of receptors with tailored properties for the recognition of a target ion-pair for a specific application remains unmet, as well as the translation from fundamental studies to proof-of-concept studies under “real-world” conditions.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: ion pairing · macrocycles · molecular recognition · receptors · supramolecular chemistry

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