Ionic liquids as novel guests for cucurbit[6]uril in neutral water†

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Cucurbit[6]uril was dissolved through encapsulation of an imidazolium-based ionic liquid guest in a pure water environment and the dissolution ability could be tuned by augmenting the imidazolium structure.

Cucurbit[6]uril (CB[6]) is a member of the CB[*n*] family and has gained wide acceptance as an excellent host for a range of guests possessing both hydrophobic and cationic regions. Several non-covalent interactions contribute to this selective host–guest interaction, including hydrogen-bonding, ion–dipole and the hydrophobic effect.[1–3] However, a major drawback which has traditionally limited the application of CB[6] is its poor solubility in virtually any solvent other than strong acids. Thus, the seminal quantitative binding studies carried out by Mock *et al*. in the 1980s employed HCO_2H/H_2O (1 : 1) as the solvent.[4] Subsequently, Buschmann reported its ability to bind alkali and alkaline–earth cations in water.[2] And finally when Kim and co-workers reported the solubilization of CB[6] in aqueous saline solutions,[5] the full importance of studying guest binding in neutral water was realized.

Ionic liquids (IL) are attractive solvents enabling the solubility of a wide range of substrates and have versatile applications ranging from purely academic research interests to industrial applications.[6] While there are several types of ILs, 1-alkyl-3-methylimidazolium ([$C_n$mim]X) cations are among the most prevalent.[7,8] We would like to report that a variety of imidazoliums are uniquely poised to solubilize CB[6] in neutral water and differ from other ILs such as tetra-alkyl ammonium salts which are incapable of binding to CB[6].[9] There are several structural elements in the class of [$C_n$mim]X which facilitate the aqueous solubility of CB[6]. These include a beneficial interaction between the alkyl tail on the imidazolium and hydrophobic cavity of the host, and in our opinion, more importantly, the flexibility imparted to ion–dipole interactions between the carbonyl-laced CB[6] portals and the imidazolium cations which are delocalized over ~2.5 Å between the 1,3-orientation of two nitrogen atoms. This is illustrated in Fig. 1, where the flexible ion–dipole interaction can compensate for different lengths of the hydrophobic tail. In contrast to metal salts or buffers, the structure and counter ion of the alkyl imidazolium ILs could easily be modified in order to study these effects on the water solubility of CB[6] under neutral conditions. Herein we report that alkyl chain length dictates both the relative binding affinity and stoichiometry of the [$C_n$mim]X ⊂ CB[6] host–guest complex. Additionally, complexation imparts a UV absorption signal to the optically transparent IL.[10]

^{1}H NMR titration experiments were performed in neutral D_2O in order to investigate the dissolution ability of the ionic liquid guest with CB[6]. Experimentally, this was accomplished by gradually decreasing the mole ratio of the guest with a constant amount of CB[6] in 0.6 mL of deuterated solvent at room temperature. Although CB[6] itself is sparingly soluble in water (0.018 mM),[11] it quickly dissolves as complexation occurs. A small difference in size of alkyl chain length, highlighted by the following two ILs: 1-ethyl-3-methylimidazolium bromide ([C_2mim]Br) and 1-butyl-3-methylimidazolium bromide ([C_4mim]Br), leads to two different types of binding phenomena. This can be seen in Fig. 2, as [C_2mim]Br exhibits fast exchange on the NMR time scale with only one set of guest peaks being observed. On the contrary, [C_4mim]Br is in slow exchange and both bound and free guests are seen.

Besides the appearance of CB[6] signals in the ^{1}H NMR spectra, changes in chemical shifts for the IL guests indicate the specific location of the imidazolium ring inside the CB[6] portal region. This indicates the "flexibility" of the ion–dipole interaction and corresponding penetration depth of the variable alkyl chains inside the cavity. Commonly, an upfield shift is observed for protons that lie within the cavity of a hydrophobic guest such as CB[*n*]. For the ^{1}H NMR titration experiments, when the IL employed has a relatively short alkyl chain, such as ethyl ([C_2mim]Br), the signals corresponding to protons H_e and H_f in Fig. 2a exhibited an upfield shift

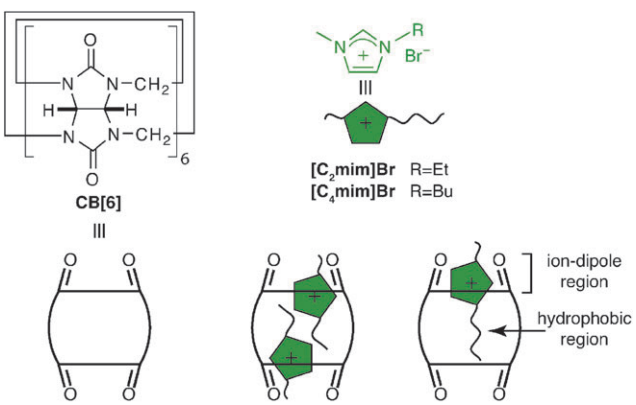

Fig. 1 Cucurbit[6]uril and different binding models with 1-alkyl-3-methylimidazoliums.

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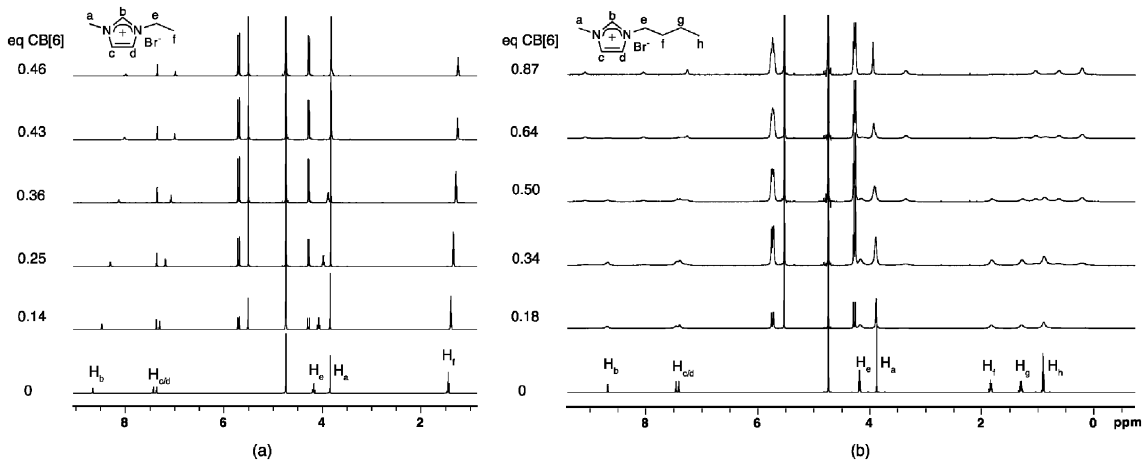

Fig. 2 Two series of ^{1}H NMR stack plots of CB[6] and IL in D_2O at the ratios of 0, 0.2, 0.4, 0.6, 0.8, 1.0 from bottom to top. (a) 1-ethyl-3-methylimidazolium bromide, (b) 1-butyl-3-methylimidazolium bromide.

suggesting that the ethyl chain was situated completely inside the hydrophobic cavity. The imidazolium protons, H_b and H_d also show an upfield shift suggesting that they are located within a shielded environment. The last imidazolium proton, H_c, does not show any shift and likely exists just at the interface between the shielding hydrophobic cavity and the deshielding, polarizable carbonyl portals of the CB[6]. This suggests that the delocalized cation on the imidazolium ring is well-located to interact with the carbonyl groups through charge–dipole interactions. Lastly, the unchanged chemical shift arising from H_a, suggests that the methyl group lies just outside the CB[6] portal and is completely excluded from the host.

When the alkyl chain is elongated by two additional methylene units into a butyl group, the ^{1}H NMR spectra (Fig. 2b) indicate a characteristic slow exchange phenomenon in which both 'free' and 'bound' guests exist in solution. An upfield shift of 0.83 ppm, 0.79 ppm, 0.68 ppm and 0.70 ppm for the butyl chain protons of H_e, H_f, H_g and H_h, respectively, was observed, indicating that these protons are in the cavity of CB[6]. Meanwhile, a downfield shift of 0.39 ppm and 0.58 ppm for protons of H_b and H_c, respectively, was observed, suggesting that they were in the deshielding region of the carbonyls. All the chemical shift changes indicate a completely encapsulated butyl chain with only a limited cavity penetration of the imidazolium ring. The imidazolium ring is certainly not as deeply penetrated as in the case with an ethyl chain. Additionally, as [C_4mim]Br exhibits slow exchange, it was possible to estimate a lower limit for the formation constant of the host–guest complex to be $\geq 1.7 \times 10^5$ M^{-1}, by directly integrating the signals for free and bound guest in the ^{1}H NMR spectra.[5]

During the course of our NMR investigations, it became clear that the appearance of complexed CB[6] solutions differed with respect to alkyl chain length of the IL, while aqueous solutions of both [C_2mim]Br and [C_4mim]Br look optically identical and are transparent. Therefore, UV-visible experiments were carried out in an effort to explain this difference. As depicted in Fig. 3, absorbance traces a and b are identical and represent solutions of [C_2mim]Br and [C_4mim]Br, respectively. These are in agreement with previous reports on the optical transparency of ionic liquids.[10] However, upon addition of an equivalent amount of CB[6] to these solutions, a significant increase in the absorbance (λ_{max} = 280 nm) was observed for both ILs. This UV signal originates from a perturbation of the system reflected by a change with HOMO–LUMO gap, and it is currently being investigated. Fig. 4 shows two sets of vials filled with aqueous solutions of [C_2mim]Br and [C_4mim]Br with CB[6] at different host–guest ratios. The top row clearly shows that complete solubility of CB[6] takes place at a 1 : 2 ratio with [C_2mim]Br. Conversely, the bottom series indicates that [C_4mim]Br is able to solubilize the host at a ratio of 1 : 1 and there is no significant difference in solution appearance as more guest is available for binding. This is also confirmed by UV-visible spectroscopy,[2,3,12–15] as the ratio of molar absorption coefficients is 1.69 ($\varepsilon_{ethyl}/\varepsilon_{butyl}$), indicating that twice as many UV active units are present inside CB[6] with [C_2mim]Br than with [C_4mim]Br at the same molar equivalents. The deviation from a ratio of exactly 2.0 can be accounted for from the higher binding affinity of [C_4mim]Br. It is worth mentioning that changing the counter ion from Br^- to BF_4^- did not change the results of the NMR or UV-visible experiments; however, the use of BF_4^- as a counter ion proved useful when Job plots were constructed.

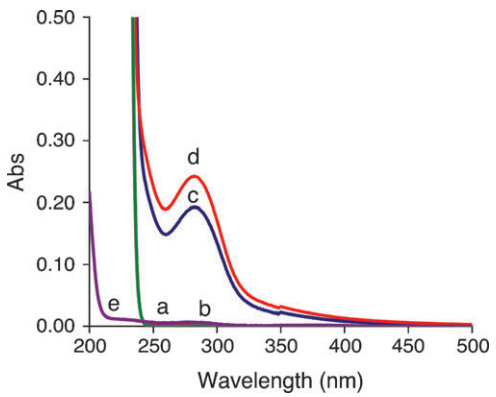

Fig. 3 UV-visible spectra of 8.3 mM [$C_n$mim]Br in H_2O without and with CB[6] (a) [C_2mim]Br; (b) [C_4mim]Br; (c) [C_2mim]Br $\subset$ CB[6];[16] (d) [C_4mim]Br $\subset$ CB[6];[16] (e) CB[6].

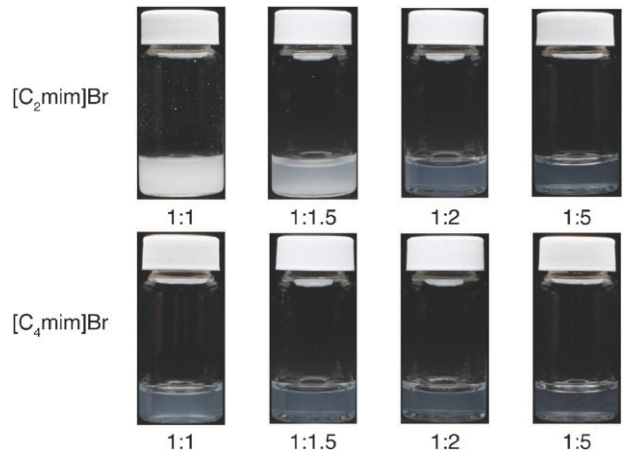

Fig. 4 A series of aqueous solutions depicting CB[6] solubility at various CB[6]:[$C_n$mim]Br ratios.

While a clear UV signal could be attributed to the [$C_n$mim]X $\subset$ CB[6] complexation, it was not possible to construct a Job Plot using UV-visible techniques as the total concentration of CB[6] and guest was continuously changing. Therefore, carefully integrated, very dilute (83 to 8.3 mM of guest) ^{1}H NMR titrations proved to be a better approach for understanding binding stoichiometries for the two ILs. A Job Plot (see electronic supplementary information†) revealed a maximum centered at 0.33 = [Host]/([Host] + [Guest]) for ethyl which clearly indicates 1 : 2 stoichiometry between the host and the guest. Previously, 1 : 2 stoichiometry has been demonstrated for caesium ions complexed to the portals of CB[6].[17] Additionally, 1 : 2 portal-type binding was observed for the catalyzed synthesis of triazole inside CB[6].[18] On the other hand, a 1 : 1 stoichiometry was observed for the slow exchange system [C_4mim]Br complexed with CB[6], this was concluded from the simple integration of 'bound' guest and CB[6] in the ^{1}H NMR spectra. This difference in stoichiometry could also be quantified by direct NMR integration for both systems. For example, when an equivalent amount of CB[6] was added to an 8.3 mM solution of either guest, the complex concentration was 8.1 mM for [C_4mim]Br and 3.8 mM for [C_2mim]Br, a 2-fold difference arising from the different binding models.

The difference in complexation stoichiometry is reasonably attributed to the length of the IL alkyl tails considering the portal to portal distance of the CB[6] host. While CB[6] can simultaneously accommodate a [C_2mim]Br molecule in each portal, an increase of only two methylene units apparently causes a steric clash in the cavity and only one imidazolium molecule is associated with the host at a time. Thus, the driving force for the complexation appears to be a combination of the hydrophobic interaction between alkyl tails and the interior of the CB[6] cavity and the charge–dipole interaction between the delocalized cation of the imidazolium ring and the CB[6] portal oxygen atoms. The flexible guest location in the CB[6] portal region mitigates the alkyl chain's penetration depth.

In summary, mono-imidazolium ionic liquids are able to pull cucurbit[6]uril into neutral water. It appears that small changes in alkyl chain length can dramatically increase the solubility of CB[6] as well as alter the binding model and complex stoichiometry. According to systematic ^{1}H NMR titration experiments, the delocalized imidazolium cations demonstrate different binding modes with cucurbituril. Furthermore the formation of 1 : 2 inclusion complexes provides opportunities for a new type of self-assembly with CB[6]. Therefore, we foresee the possibility to design larger self-assembled architectures[19] which incorporate CB[6] and exploit imidazolium-based portal binding. Additionally, we are currently undertaking detailed thermodynamics investigations for this type of portal binding with variable cavity penetration.

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