Directed Phase Transfer of a Fe$^{II}_4$L$_4$ Cage and Encapsulated Cargo

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Supporting Information Placeholder

ABSTRACT: Supramolecular capsules can now be prepared with a wide range of volumes and geometries. Consequently, many of these capsules encapsulate guests selectively by size and shape, an important design feature for separations. To successfully address practical separations problems, however, a guest cannot simply be isolated from its environment; the molecular cargo must be removed to a separate physical space. Here we demonstrate that a Fe$^{II}_4$L$_4$ coordination cage **1** can transport a cargo spontaneously and quantitatively from water across a phase boundary and into an ionic liquid layer. This process is triggered by an anion exchange from **1**[SO$_4$] to **1**[BF$_4$]. Upon undergoing a second anion exchange, from **1**[BF$_4$] to **1**[SO$_4$], the cage – together with its encapsulated guest – can then be manipulated back into a water layer. Furthermore, we demonstrate the selective phase transfer of cationic cages to separate a mixture of two cages and their respective cargos. We envisage that supramolecular technologies based upon these concepts could ultimately be employed to carry out separations of industrially relevant compounds.

This study explores the idea of using coordination cages[1-14] to transport guests across a phase boundary, with the ultimate aim of addressing practical separations problems. Because these cages are not charge neutral,[15-20] they derive properties from both cation and anion. Counterions have previously been shown to play a significant role in the stability,[21-24] shape,[25-35] solubility,[36] and other physicochemical properties[37,38] of coordination cages. We further demonstrate in this work that exchanging cage counterions can drive spontaneous and quantitative transport of cages from water across a phase boundary and into an ionic liquid.[39-41] In an advance over cation transport driven by anionic phase transfer catalysts,[42,43] our strategy allows the simultaneous transfer of selectively-bound guest molecules. To the best of our knowledge, ours is the first example of the directed transport of cages and their cargoes between two liquid phases.

When cage **1** (Figure 1) is prepared as the SO$_4$$^{2-}$ salt, the complex is soluble in water.[36] Paired with fluorinated anions (triflate or BF$_4$$^-$), however, **1** becomes insoluble in water. This feature allows the design of a system in which cationic cage **1** can be transported between liquid phases, as shown in Figure 1. Having previously demonstrated that coordination cages can be soluble and stable in ionic liquids,[44] we now utilize the hydrophobic ionic liquid 1-hexyl-3-methylimidazolium tetrafluoroborate ([hmim][BF$_4$])[45,46] as both a salt to supply BF$_4$$^-$ anions and as a solvent to act as a receiving phase for **1**[BF$_4$]. Furthermore, by exchanging the BF$_4$$^-$ counterion for SO$_4$$^{2-}$, we can ultimately manipulate cage **1** back into its original aqueous environment.

Because our use of non-deuterated [hmim][BF$_4$] in this study rendered challenging the use of ^{1}H NMR techniques to observe cage peaks in ionic solution, we used ^{19}F NMR to track an encapsulated, fluorinated guest throughout each step of the cycle in Figure 1. The guest was chosen to be 1-fluoroadamantane because it binds strongly and exchanges slowly within cage **1** in water, [hmim][BF$_4$], and acetonitrile. In water, no measurable uptake of 1-fluoroadamantane was observed by ^{19}F NMR within the first three hours after adding the guest (SI Section 5.5). Two weeks of stirring at 273 K were required for the host-guest complex to approach equilibrium. While the equilibration of 1-fluoroadamantane $\subset$ **1** was more rapid in acetonitrile (taking three days), no measurable uptake of guest was observed by ^{19}F NMR within the first 45 min after guest addition (SI Section 5.3). By comparison, each step in the cycle presented in Figure 1 takes less than 15 min to complete. Because 1-fluoroadamantane $\subset$ **1** equilibrates slowly, and because 1-fluoroadamantane is poorly soluble in water, any free 1-fluoroadamantane peaks in the ^{19}F NMR may therefore be inferred to result from release of the encapsulated guest upon decomposition of the cage. We used the integration of the ^{19}F peak assigned to encapsulated 1-fluoroadamantane to gauge the amount of intact cage carried forward in each step of the cycle.

An aqueous solution of **1**[SO$_4$] (2.0 mM) was allowed to equilibrate with 1-fluoroadamantane (15 equiv.) for two weeks at 293 K. The resulting solution was then filtered to remove any unencapsulated, non-dissolved 1-fluoroadamantane (Figure 1a). Upon the addition of hydrophobic [hmim][BF$_4$] (1.0 mL) to 1-fluoroadamantane $\subset$ **1**[SO$_4$] in water (2.0 mM, 1.0 mL), an ionic liquid layer formed beneath the existing water layer (Figure 1b). Because cage **1**[BF$_4$] is insoluble in water, the cage rapidly underwent anion exchange from **1**[SO$_4$] to **1**[BF$_4$], with **1**[BF$_4$] partitioning into the ionic liquid layer upon shaking (Figure 1c; SI Video 1), leaving the water layer colorless. The presence of a ^{19}F NMR peak from free 1-fluoroadamantane (–126.71 ppm) in the ionic liquid layer indicated that a small portion of cage decomposed upon being transferred from the water into the ionic liquid layer. Nevertheless, 97% of 1-fluoroadamantane $\subset$ **1** (-120.79 ppm) remained intact (SI Section 6.2). The ^{1}H and ^{19}F

NMR spectra of the residual D₂O layer (SI Section 6.2) revealed no 1-fluoroadamantane ⊂ **1** remaining in this layer. The stability of the cage throughout transport from D₂O to [hmim][BF₄] was further confirmed by UV-Vis spectroscopy (SI Section 6.3).
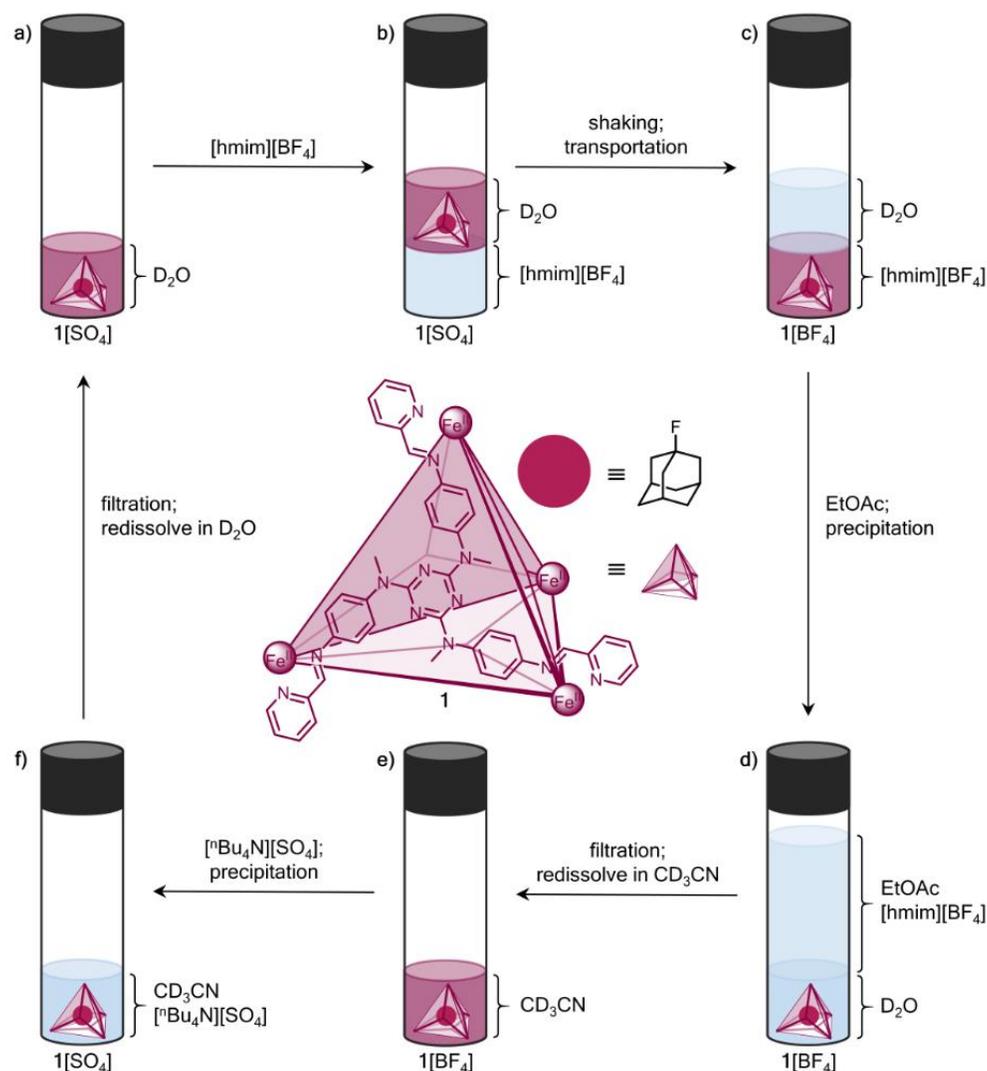

Figure 1. a) 1-Fluoroadamantane ⊂ **1**[SO₄] dissolved in water. b) Addition of [hmim][BF₄]. c) Upon shaking, 1-fluoroadamantane ⊂ **1** transferred from the water to the ionic liquid layer. d) Upon addition of EtOAc, 1-fluoroadamantane ⊂ **1**[BF₄] was filtered off and redissolved in CD₃CN. e) Upon addition of [ⁿBu₄N][SO₄], 1-fluoroadamantane ⊂ **1**[SO₄] precipitated. f) Solid 1-fluoroadamantane ⊂ **1**[SO₄] was filtered off and redissolved in water, completing the cycle.

To manipulate cage **1** back into water, a second anion exchange – to convert **1**[BF₄] back into **1**[SO₄] – is required. Before this conversion may be accomplished, however, **1**[BF₄] must be isolated from the ionic liquid layer. This was done by adding ethyl acetate (10 mL) to the water/ionic liquid biphasic system. The ethyl acetate mixed with [hmim][BF₄], thus lowering the solubility of **1**[BF₄] in the organic/ionic liquid layer, and caused it to precipitate from solution (Figure 1d). Precipitated cage **1**[BF₄] was then isolated *via* filtration, washed thoroughly with ethyl acetate (18 × 5 mL) to remove residual ionic liquid, and redissolved in deuterated acetonitrile (1.0 mL), as shown in Figure 1e. The ¹⁹F NMR spectrum of 1-fluoroadamantane ⊂ **1**[BF₄] in CD₃CN (-120.17 ppm) indicated that 74% of the cage from the previous step remained intact (SI Section 6.4), and no peak for free 1-fluoroadamantane was observed. This observation was con-

firmed by ¹H NMR. After **1**[BF₄] was dissolved in acetonitrile, acetonitrile-soluble tetrabutylammonium sulfate was added (50% in water, 4.8 equiv.) to convert **1**[BF₄] back into **1**[SO₄]. Anion exchange again caused the cage to precipitate from solution (Figure 1f). Precipitated **1**[SO₄] was then isolated *via* filtration, washed with diethyl ether (3 × 1 mL) to remove residual ionic liquid, and redissolved in water (Figure 1a). The ¹⁹F NMR spectrum of 1-fluoroadamantane ⊂ **1**[SO₄] in D₂O (-120.42 ppm) indicated that 72% of cage from the previous step remained intact (SI Section 6.5). This final step thus closes the transport cycle of **1** from water, to an ionic liquid, and finally back to water.

The specific transport cycle outlined in Figure 1 is not the only possible manifestation of this concept; both the ionic liquid and the cage can be systematically modified. Since [hmim][BF₄] is known to be susceptible to hydrolysis, an

ionic liquid that is more compatible with water can instead be chosen. 1-Ethyl-3-methylimidazolium triflimide ([emim][NTf₂]), for example, is a hydrophobic ionic liquid that is more stable to hydrolysis than [hmim][BF₄]. We have previously shown that [emim][NTf₂] is a good solvent for the fluorinated analog of **1**, synthesized with fluorinated sub-component **C** instead of **B** (Figure 2). This fluorinated cage cannot be used for inter-phase transport, however, as it is insoluble in water. Neither can **1** be transported into [emim][NTf₂] – it is insoluble in this ionic liquid and precipitated out of both phases upon anion exchange from **1**[SO₄] to **1**[NTf₂]. We found, however, that the physicochemical properties of the cage can be tuned by incorporating both **B** and **C**. Combining 4 equivalents of **A** with 6 equivalents each of subcomponents **B** and **C**, we obtained a mixture of cages **2**[SO₄], which is soluble in both water and [emim][NTf₂]. The preparation of **2** thus highlights the utility of subcomponent self-assembly in preparing materials with tunable properties – solubility, in the present case. The library of cages **2**[SO₄] acted in concert to bind 1-fluoroadamantane and were readily transported together from water into the ionic liquid layer upon addition of [emim][NTf₂]. We anticipate that this strategy will be applicable to adapting other cationic, water-soluble cages for directed phase transfer.
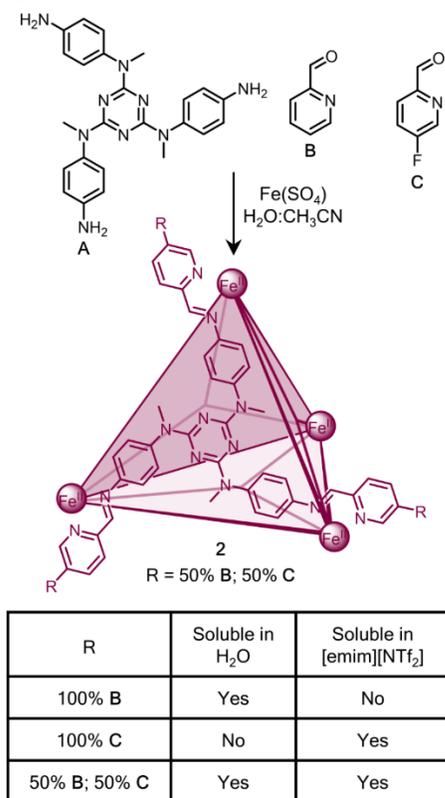

R	Soluble in H₂O	Soluble in [emim][NTf₂]
100% B	Yes	No
100% C	No	Yes
50% B; 50% C	Yes	Yes

Figure 2. Cage **1** composed of 12 equivalents of **B** is soluble in water but insoluble in [emim][NTf₂]; an analogous cage composed of 12 equivalents of **C** is soluble in [emim][NTf₂] but insoluble in water; mixed cages **2**, prepared from 6 equivalents of **B** and 6 equivalents of **C** is soluble in both [emim][NTf₂] and water.

The cycle described above (Figure 1) is enabled by counteranion exchange of a cationic coordination cage. If, however-

er, a cage has an overall negative charge, transport from water to an ionic liquid would necessarily be driven by exchange of the cage's countercations. When hydrophobic imidazolium ionic liquids [hmim][BF₄] or [emim][NTf₂] are added to an aqueous solution of anionic cage [Me₄N]**3** (Figure 3),[47] however, no transition from water to the ionic liquid is observed. While these ionic liquids are only slightly soluble in water, the combination of anionic cage and imidazolium cation yields a water-soluble salt. This feature allowed the design of the system of Figure 3, in which an aqueous mixture of two different cages (**2**[SO₄] and [Me₄N]**3**) were separated, thereby also separating a mixture of two different encapsulated guests.

An aliquot of 1-fluorobenzene ⊂ [Me₄N]**3** (0.7 mL, 2.0 mM) in D₂O was thus added to an aliquot of 1-fluoroadamantane ⊂ **2**[SO₄] (0.7 mL, 2.0 mM) in D₂O (Figure 3a). ¹H and ¹⁹F NMR confirm that these host-guest complexes were stable in solution together (SI Section 7.1).
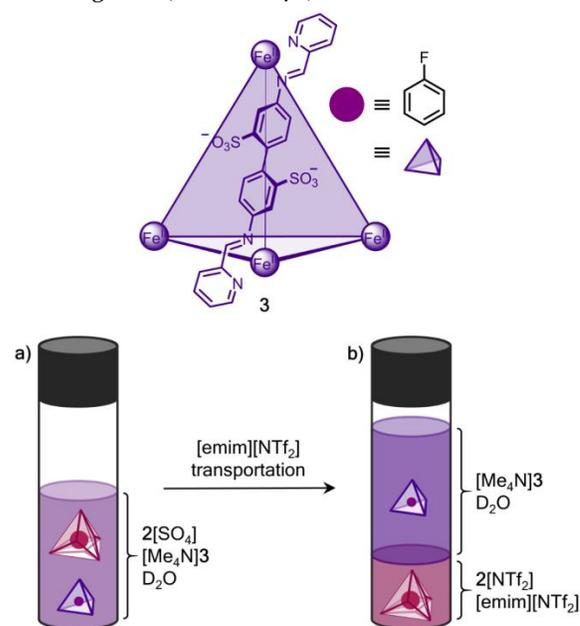

Figure 3. a) 1-Fluoroadamantane ⊂ **2**[SO₄] and 1-fluorobenzene ⊂ [Me₄N]**3** dissolved in water. b) Upon the addition of [emim][NTf₂], 1-fluoroadamantane ⊂ **2** transferred from the water to the ionic liquid layer, whereas 1-fluorobenzene ⊂ [Me₄N]**3** remained dissolved in water.

To this aqueous mixture of host-guest complexes, [emim][NTf₂] (1.4 mL) was added, initiating the transport of 1-fluoroadamantane ⊂ **1** from the water to the ionic liquid layer (Figure 3b). By measuring the ¹⁹F NMR spectra of the resulting water and ionic liquid layers, we observed clean separation of each cage into a different phase: 1-fluorobenzene ⊂ [Me₄N]**3** was found exclusively in the water layer, and 1-fluoroadamantane ⊂ **2**[NTf₂] was found exclusively in the ionic liquid. No peak for encapsulated 1-fluoroadamantane was observed in the ¹⁹F NMR of the water layer, wherein the ¹⁹F NMR signal from 1-fluorobenzene ⊂ [Me₄N]**3** remained unchanged. Likewise, no peak for 1-fluorobenzene ⊂ [Me₄N]**3** was observed in the ionic liquid layer. In the ionic liquid layer, 1-fluoroadamatane was released from **2**[NTf₂] after the addition of triflic acid (SI Section 8). Phase transfer of cation-

3

ic cage **2** thus rendered straightforward the clean separation of two physicochemically similar host-guest complexes.

This study demonstrates that anion exchange is capable of driving the transport of cationic cages between two liquid phases. Such transport thus provides a new mechanism to separate physicochemically similar cages and cargoes. Added layers of complexity may be envisaged, involving the introduction of further solvent layers and cages with varying solvent preferences. This work thus adds to our understanding of how supramolecular capsules may contribute to solving practical separations problems.[48-50] Ultimately, supramolecular capsules could provide an energy-efficient alternative to thermal separations,[51] with different cages selectively encapsulating hydrocarbons of different sizes,[52-56] in complimentary fashion to the means by which different fractions are separated by boiling point through distillation.

ASSOCIATED CONTENT

Supporting Information

Synthetic procedures and characterization for cages **1**[SO$_4$], **1**[BF$_4$], **2**[SO$_4$], [Me$_4$N]**3**, and related subcomponents, if applicable. Synthetic procedures for ionic liquids [hmim][BF$_4$] and [emim][NTf$_2$]. Guest uptake kinetics measured for 1-fluoroadamantane $\subset$ **1**[SO$_4$] in water; 1-fluoroadamantane $\subset$ **1**[BF$_4$] in acetonitrile. Experimental details of transport cycle represented in Figure 1; characterization of Figure 1a, 1c, and 1e. Experimental details of separation represented in Figure 3; characterization of 3a and 3b. (PDF)

Video depicting transport in Figure 1a-c. (AVI)

This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interests.

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