Inhibition of C(2)-H/D exchange of a bis(imidazolium) dication upon complexation with cucubit[7]uril†

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Inclusion of the α,α′-bis(3-(1-methylimidazolium))-*p*-xylene dication in cucurbit[7]uril (CB[7], $K_{CB[7]}$ = (4.3 × 10^9 M^{-1}), with C–H···O=C hydrogen bonding between the guest C(2)-protons and the carbonyl oxygens of the host portals, inhibits the H/D exchange for the C(2)-proton with k_{OD} (25 °C, D_2O) decreasing from 1.2 × 10^3 M^{-1} s^{-1} (pK_a = 22.3) in the absence of CB[7] to 0.9 M^{-1} s^{-1} (pK_a = 25.4) in the presence of 1.1 equiv. CB[7].

The cucurbiturils (CB[*n*], where *n* = 5–10) are a family of macrocyclic host molecules, comprised of *n* glycoluril units bridged by *n* pairs of methylene groups (Chart 1), whose binding behaviour toward cationic and neutral guests have been of increasing interest recently.[1] The cucurbiturils contain an interior hydrophobic cavity, with polar carbonyl groups surrounding the two identical portals. The cucurbit[7]uril (CB[7]) in particular has received considerable recent attention because of improved synthetic methods,[2] its solubility in aqueous solution, and its capacity to include aromatic molecules[3] and mediate their chemical and photochemical reactivity.[4–10] CB[7] has been reported to catalyze the *trans*-to-*cis* photoisomerizations and/or photodimerizations of diaminostilbene,[4] 1,2-bis(4-pyridyl)ethylene and stilbazoles,[5] and protonated 2-aminopyridine.[6] It has also been applied as molecular drugs carrier,[7] as host for polyaromatic cations,[8] ferrocenes,[9] and for the protection of organic dyes from photobleaching.[10]

We have recently observed that CB[7] inclusion can facilitate a switching in the fluorescence behaviour of protonated 2-aminoanthracene[11] and other aromatic amines and alcohols, as a result of increases in their ground-state and excited-state pK_a values upon hydrogen bonding between the ammonium or hydroxyl group and the portal carbonyl oxygens. Nau and coworkers have also reported a ground-state pK_a shift of the protonated form of Neutral Red, upon inclusion in CB[7].[12] The effect of CB[7] complexation on the acidity of ammonium N–H and hydroxyl O–H groups prompted us to extend this research to even weaker carbon acids (C–H), such as the C(2)-proton on imidazolium cations. Imidazolium salts have been studied for more than 40 years as models of carbon acids,[13] and for their applications as ionic liquids[14] and N-heterocyclic carbene (NHC) precursors.[15] Stable NHCs may be formed by deprotonation of the C(2)-proton of the imidazolium cations, evidence of which is H/D exchange of the proton in D_2O solution. Recently, the kinetic acidity of imidazolium cations, including H/D exchange rates,[16–18] carbon-proton acidity,[19,20] and carbene precursor stability[15] has been of great interest to physical and organic chemists, as the formation of NHCs is often a crucial step in catalytic organic and organometallic reactions.[15]

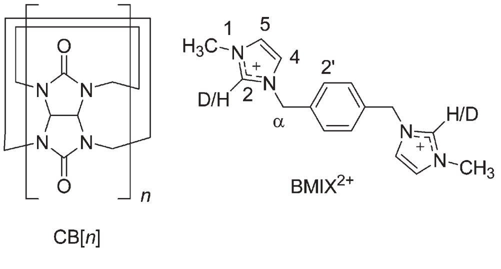

Chart 1 The structures of cucurbit[*n*]urils and α,α′-bis((3-(1-methylimidazolium))-*p*-xylene (BMIX^{2+}, with proton labelling scheme).

In this communication, we report the formation of a very stable guest–host complex of the α,α′-bis(3-(1-methylimidazolium))-*p*-xylene dication (BMIX^{2+}, Chart 1), prepared as the bromide salt,[21] with CB[7] in aqueous solution.

A study of the hydrogen/deuterium exchange reactions of the C(2)-proton for BMIX^{2+} has been carried out in the absence and presence of CB[7] in D_2O at 25 °C and I = 0.2 (NaCl). The H/D exchange in deuterium oxide solution can be monitored by ^{1}H NMR spectroscopy and the first- and second-order rate constants acquired. Amyes and coworkers[17b] have carried out detailed measurements of the exchange rate constants for several 1,3-dialkylimidazolium and benzimidazolium cations in D_2O. Recently the H/D exchange rate constants for the C(2)-proton of a series of imidazolium cations with alkyl, aryl, and calixarene substituents in CD_3OD containing 3% H_2O were reported.[17c] Buncel and coworkers have demonstrated that the lability of the C(2)-proton in aqueous solution is increased by protonation or metalation of imidazoles compared with the neutral substrate.[16a] The effect of supramolecular inclusion of imidazolium cations on the lability and acidity of the C(2)-proton has not previously been investigated.

The second-order rate constants may be used to estimate relatively reliable pK_a values for the carbon acids.[17b] The pK_a values for the imidazolium, 1,3-methylimidazolium and 1,3-dimethyl- and 1,3-bis((*S*)-1-phenylethyl)benzimidazolium cations have been determined experimentally to be 23.8, 23.0, 21.6, and 21.2, respectively.[17b] Theoretical pK_a values for a series of 1,3-dialkylimidazolium and 1,3-diarylimidazolium cations were determined to be in the range of 22–30.[20]

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We first investigated the guest–host interaction of $BMIX^{2+}$ with CB[7] using ^1H NMR spectroscopy in a 0.1 M NaCl–D_2O solution. Fig. 1 shows the appearance of separate proton resonances for free and bound guest molecules in the presence of 0.4 equiv. CB[7], which indicates that the chemical exchange rate between free guest and CB[7]-complexed guest is slow on the ^1H NMR time scale.

In the presence of 1.1 equiv. of CB[7], the resonances for one of the imidazolium ethylene protons (H(4)), the xylyl methylene protons (H(α)), the aromatic protons (H(2′)) and the C(2)-proton in the ^1H NMR spectrum of the inclusion complex have moved upfield from those of the free guest, indicative of their positioning within the cavity of CB[7]. The resonance for the methyl protons resonances (H(1)) moved downfield, while the other imidazolium ethylene resonance (H(5)) exhibited no chemical shift change. This behaviour indicates that the methyl group and the ethylene C(5)–H group are likely situated outside of the cavity of CB[7], as the downfield shift of the methyl proton resonance may be attributed to the deshielding effect of the carbonyl-rimmed portal of CB[7].[1]

The 1 : 1 binding stoichiometry of the $\{BMIX{\cdot}CB[7]\}^{2+}$ complex was also revealed by a Job′s Plot based on the continuous variation method by using absorption measurements, and was supported by the ESI–MS spectrum, which exhibited peaks at *m*/*z* = 1509 for $\{BMIX{\cdot}CB[7] + Br\}^+$ and 715 for $\{BMIX{\cdot}CB[7]\}^{2+}$. It was not possible to calculate the guest–host stability constant directly from either ^1H NMR or UV–visible titrations of $BMIX^{2+}$ with CB[7] owing to its very high value. Instead, a ^1H NMR competition experiment was carried out by using a known strong binding guest, the (trimethylammonio)methylferrocene ($FcTMA^+$) cation, as a competitor ($K_{CB[7]} = (3.31 \pm 0.62) \times 10^{11}\ M^{-1}$).[3] Using a limiting amount of CB[7], with $[BMIX^{2+}] \gg [FcTMA^+]$, a stability constant of $(4.3 \pm 0.8) \times 10^9\ M^{-1}$ was determined for the $\{BMIX{\cdot}CB[7]\}^{2+}$ complex at 25 °C in D_2O (0.1 M NaCl). This value is similar to the stability constant of $1.84 \times 10^9\ M^{-1}$ reported for the complex between the α,α′-diammonio-*p*-xylene dication and CB[7].[3]

The exchange of the C(2)-proton of $BMIX^{2+}$ in buffered D_2O (pD = 5.0–8.1) at 25 °C and *I* = 0.2 (NaCl) in the absence of CB[7] was followed by ^1H NMR spectroscopy. At pD of 6.1 (DOAc/OAc^- buffer), for example, 71% of the C(2)-protons were exchanged by deuterium after six days, while in the presence of 1.1 equiv. CB[7] no exchange was detected after six days, with only 5% deuterium exchange observed after one month. Only at elevated pD values (8.8–10.5) was facile deuterium exchange of the C(2)-protons for the $\{BMIX{\cdot}CB[7]\}^{2+}$ complex observed. The first-order rate constants for H/D exchange of the C(2)-proton in the $BMIX^{2+}$ dication in the absence and presence of CB[7] at different pD environments were determined from the plots of reaction progress ln*R* ($R = I_t/I_0$, where *I* is the integration of the C(2)–H proton resonance, using H(α) as a non-exchanging integration reference) against time (Fig. 2). From the linearity of the plots it appears that the two imidazolium C(2)-protons exchange independently of one another with similar rate constants.

Under these conditions, the second-order rate constants k_{DO} for the DO^- catalyzed deuterium exchange can be obtained from a linear fit (fixed slope = 1) to the equation of $\log k_{ex} = \log(k_{DO}K_W/\gamma_{OL}) + pD$ by using the first-order rate constants k_{ex} as a function of the pD value (Fig. 3).[17b] The second-order rate constants for C(2)-proton deuterium exchange are determined from the *y*-axis intercepts of the linear fits.

The value of $(1.2 \pm 0.1) \times 10^3\ M^{-1}\ s^{-1}$ for $BMIX^{2+}$ in the absence of CB[7] may be compared with the value of $2.47 \times 10^2\ M^{-1}\ s^{-1}$ for the 1,3-dimethylimidazolium cation at the same

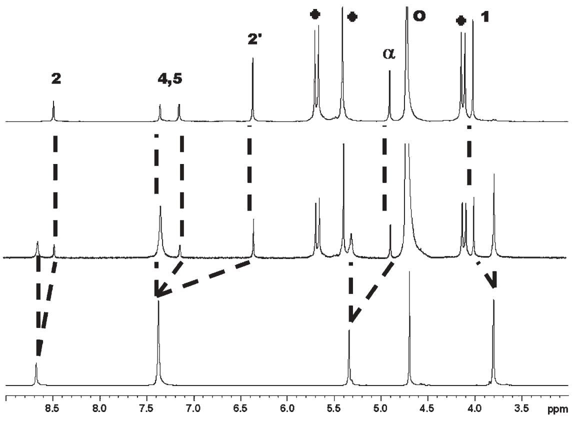

Fig. 1 The ^1H NMR spectra of the free $BMIX^{2+}$ guest (lower spectrum) and after the addition of 0.4 equiv. CB[7] (middle) and 1.1 equiv. CB[7] (upper), with CB[7] protons labelled as (●) and HOD as (○).

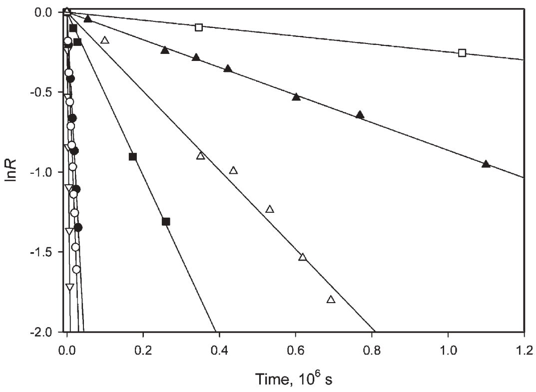

Fig. 2 Semilogarithmic plot of ln*R* against time for the C(2)-proton deuterium exchange for $BMIX^{2+}$ (2 mM) at pD = 5.16 (□, only two points shown), 6.17 (△), 7.44 (○), and 8.07 (▽), and for $\{BMIX{\cdot}CB[7]\}^{2+}$ (2 mM) at pD = 8.81 (▲), 9.51 (■), and 10.15 (●).

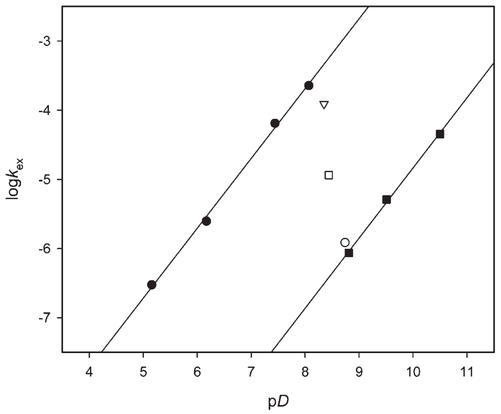

Fig. 3 Plots of $\log k_{ex}$ against pD for the deuterium exchanges of the C(2)-protons on $BMIX^{2+}$ (●, 2 mM) and $\{BMIX{\cdot}CB[7]\}^{2+}$ (○, 5 mM; ■, 2mM; □, 1.0 mM; ∇, 0.5 mM) in D_2O at 25 °C.

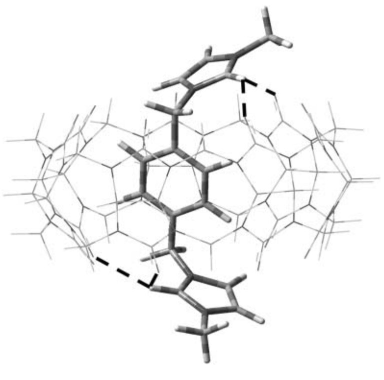

Fig. 4 Energy-minimized structure (HF/3-21G** basis set) of the $\{BMIX{\cdot}CB[7]\}^{2+}$ guest–host complex.

temperature (I = 1.0 M (KCl)).[17b] In the presence of CB[7], the exchange rate constant is reduced to 0.9 ± 0.1 $M^{-1}\ s^{-1}$ from the linear fits. The pK_a values of the $BMIX^{2+}$ cation in the absence and in the presence of CB[7] were estimated to be 22.3 ± 0.5 and 25.4 ± 0.5, respectively, based on the second-order rate constants k_{DO} and with $k_{DO}/k_{HO} = 2.4$, $K_W = 10^{-14}$, and $k_{HOH} = 10^{11}\ s^{-1}$ for the reverse protonation of the carbene by solvent water.[17b] At lower concentrations of $\{BMIX{\cdot}CB[7]\}^{2+}$ (0.5 and 1.0 mM in Fig. 3), the rates increase as some of the more reactive free $BMIX^{2+}$ is present in solution.

The decreases in the acidity ($\Delta pK_a = 3.1$) and lability of the C(2)-proton might be explained by the C–H···O=C hydrogen bond formation upon $BMIX^{2+}$ complexation with CB[7]. A somewhat larger pK_a value for the C(2)-proton on the 1,3-di-*tert*-butylimidazolium cation in DMSO than in THF has also been attributed to stronger C–H···O hydrogen bonding in the former solvent.[19b] An energy-minimized structure of the $\{BMIX{\cdot}CB[7]\}^{2+}$ complex from *ab initio* calculations (HF/3-21G** basis set) reveals multipoint C–H···O=C hydrogen bonding contacts (Fig. 4).

The distances between the C(2)-hydrogens and the carbonyl oxygens are 2.43 and 2.46 Å on one portal, and 2.31 and 2.44 Å on the other portal, while the C–H···O bond angles vary from 106° to 146°. The CB[7] host molecule not only acts as a steric barrier (including most of the imidazolium cation), but also a hydrogen bond acceptor for the C(2)-protons, by positioning the guest in the cavity of CB[7] for optimal hydrogen bonding interactions. The inhibition of H/D exchange in this system is reminiscent of the well-studied use, in determinations of protein structure and dynamics, of the dependence of amide H/D exchange on H-bonding and exposure of the peptide linkage to the solvent.[22]

In summary, we report a strong complexation between a bis(imidazolium) dication, $BMIX^{2+}$, with the host CB[7] in aqueous solution. The H/D exchange of the C(2) protons on $BMIX^{2+}$ has been significantly inhibited upon CB[7] complexation, resulting in a pK_a shift of the carbon acid upon multipoint C–H···O=C hydrogen bonding with the host molecule. This guest–host complexation has the potential to be employed in controlling the reactivity/stability of a range of imidazolium carbon acids, which are often employed as N-heterocyclic carbene precursors in catalytic organic and organometallic chemistry. Thiazolium and oxazolium cations have been shown to have more acidic (C(2)–H pK_a values of 23.0, 19.5, and 16.9 for the 1,3-dimethylimidazolium, 1-methylthiazolium, and 1-methyloxazolium cations, respectively) and labile C(2)-protons ($k_N : k_S : k_O = 1 : 10^{3.5} : 10^{5.5}$) than the corresponding imidazolium cations[17a,17b] and we are currently examining the effects of CB[7] complexation on a series of these azolium cations.

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