Selective Recognition of Quaternary Ammonium Cations

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Selective recognition of ammonium cations fundamentally relies on their degree of substitution. In biological systems, proteins can preferentially bind more substituted ammonium cations over less substituted homologues. To date, a general methodology to mimic this behavior remains elusive as synthetic hosts principally observe the inverse order (i.e., 1°>2°>3°>4°). Here we show that, through combining supramolecular recognition with solid-phase abstraction, we can overturn the canonical order of synthetic receptor selectivity across a diverse range of ammonium cation scaffolds. Quaternary ammonium cations access a lower energy solid-state than tertiary counterparts through multipoint binding to an adaptive array of isostructural BINOL·counterion networks. The preferential abstraction of quaternary ammonium cations from mixtures of homologous cations proceeds under thermodynamic control with excellent selectivity and remains operative even under aqueous conditions.

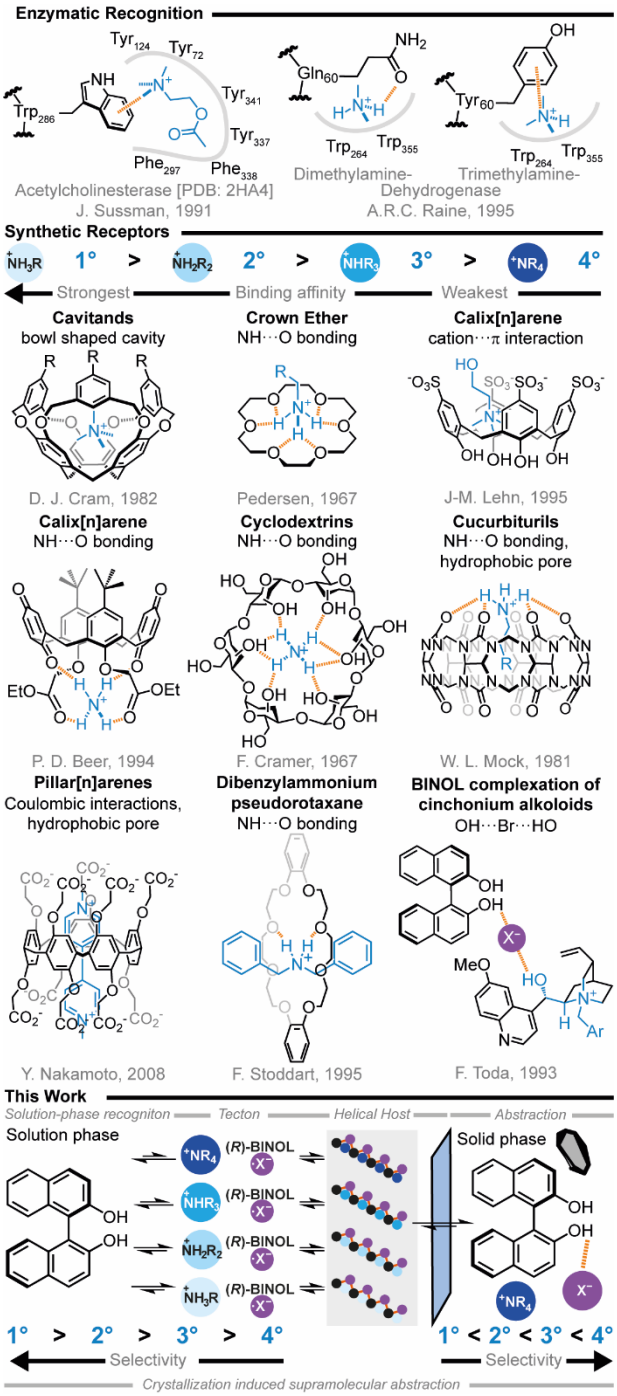

Figure 1 – Ammonium cation recognition and synthetic receptor selectivity.

Biological receptors selectively bind key nitrogen-containing signaling molecules based on their level of substitution. The action of small neurotransmitters such as dopamine, arginine and acetylcholine (Ach) is mediated by this selective ammonium cation recognition.[1] In enzymes such as trimethylamine dehydrogenase and dimethylamine dehydrogenase, a simple substitution in the active site (Gln60 to Tyr60) changes the cation selectivity from favoring the secondary dimethylammonium cation to the more substituted tertiary trimethylammonium cation.[2] Quaternary ammonium cations can also act as stronger inhibitors when in the presence of less substituted analogues, for example the tetraethylammonium cation (Et_4NH^+) inhibits the action of the K^+ ion channel (Kv1.5) more strongly than its tertiary counterpart (Et_3NH^+).[3] To achieve the high levels of discrimination observed in ammonium cation recognition, Nature has produced, via evolution, highly structured yet flexible hydrophobic binding cavities capable of forming multiple interactions in protein tertiary structures.

In efforts to emulate this selectivity, the field of supramolecular chemistry has made remarkable advances in the design of host moieties with direct non-covalent interactions to guest substrates. Seminal work by Cram, Pedersen and Lehn exploited host molecular shape and strong directional interactions in the development of complex recognition systems.[4–6] Subsequently, a number of synthetic ammonium recognition moieties were developed, including calixarenes,[7–11] cucurbiturils,[12–14] cyclodextrins,[15–18] and pillarenes (**Fig 1**).[19,20] These systems have proven crucial in the development of mechanically interlocked molecules and molecular devices through the positional control this powerful recognition affords.[21,22] However, due to the superior hydrogen bond donor ability for less substituted ammonium cations (α parameters: Et_3NH^+ = 4.8, Et_4N^+ = 2.7),[23] and the strength of cation–π interactions (Me_3NH^+ = 15.9 kcal mol^{-1}, Me_4N^+ = 9.5 kcal mol^{-1} – with benzene),[24] all supramolecular recognition units that rely on strong directional interactions preferentially bind less substituted ammonium cation homologues. Although a limited number of systems have been designed to recognize specialized guest substrates, relying on the use of multiple functional handles or predetermined covalent molecular geometry,[25–32] never has a general methodology been developed that allows quaternary ammonium cations to be selectively recognized over less substituted homologues.[9,11,29,33–36]

To realize a general method for quaternary ammonium cation recognition we reasoned that recognition principles from both natural and synthetic binding environments could be combined, through taking advantage of the solid crystalline state (**Figure 1**). Firstly, solution-based recognition of an ammonium cation allows the formation of a ternary complex that can serve as a supramolecular tecton. The formation of this supramolecular tecton can take advantage of strong directional interactions as commonly applied in synthetic recognition processes. Secondly, this supramolecular tecton can form extended assemblies through the generation of concatenated chains. These self-assembled superstructures are highly flexible and can present a variety of binding architectures, acting as supramolecular hosts for a range of ammonium cation guests. Thirdly, abstraction of these networks to the solid phase provides a structured and hydrophobic binding environment into which an ammonium cation guest may reside. Here, multipoint binding to the cation acts to stabilize the self-assembled superstructure generating a more stable system when the quaternary ammonium cation is present. Finally, ensuring that these functional hydrogen bonded networks are equilibrating under thermodynamic control allows for selection of the more substituted ammonium cation over its less substituted congeners. We hypothesized that the recognition of quaternary ammonium salts by (*R*)-BINOL, previously employed for enantiodiscrimination between *N*-stereocenters,[37] could be utilized to overturn the more energetically demanding discrimination between differentially substituted cations by fulfilling these criteria.

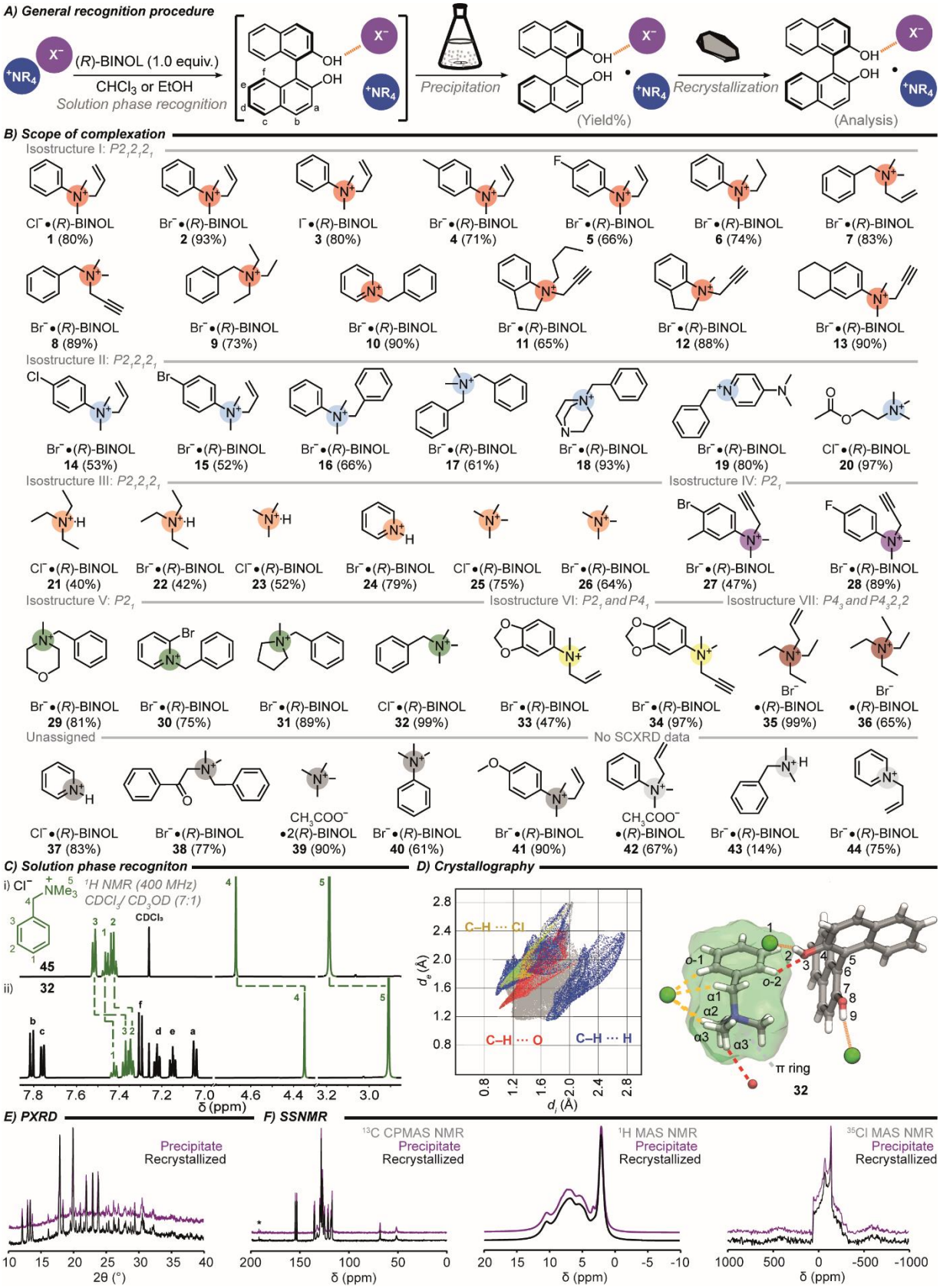

Figure 2 – A) General recognition procedure. **B**) Recognition of ammonium cations with (*R*)-BINOL ordered by isostructure formed. **C**) ^{1}H NMR stack plot of **45** with and without (*R*)-BINOL in $CDCl_3$:CD_3OD (7:1). **D**) Colored Hirshfeld plot of the ammonium cation interactions within the crystal structure **32** and a render of key contacts. **E**) PXRD (Cu radiation, λ = 1.54056 Å) plots of crystallized and precipitated material **32**. **F**) Overlaid ^{13}C SSNMR

(^{13}C CPMAS NMR, 500 MHz, ν = 8 kHz), ^{1}H SSNMR (^{1}H MAS NMR, 400 MHz, ν = 40 kHz) and ^{35}Cl SSNMR (^{35}Cl MAS NMR, 400 MHz, ν = 20 kHz) spectra of precipitated and crystallized forms of **32**.

A large and diverse range of ammonium salts derived from commonly used amines and heterocycles can be abstracted from solution to the solid phase through simple combination with (*R*)-1,1′-bi-2-naphthol ((*R*)-BINOL) (**Figure 2A & 2B**). Methylation, allylation, propargylation and benzylation of several tertiary amine and pyridine substrates produced quaternary ammonium salts which could undergo complexation with (*R*)-BINOL. These microcrystalline solids form without the presence of any additional functional handles on the ammonium cation core. Protonation to form tertiary ammonium salts also provided suitable substrates for recognition, showing flexibility in the supramolecular behavior. To probe the origin of this recognition, ^{1}H NMR spectroscopy titration experiments were conducted. Upon addition of (*R*)-BINOL (1.0 equiv.) to a sample of **45** in a mixture of $CDCl_3$:CD_3OD (7:1) significant upfield shifts of benzylic and methyl protons (**Figure 2C,** labeled H^4 and H^5 respectively) were observed, consistent with ternary complex formation generating the supramolecular tecton. When conducted under suitable conditions ($CHCl_3$ or EtOH, 0.4–2.0 M), these solution-phase interactions manifest as a solid-phase abstraction of the ternary complex through self-assembly of supramolecular tectonic units. The nature of the anionic counterion proves crucial to this recognition process. While the use of halogen and acetate counterions promotes supramolecular tecton formation through a hydrogen bonding recognition event, exchange to a non-coordinating hexafluorophosphate anion (PF_6^-) inhibits supramolecular tecton formation.

To understand the interactions responsible for the self-assembly of the supramolecular tectons into crystalline hosts, single crystals of each complex were grown and analyzed by single crystal X-ray diffraction (SCXRD). Each SCXRD structure confirmed the existence of a continuous hydrogen bonding network between the anionic counterion and the hydroxyl functionalities of (*R*)-BINOL (**Figure 2D**, **32**, $C_2^1(9)$, $d_{1\text{-}3}$ = 3.005 Å and $d_{8\text{-}1}$ = 3.038 Å, helix repeat length = 9.845 Å) responsible for the formation of the helical host structure.[38] In addition, multiple interactions between the ammonium cation and this helix were identified. In the SCXRD of **32**, short C–H···Cl contacts from α-carbon protons ($d_{\alpha1}$ = 2.741 Å, $\theta_{\alpha1}$ = 144.74°, $d_{\alpha2}$ = 2.813 Å, $\theta_{\alpha2}$ = 149.30°, $d_{\alpha3}$ = 2.870 Å, $\theta_{\alpha3}$ = 146.32°) and an *ortho* proton of the benzyl ring ($d_{o\text{-}1}$ = 2.8431 Å, $\theta_{o\text{-}1}$ = 153.12°) were observed alongside C–H···O interactions from an α-carbon proton ($d_{\alpha3`}$ = 2.483 Å, $\theta_{\alpha3`}$ = 152.45°) and a further *ortho*-benzyl proton ($d_{o\text{-}2}$ = 2.456 Å, $\theta_{o\text{-}2}$ = 140.21°). Additionally, a cation···π interaction from the charged N^+ center to the centroid of a phenolic ring of (*R*)-BINOL (d = 4.331 Å) is present. The comparative significance of contacts present in the crystal structure can be illustrated on a Hirshfeld fingerprint plot (**Figure 2D**). The sharp C–H···O (red, **Figure 2D**) and C–H···Cl (yellow, **Figure 2D**) areas of the plot exemplify the interactions observed in the crystal structure analysis of **32**. These results are consistent with multiple, weak interactions from the cationic guest acting to stabilize the assembly of the supramolecular tectonic units in the crystalline helical host.

To validate that SCXRD analysis pertaining to the host crystalline network can be propagated to the material precipitated from the reaction mixture, **32** was prepared by both precipitation and crystallization and characterized by powder X-ray diffraction (PXRD) and solid-state NMR (SSNMR) spectroscopy (**Figure 2E & 2F**). A comparison of the two PXRD patterns (**Figure 2E**) reveals that both the precipitated and crystallized forms of **32** are indistinguishable, with the same reflections observed. Solid-state ^{1}H magic-angle spinning (MAS) NMR, ^{13}C CPMAS NMR and ^{35}Cl MAS NMR spectra (**Figure 2F. & SI Figure 14.1–14.10**) obtained for both forms of **32**, corroborate that the ^{1}H, ^{13}C and ^{35}Cl local environments are alike in both samples (**Figure 2F**). Irrespective of the method of preparation (precipitation or recrystallization), identical material is produced.

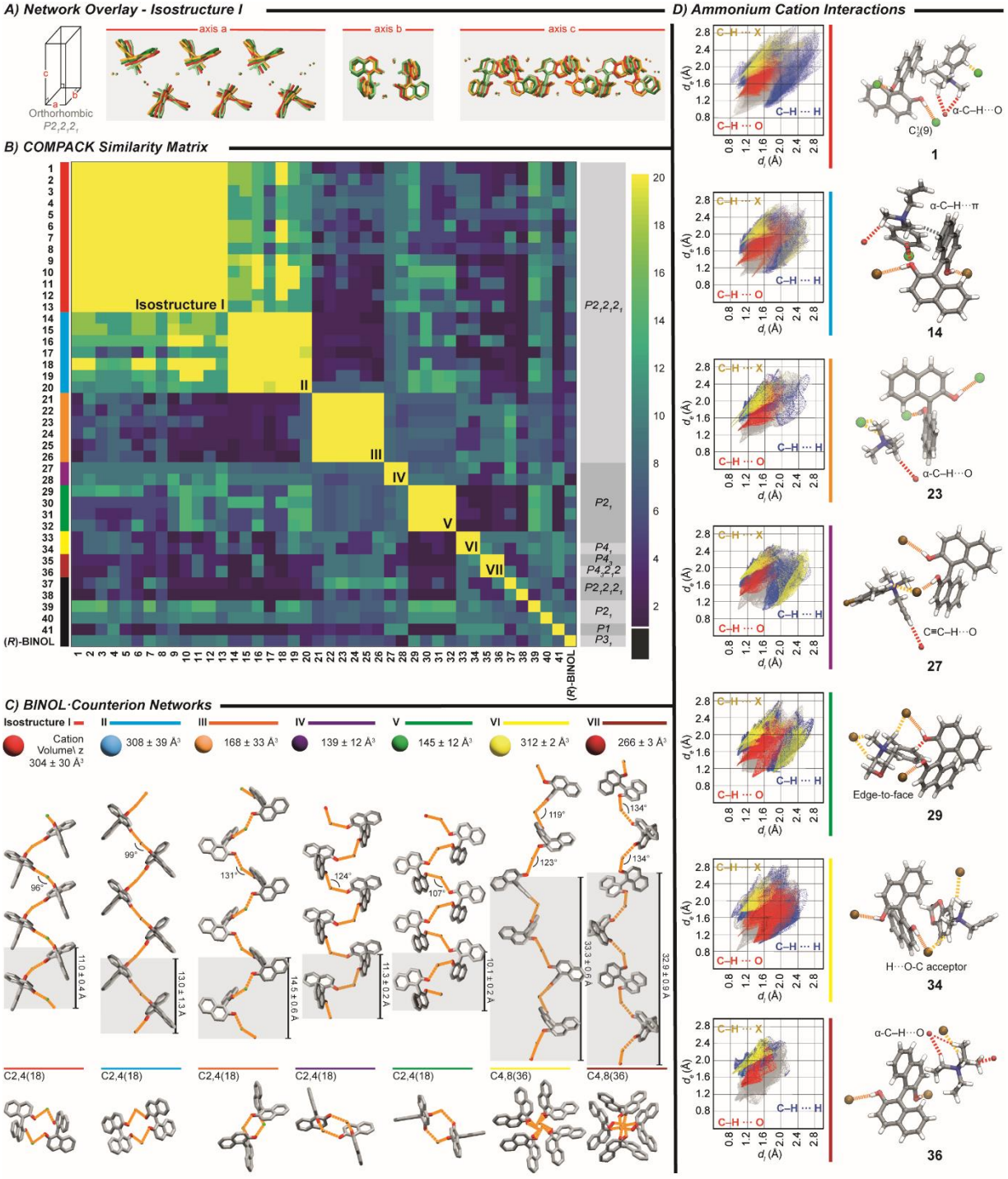

Figure 3 – A) Overlays of the BINOL·counterion network for **1**–**4**. **B**) Heatmap matrix showing the COMPACK similarity score between crystal structures. Isostructures are color coded throughout the figure. The (*R*)-BINOL crystal structure was obtained from the CSD with code WANNII.[39] **C**) The assembly of the (*R*)-BINOL·counterion networks in each isostructure. **D**) Colored, overlaid, composite Hirshfeld plots for each isostructure and significant contacts that the ammonium cation can make to each isostructure.

Global analysis of the SCXRD data reveals that a variety of helical crystalline hosts are created by supramolecular tecton self-assembly. All SCXRD structure combinations (**1**–**41**) were subject to an *in-silico* COMPACK analysis (see **SI** for details) generating a structure similarity score to establish packing isostructurality (**Figure 3A, B**).[40] This comparison revealed 12 distinct helical arrangements across the 41 structures analyzed and identified 7 isostructural families generated from differing ammonium cations whilst retaining the same helical host. Each member of an isostructural host family has an almost identical arrangement of (*R*)-BINOL and counterion participating in a $C_2^1(9)$ hydrogen bond chain (**Figure 3A**). Outside of these isostructural families, the helical host structure displayed additional flexibility. In the case of **39**, the hydrogen bonding network was further extended through incorporation of an acetate counterion into the helix affording a $C_2^2(11)$ hydrogen bond chain. Alternatively, in **38** the ammonium cation itself can bridge the helical arrangement through the carbonyl functionality and acidic α-C–H bonds present. In all cases a helical repeat was observed. In contrast, stark differences between the isostructural hosts are readily apparent. The flexible nature of the assembly of the helical host generates a wide range of helix repeat lengths (9.84–33.90 Å) and recognized ammonium cation volumes (140–312 Å^3) that can adapt to accommodate a diverse range of ammonium cation guests (**Figure 3C**). This adaptability of the crystalline host allows a wide variety of recognition environments to be displayed to the ammonium cations enhancing its ability to sequester a diverse range of guests, without requiring any additional functionality to be present.

To interrogate interactions between the guests and self-assembled supramolecular hosts across packing isostructures, composite Hirshfeld fingerprint plots were created (**Figure 3D**). Composite plots were made by mapping the interactions of ammonium cations with their (*R*)-BINOL·counterion network on a 3D surface and visualizing them as their own 2D Hirshfeld fingerprint plots. By coloring the specific interactions and overlaying the plots with others defined to be in the same isostructure, these overlaid Hirshfeld plots were made to illustrate the dominant interactions between ammonium cations and the host network within each isostructure. Through interpretation of these plots and inspection of crystal structures, ammonium cation features that select for given superstructures can be rationalized. In all cases there is a relatively strong C–H···O interaction, depicted by a pointed red area on the composite plots. This corresponds to at least one α-C–H···O hydrogen bond between the ammonium cation guests and the (*R*)-BINOL network being present and is the main criteria required for isostructure I. This interaction is also seen in isostructure II, but the supramolecular recognition varies in that it must additionally incorporate a C–H···π interaction between the ammonium cation and the (*R*)-BINOL network. Isostructure III encapsulates the smallest cations via forming several C–H···O and C–H···X contacts, whereas isostructure IV contains cations from the library which form propargylic C–H···O hydrogen bonds and in isostructure V there are aromatic (edge to face) interactions which allow the guests shown to interact with multiple (*R*)-BINOL units. A methylene dioxy functionality is commonly present as a hydrogen bond acceptor in cations observed to stabilize isostructure VI and in isostructure VII two ammonium cations are seen to be bridged, non-continuously, by a counter-anion. These observations are consistent with the formation of the isostructural host family being dictated through distinct multipoint interaction patterns made between the ammonium cation and the (*R*)-BINOL derived helical host.

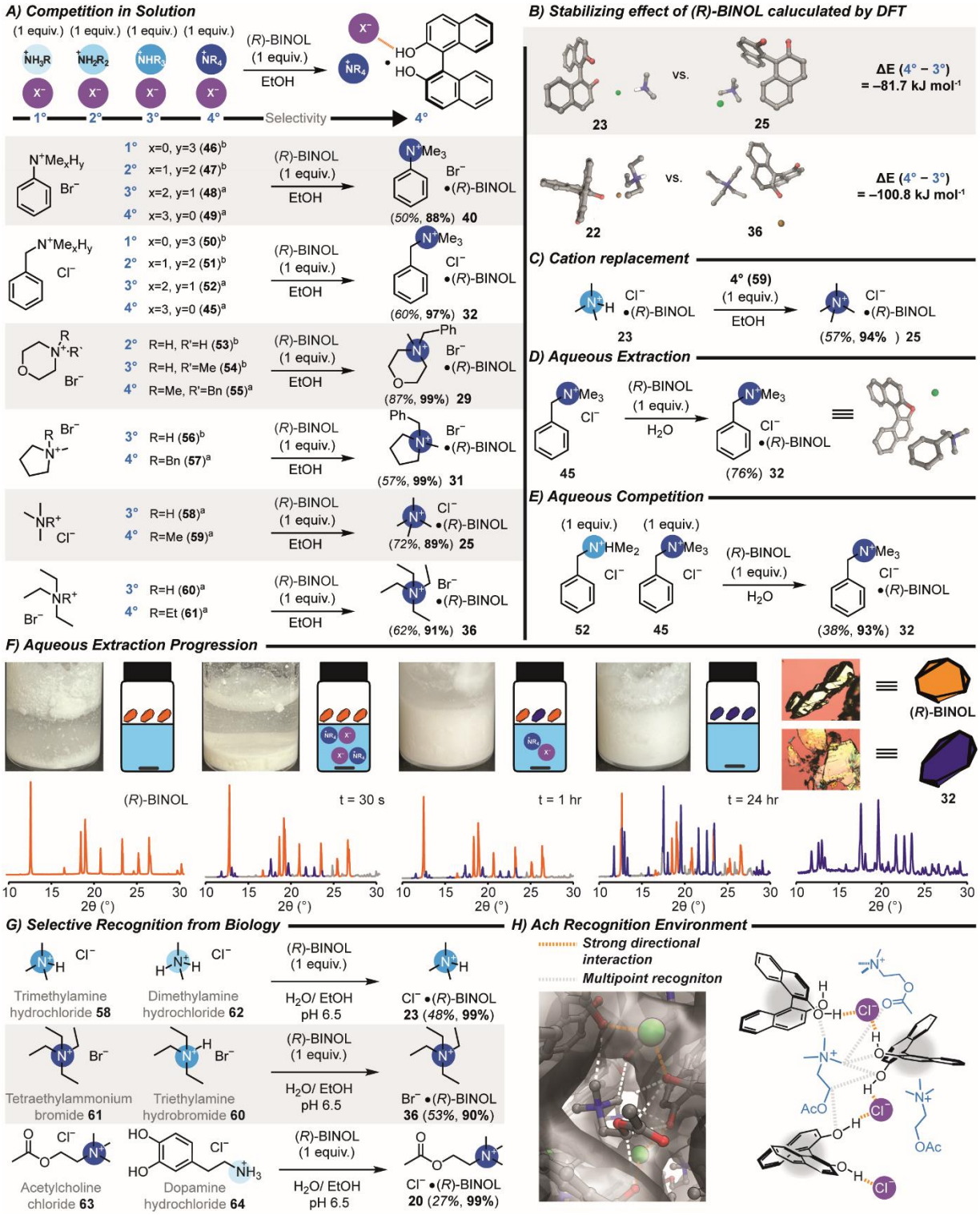

Figure 4 – A) Selectivity experiments between varyingly substituted analogues of ammonium cations (*Yield*%, Selectivity%). **B**) DFT calculated energy differences of the stabilizing effect of (*R*)-BINOL of homologous tertiary and quaternary complexes. **C**) Slurry exchange from tertiary complex **23** to quaternary complex **25**. **D**) Aqueous extraction of quaternary ammonium salt **45**. **E**) Aqueous competition to bind quaternary ammonium salt **45** (*Yield*%, Selectivity%). **F**) Pictures and graphical representations of (*R*)-BINOL stirred with aqueous media containing **45** over varying time periods and PXRD patterns showing the composition of the solid transforms from pure (*R*)-BINOL to increasing prevalence of **32** over time. Pictures of the single crystals of pure **32** and (*R*)-

BINOL are used to depict the morphological differences. **G**) Selective recognition of biologically relevant molecules from a mixture of less substituted congeners. **H**) Analysis of the crystalline hosts recognition environment in **20**, the gray surface represents the QuickSurf calculated isosurface of the helical host of **20**, strong directional interactions are labelled orange, interactions of Ach to the helix are shown in light gray.

Quaternary ammonium salts selectively form ternary complexes with (*R*)-BINOL when in competition with a mixture of primary, secondary and tertiary ammonium salts (**Figure 4A**). Here, the selective abstraction of several analogous ammonium species from solution proceeds with the reverse selectivity than that observed by Pedersen, Cram and Lehn and is at odds with what would be expected if selectivity were to be predicted by hydrogen bond donor ability. The self-assembled host encapsulates more highly substituted cations into a lower energy superstructure than with less substituted homologues, independent of the isostructure accessed. The melting points of homologous methylammonium complexes (**23** = 219 °C, **25** = 316–317 °C) and ethylammonium complexes (**22** = 198 °C, **36** = 251–252 °C) are consistent with quaternary ammonium cation complexes proving more stable than complexes containing the less substituted congener. To probe the origin of this difference in complex stability, density functional theory (DFT) calculations using the PBE functional[41] and Grimme-D3 dispersion correction[42] (**Figure 4B** & **eSI Section 17.1**)[41–46] were used to calculate the stabilizing effect of (*R*)-BINOL by comparing the energy difference between the crystal structure and the tertiary or quaternary salt per asymmetric unit. Calculations on complexes **23** and **25** from isostructure IV reveal that (*R*)-BINOL stabilizes the quaternary tetramethyl-ammonium cation more than the analogous tertiary cation complex by 81.7 kJ mol^{-1}. The same observation is true for corresponding ammonium cations from different isostructural hosts as calculations confirm that the stabilizing effect of (*R*)-BINOL for the tetraethyl variant **36** (isostructure VII) is 100.8 kJ mol^{-1} lower in energy than for the homologous $Et_3N^+HBr^-$ complex **22** (isostructure IV). Experimental evidence additionally confirms the supramolecular solid-phase abstraction process operates under thermodynamic control. When tertiary ammonium complex **23** is vigorously stirred with a closely related quaternary ammonium analogue ($Me_4N^+Cl^-$, **59**) for 72 hours, the solid is converted to quaternary ammonium complex **25** (**Figure 4C**). As the system does not require specific non-covalent interactions to be present but instead relies on multipoint binding to a spontaneously generated host, the canonical synthetic receptor selectivity is overturned.

The same complexation phenomenon remains functional in water. By simply mixing (*R*)-BINOL with aqueous media containing **45**, the quaternary ammonium salt is sequestered in the form of **32** (**Figure 4D**). Despite having limited solubility in water, the solid can sequester **45** as **32** with increasing yield over time (**Figure 4F**), as seen by PXRD through the increase in the prevalence of **32** versus that of (*R*)-BINOL and the change in solid morphology. Competition between **52** and **45** in water selectively yields **32** (93% selectivity, **Figure 4E**). Not only is the hydrogen bonded network functional in an aqueous environment but it remains highly selective towards the quaternary ammonium salt versus its less substituted congener.

To test the robustness of our process we sought to reproduce the selective recognition of more substituted ammonium cations observed in Nature.[1–3] The selective binding of the more substituted tertiary trimethylammonium cation in trimethylamine dehydrogenase, the K^+ ion channels recognition of the tetraethyl ammonium cation, and the discrimination between neurotransmitters such as dopamine and Ach can all be emulated by our (*R*)-BINOL-based recognition procedure (**Figure 4G**). Addition of (*R*)-BINOL (1 equiv.) to a mixture of trimethyl ammonium hydrochloride (**58**) (1 equiv.) and dimethyl ammonium hydrochloride (**62**) (1 equiv.) in EtOH:H_2O (9:1) solution yielded the crystalline **23** in excellent yield and almost complete selectivity. Similarly, tetraethylammonium bromide (**61**) and triethylammonium hydrobromide (**60**) could be differentiated by our system, efficiently extracting the more substituted cation as **36**. Finally, competition of the neurotransmitters acetylcholine chloride (**63**) and dopamine hydrochloride (**64**) for inclusion in the supramolecular host, after aqueous washing to remove co-precipitated uncomplexed salts, yielded exclusively **20**. Interrogation of the host-guest

complex **20** reveals that the strong directional interactions made between (*R*)-BINOL and chloride counterion act to encapsulate the Ach cation into a favorable recognition environment via providing multipoint interactions to the guest (**Figure 4F**). By exploiting this strong directionality common to synthetic systems, the host can self-assemble to provide a multipoint recognition environment delivering the same selectivity observed in the natural world.

In summary, by combining the recognition principles operative in natural and synthetic binding environments a system under thermodynamic control can be accessed in which more substituted ammonium cations can be selectively recognized. Here, the cations form ternary complexes with (*R*)-BINOL which acts as a supramolecular tecton in solution. These tectons self-assemble into a dynamic and flexible hydrogen bonded network of (*R*)-BINOL and counterion. Subsequently the host complex is abstracted into the solid phase in the form of a crystalline helical host. The isostructure of the host that encapsulates ammonium cations adapts to provide a suitable multipoint recognition environment. Quaternary ammonium cation complexes access a lower energy solid-state than less substituted salts and are selectively abstracted from solution. Our system overturns the long-standing selectivity based on hydrogen bonding ability and cation–π interaction strength and competitively abstracts more substituted quaternary ammonium cations, even under aqueous conditions and from complex mixtures of biologically relevant molecules. With these advantages demonstrated, we hope that continued exploration of the solid state as a supramolecular host will lead to further unprecedented behavior in contrast to chemistry in the solution state.

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Supplementary Materials

Experimental Specifications (**eSI section 1**), General Procedures (**eSI section 2 to 6**), NMR spectra (**eSI section 7 to 13**), PXRD and Solid-State NMR spectra (**eSI section 14**), Crystallographic Data (**eSI section 15**) and Computational calculations (**eSI section 16**).