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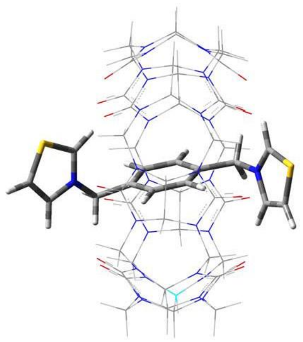

The stability of a bis(thiazolium) dication was improved upon inclusion by cucurbit[7]uril, as demonstrated by the slowed-down C(2)-H/D exchange.

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ARTICLE

High-Affinity Host-Guest Complex of Cucurbit[7]uril with a Bis(thiazolium) Salt

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A biologically- and pharmaceutically-relevant bis(thiazolium) dication model compound, α,α′-bis(thiazolium)-*p*-xylene (BTX^{2+}), forms a strong 1:1 host-guest inclusion complex with cucurbit[7]uril (CB[7]). The complexation stoichiometry, binding affinity and geometry were studied via ^1H NMR and UV-visible titrations, ESI-MS, and molecular modeling (*ab initio* calculations). The hydrogen/deuterium exchange reactions of the C(2)-proton of BTX^{2+} was conducted in the absence and presence of CB[7] in D_2O at 25 °C and at an ionic strength of 0.20 M. The inhibition of C(2)-H/D exchange of the guest bis(thiazolium) dication upon complexation with CB[7] exhibited a second-order rate constant that decreased by more than four-fold in the presence of CB[7]. The supramolecular-controlled stability of thiazolium cations through complexation with CB[7] host molecules is anticipated to have applications for stability enhancement of thiazolium based drugs and to potentially draw interest in the application of CB[n] host molecules with regard to the formulation and delivery of these drugs.

1. Introduction

Aromatic heterocyclic groups containing nitrogen and sulphur have an important role in biological activity of many compounds. These compounds are widely used for the synthesis of biocides, fungicides, and pharmaceuticals.[1] For instance, the thiazole moiety represents an important structural component of vitamin B1 and epothilone, a potent anti-cancer drug.[2] Thiazolium compounds and their analogues have also been studied for their antimalarial activities,[3] and bis(thiazolium) salts, in particular, have been considered to represent the second generation of bis-cationic antimalarial agents, and their effectiveness has been validated by clinical development.[4] Bis(thiazolium) salts are able to inhibit phosphatidylcholine biosynthesis in *Plasmodium* and to block parasite proliferation in the low nanomolar range.[5] On the other hand, thiazolium salts have been studied for more than four decades as models of carbon acids,[6] and for their applications as N-heterocyclic carbene (NHC) precursors leading to the synthesis of novel compounds with applications in various fields including medicine.[7] Labile nucleophilic NHCs may be formed by the deprotonation of the C(2)-proton of the thiazolium cations, and the NHC formation often brings the issue of thiamine and thiazolium-based drug stability to the forefront. For instance, dimerization of thiazolium cations was found to take place and such dimerization was attributed to the nucleophilic nature of C-2 carbene of deprotonated thiazolium salts.[8]

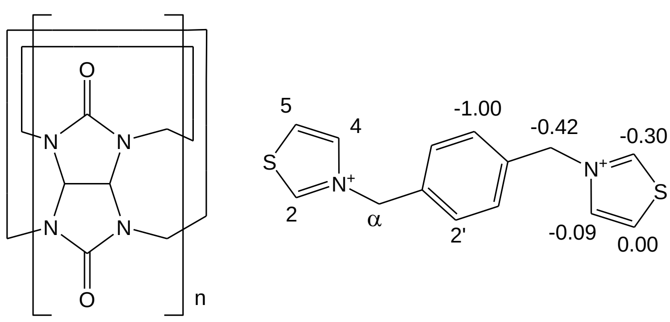

Fig. 1. The structures of cucurbit[*n*]urils (CB[*n*]) and α,α′-bis(thiazolium)-*p*-xylene ($[BTX]^{2+}$, with proton labeling and limiting complexation induced ^1H NMR chemical shift changes).

The cucurbit[n]urils (CB[n], where n = 5–10, 14) are a family of macrocyclic host molecules, consisting of n glycoluril units bridged by n pairs of methylene groups (Figure 1). The binding behaviour of CB[n] macrocycles toward cationic and neutral guests has attracted significant attention in recent years.[9] CB[n] has two hydrophilic rims and a hydrophobic cavity, and the width of the CB[n] cavity varies according to the number of glycoluril units, which provides these macrocycles with the ability to encapsulate molecules with various sizes in a highly selective manner. The acquired host-guest complexes often have high binding affinities. For instance, CB[7] can bind to positively charged cations (typically ammonium cations) through a combination of ion-dipole interactions, the hydrophobic effect and complementary size-fitting with binding affinities up to 10^{15} M^{-1}.[10] These high binding affinities, in combination with their high selectivity, provides them with superior binding behaviour to that exhibited by cyclodextrins and calixarenes. Due to the small cavity size of CB[5] and flexible nature of the cavity of CB[10], the CB[6], CB[7] and CB[8] hosts have received the greatest attention as supramolecular hosts and as drug delivery vehicles.[11,12] Compared with CB[6] and CB[8], the CB[7] host has received the most attention due to its good solubility and strong complexation with a diverse range of cationic and organometallic drugs.[13]

Haake *et al.* have determined the C(2)-H/D exchange rate constants of analogous 3,4-dimethyloxazolium, 3,4-dimethylthiazolium, and 1,3,4-trimethylimidazolium cations, that the ratio of the exchange rate is approximately $10^{5.5}$:$10^{3.5}$:1.[14] We have demonstrated that the inclusion of an bis(imidazolium) dication, α,α'-bis(3-(1-methylimidazolium))-*p*-xylene (BMIX^{2+}) in the host molecule cucurbit[7]uril (CB[7], Chart 1) significantly inhibits (about 1000 fold) the C(2)-H/D exchange reaction in D_2O as well as increasing the pK_a value by about 3 pK units.[15] To expand that work further, we investigated the complexation by CB[7] of a biologically- and pharmaceutically-relevant bis(thiazolium) model dication, α, α'-bis(thiazolium)-*p*-xylene (BTX^{2+}, Figure 1). The H/D exchange reactions of the C(2)-proton for BTX^{2+} have been performed in the absence and presence of CB[7] in D_2O at 25 ℃ and I = 0.20 (NaCl). To the best of our knowledge, there have been no previous investigations on the supramolecular inclusion of thiazolium cations and the effect of supramolecular inclusion on the lability of the C(2)-proton of thiazolium. The complexation of this thiazolium dication with CB[7] host molecules was thus investigated and the inhibition of C(2)-H/D exchange of these guest carbon acids upon complexation with CB[7] was observed. The complexation-induced stability of thiazolium cations is anticipated to have relevance for the stability of thiazolium-based drugs and molecules and to potentially draw interest in the drug formulation and delivery of thiazolium based drugs.

2. Experimental

2.1 Materials

The host molecule CB[7] was synthesized according to a literature method.[16] The (trimethylammonio)methylferrocene tetrafluoroborate ([TMAF]BF_4) was prepared by methylation of dimethylaminomethylferrocene (Aldrich) using a reported method.[17] The acetate and phosphate buffer solutions (total buffer concentration of 0.050 M for acetate for each kinetic experiment) were prepared by the requisite addition of DCl (Aldrich, 35 wt % in D_2O) to D_2O solutions of sodium acetate (Aldrich). The ionic strength was adjusted to 0.20 M using NaCl.

2.2 α,α'-bis(thiazolium)-*p*-xylene dibromide ([BTX]Br_2)

The α,α'-bis(thiazolium-*p*-xylene dibromide (BTX)Br_2 was synthesized by a modification of the method used to make the corresponding bis(imidazolium) salt.[18] Thiazole (0.48 g, 5.5 mmol, Aldrich) was mixed with α,α'-dibromo-*p*-xylene (0.71 g, 2.7 mmol, Fluka) in 15 mL of THF under reflux for ~24 h to produce a white precipitate. The crude product was filtered and washed with THF and ether, and was further purified by a soxhlet extraction with acetonitrile. This product was subsequently dried in a vacuum oven to yield a white powder (yield: 0.65 g, 55%; Purity > 98% by HPLC). ^{1}H NMR (D_2O, 400 MHz) δ 9.91 (s, 2H, H2), 8.21 (s, 2H, H4), 8.11 (s, 2H, H5), 7.45 (s, 4H, H2'), 5.71 (s, 4H, Hα) ppm. ^{13}C NMR (D_2O, 100 MHz) δ 136.9 (C4), 133.9 (C2), 130.0 (C2'), 126.3 (C5), 57.9 (Cα) ppm. HR-ESI-MS: calcd for $C_{14}H_{14}N_2S_2Br$ $(M\text{-}Br)^+$ *m/z* 354.9755 and 352.9776; found *m/z* 354.9764 and 352.9786; calcd for $C_{14}H_{14}N_2S_2$ $(M\text{-}2Br)^{2+}$ *m/z* 137.0294; found *m/z* 137.0222. Elemental analysis: C 38.72%, N 6.32%, H 3.05%. Melting point: 305 - 307 ℃.

2.3 Instrumentation

The 1D and 2D NMR spectra were recorded using a Bruker AV-400M NMR spectrometer. The ESI-MS spectra were acquired using a Waters 2Q Single Quadrupole MS spectrometer equipped with an ESI/APcI multiprobe. The UV-visible spectra were all acquired on a Hewlett Packard 8452A diode array UV-visible spectrometer using quartz cells with a 1.00 cm path length. All of the modeled structures of the host-guest complexes involved in this project were computed by energy-minimizations using Gaussian 03 (Revision C.02) programs run on the computing facilities of the High Performance Virtual Computing Laboratory (HPVCL) at Queen's University (see supplementary information). The structures of the complexes were originally constructed using ChemDraw and Chem3D (ChemOffice 7.0, CambridgeSoft) programs and subsequently imported into Gaussian 03. The basis set used for the calculations was HF/3–21G**.

2.4 Competitive ^{1}H NMR titrations

It has been demonstrated previously that the competitive ^{1}H NMR method provides a practical and useful approach for the determination of binding constants for strongly bound host-guest systems.[19] The ^{1}H NMR competition experiments were performed using a 400 MHz NMR spectrometer and the temperature was maintained at 298 K with a temperature control module. Each sample contained CB[7] and an excess of the two competitive guests (trimethylammonio)methylferrocene (TMAF$^+$) with the known binding constant of (3.31 ± 0.62) × 10^{11} M^{-1},[20] and BTX^{2+} with an unknown binding constant). The resonances corresponding to bound and free guests in non-overlapping regions of the spectrum were integrated, which allowed for the determination of the concentration of the free guests and the two host-guest complexes. Equations 2.1-2.4

define the thermodynamics of the host-guest and competition experiments. Substitution of the various concentrations measured by ^{1}H NMR integrations into eq. 2.3 yielded a value of K_{rel}. The unknown binding constant K_{G2} could be acquired using eq. 2.4 based on the K_{rel} values (determined from 2.3) and the reference K_{G1} value (here G1 denoted the known $TMAF^+$ and G2 denoted BTX^{2+}).

$$CB[7] + G1^+ \underset{}{\overset{K_{G1}}{\rightleftharpoons}} \{CB[7]\cdot G1\}^+ \quad (2.1)$$

$$CB[7] + G2^{2+} \underset{}{\overset{K_{G2}}{\rightleftharpoons}} \{CB[7]\cdot G2\}^{2+} \quad (2.2)$$

$$K_{rel} = ([\{CB[7]\cdot G2\}^{2+}][G1^+]/([\{CB[7]\cdot G1\}^+][G2^{2+}] \quad (2.3)$$

$$K_{G2} = K_{G1}K_{rel} \quad (2.4)$$

2.5 Kinetics of C(2)-H/D exchange

^{1}H NMR spectra of the guest BTX^{2+} in the absence and in the presence of CB[7] obtained during the deuterium exchange of the C(2)-proton at different pD (pD = pH + 0.41) conditions (buffered by DAc/Ac^- in D_2O, I = 0.20 adjusted with NaCl, 400 MHz NMR) were obtained. Other proton integrations, such as the methylene protons (4H) resonance in BTX^{2+}, were used as an internal reference resonance for determining the integration of the C(2)-proton. In order to acquire accurate integrals for the C(2)-proton, a relaxation delay, between the pulses, of d_1 = 75 s (> $5T_1$) was used.

2.6 Determination of first-order rate constants

The proton/deuterium exchange was monitored via ^{1}H NMR spectroscopy as described above. Values describing the reaction progress, R, can be calculated from the integrations of the of C(2)-proton resonances $[(I_{2H})_t]$ at time t, with an internal reference $[(I_{2H})_0]$, at the beginning of the experiment (or at t = 0), according to the equation 2.5.

$$R = (I_{2H})_t/(I_{2H})_0 \quad (2.5)$$

$$\ln R = -k_{ex}t \quad (2.6)$$

From equation 2.6, the first-order rate constant k_{ex} can be determined from the slope of the linear semilogarithmic plot of the reaction progress against the reaction time. Therefore, the first-order rate constant k_{ex} values, in the presence and in the absence of CB[7], at various pD conditions can be determined.[21.22]

2.7 Determination of second-order rate constants

The second-order rate constant, k_{DO}, is calculated from the y-axis intercept of the linear fit with a fixed slope of one by plotting $\log k_{ex}$ (first-order rate constants) against pD values according to the equation 2.7.[21]

$$\log k_{ex} = \log(k_{DO}K_W/\gamma_{OL}) + pD \quad (2.7)$$

The value of pK_W = 14.87 (for deuterated water). Under our experimental conditions the activity coefficient for deuterium oxide is γOL = 0.83, as estimated from the solvent conditions and the ionic strength.[21]

3. Results and discussion

3.1 ^{1}H NMR Study

In the ^{1}H NMR spectra of CB[n] host-guest complexes, the guest proton resonances show complexation-induced shifts (CIS, $\Delta\delta = \delta_{bound} - \delta_{free}$). These CIS values are very informative regarding the average location of the guest with respect to the CB[n] cavity.[22] Large upfield shifts (negative CIS values) are normally observed for guest protons located in the shielding (central) region of the cavity, while guest protons in the shallower area experience smaller upfield shifts. Zero CIS value indicates that the guest protons are located outside of the cavity and very often, positive CIS values are exhibited by guest protons situated outside the cavity especially when they are facing the carbonyl-lined portals of CB[n]. The host-guest interaction between BTX^{2+} with CB[7] was initially investigated via ^{1}H NMR spectroscopy in a 0.1 M NaCl-D_2O solution.

As shown in Figures 1 and 2, in the presence of 1.1 equivalents of CB[7], the resonances for one of the thiazolium ethylene protons (H4), the xylyl methylene protons (Hα), and the aromatic protons (H2') in the ^{1}H 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 relatively large CIS value for the aromatic protons (H2') (-1.00 ppm), intermediate CIS values for the xylyl methylene protons (Hα) (-0.42 ppm) and H2 (-0.30 ppm), and the comparatively small CIS values for thiazolium ethylene protons (H4 -0.09 ppm and H5 0.00 ppm) suggest an inclusion geometry where the aromatic ring is preferentially located near the centre of the cavity, the methylene groups are positioned further out, and proton H2 is in the vicinity of the CB[7] carbonyl groups. The other thiazolium ethylene resonance (H4 and H5) exhibited little or no change in its chemical shift, indicating that the thiazolium ring is most likely located outside of the cavity, presumably due to the thiazolium cation-dipole (carbonyl portals) interactions. In addition, the appearance of separate proton resonances for free and bound guest molecules in the presence of 0.40 equivalents of CB[7] indicates that the chemical exchange rate between the free guest and the CB[7]-complexed guest is slow on the ^{1}H NMR timescale. Similar slow exchange behaviour upon complexation with CB[7] has been exhibited by a bis(imidazolium) dication that we reported previously.[15] Additionally, DOSY and NOESY NMR data also supported the formation of host-guest inclusion complex (see electronic supplementary information for details).

The complexation constant between BTX^{2+} and CB[7] was determined by using a competitive ^{1}H NMR titration method using the (trimethylammonio)methylferrocene cation ($TMAF^+$) as the competitor ($K_{CB[7]}$ = (3.31 ± 0.62) × 10^{11} M^{-1}.[20] As the estimated binding constant of BTX^{2+} with CB[7] was in the range of 10^8 to 10^{10} M^{-1}, based on our previous experience with the α,α'-bis(imidazolium)-*p*-xylene dication ($BIMX^{2+}$, $K_{CB[7]}$ = (4.3 ± 0.8) x 10^9 M^{-1}),[14] ~1.8 mM $TMAF^+$ and more than 10 equiv. of BTX^{2+} (21.4 mM) were added to a limiting quantity of CB[7] in D_2O. All of the guest (free and bound) and host concentrations were calculated based the integrations of their respective non-overlapping proton resonances. By the method described in the experimental section (see supplementary information for the competitive binding ^1H NMR spectrum and the binding constant calculation), the calculated binding constant, $K_{CB[7]}$, for the BTX^{2+} was found to be (1.66 ± 0.31) × 10^{10} M^{-1}. The somewhat greater binding constant for BTX^{2+} compared with $BIMX^{2+}$ may be due to a greater charge localization on the thiazolium ring compared to the imidazolium ring.

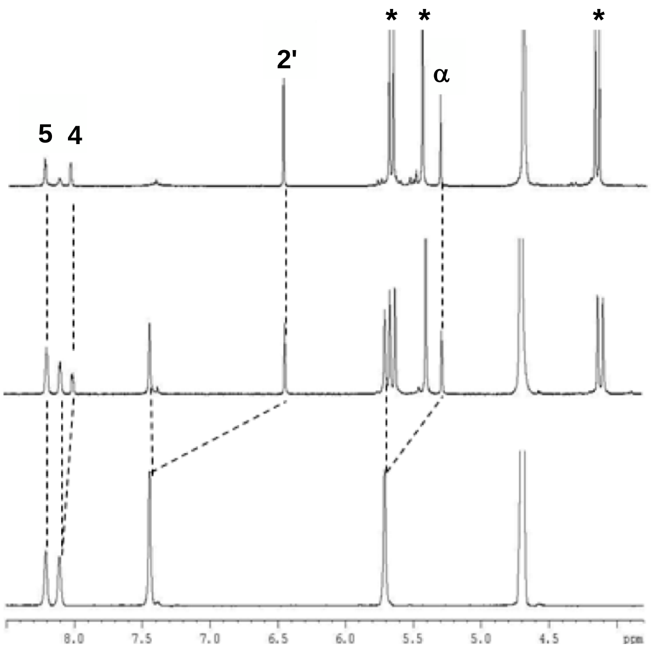

Fig. 2. The ^1H NMR spectrum of the free BTX^{2+} guest (bottom spectrum) and spectra recorded after the addition of 0.4 equivalents of CB[7] (middle) and 1.1 equivalents of CB[7] (top spectrum), with CB[7] protons labelled as (*).

3.2 UV-Visible Absorption Study

The 1:1 binding stoichiometry has also been confirmed by the continuous variation method. A Job's plot for the $\{CB[7]{\cdot}BTX\}^{2+}$ system (with [CB[7]] + [BTX^{2+}] fixed at a constant concentration of 0.10 mM), as monitored using UV-visible spectroscopy (Figure 3), reached a maximum at a [CB[7]]/([CB[7]]+[BTX^{2+}]) ratio of 0.50. This indicates that the dominant species encountered near this concentration region is the 1:1 complex between CB[7] and BTX^{2+}.

3.3 *Ab initio* calculations

^1H NMR and optical measurements have demonstrated the formation of a 1:1 inclusion complexes between BTX^{2+} and CB[7]. Attempts to grow single crystals to confirm the complex in the solid-state have been unsuccessful. Therefore, we relied on *ab initio* calculations to obtain further evidence of the existence of the 1:1 $\{BTX{\cdot}CB[7]\}^{2+}$ host-guest complex and provide a detailed geometry of the inclusion complex. The gas-phase structure of the CB[7] host-guest complex with BTX^{2+} has been determined from ab initio calculations (HF method with 3-21G** basis set). As illustrated in Figure 3, the position of BTX^{2+} inside the CB[7] cavity is consistent with the picture deduced from the experimental variations of the guest proton resonances (Δδ values) in the presence of CB[7] via ^1H NMR spectroscopy (Figure 2). According to the ab initio calculations, the aromatic ring of the molecule is positioned almost at the centre of the cavity, and the methylene groups are positioned in a shallow area of the cavity near the portals. Meanwhile, the thiazolium moieties are located outside of the portal and are exposed to the outside environment (hence the small CIS values observed in the ^1H NMR spectra of the bound species). It is noteworthy that the location of protons Hα and H2 are all in positions that allowed them to interact with the hydrophobic cavity CB[7], which is consistent with the relatively large CIS values observed during the ^1H NMR titration once the guest is encapsulated within the cavity (Figure 2).

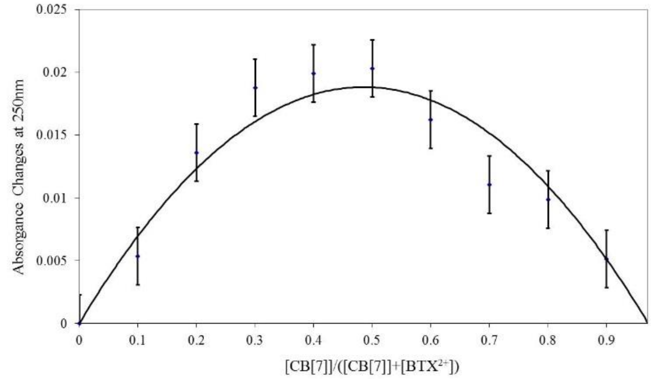

Fig. 3. Job's plot indicating 1:1 host-guest complex stoichiometry for $\{BTX{\cdot}CB[7]\}^{2+}$ complex based on the continuous variation UV-visible titration monitored at 250 nm.

The energy-minimized structure of the $\{BTX{\cdot}CB[7]\}^{2+}$ complex predicted from *ab initio* calculations also exhibits multipoint C–H---O=C (carbonyl portals) hydrogen bonding contacts. The distances between the C(2)-hydrogens and the carbonyl oxygen atoms are 2.498 and 2.500 Å on one portal, and 2.447 and 2.557 Å on the other portal, while the C–H…O bond angles vary from 107.2° to 127.8°. The CB[7] host molecule apparently not only acts as a steric barrier, but also as a hydrogen bond acceptor for the C(2)-protons, by positioning the guest within the cavity of CB[7] for optimal hydrogen bonding interactions.

3.4 ESI-MS

The 1:1 complexation between BTX^{2+} and CB[7] is supported by the appearance of a strong doubly charged peak at m/z = 718 of the complex $\{BTX{\cdot}CB[7]\}^{2+}$ in the ESI-MS spectrum (Figure 3). This provides further evidence of the formation of a 1:1 complex, and is consistent with the results of the Job's plot.

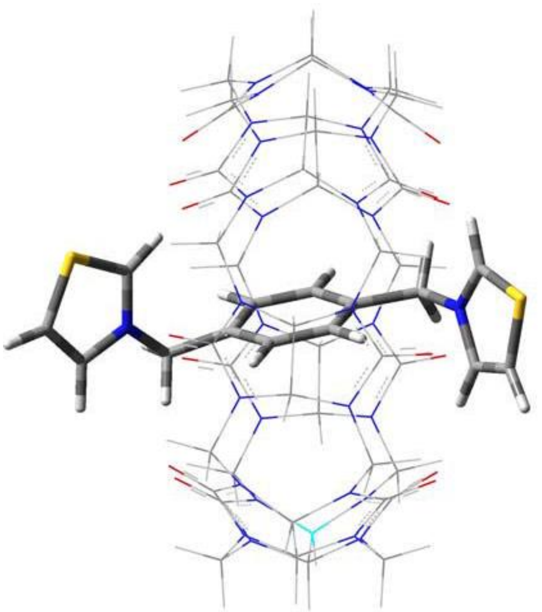

Fig. 4. Energy-minimized structure (HF/3-21G** basis set) of the $(CB[7]{\cdot}BTX)^{2+}$ host-guest complex.

3.5 C(2)-H/D Exchange Kinetics

With the knowledge of the strong complexation affinity, the binding mode and geometry between the thiazolium dication and CB[7], the C(2)-H/D exchange kinetics of the bis(thiazolium) cation in the absence and in the presence of CB[7] were studied. The exchange of the C(2)-proton of BTX^{2+} in buffered D_2O (pD = 3.9–4.8) at 25 ℃ and I = 0.20 (NaCl) in the absence and in the presence of CB[7] was monitored by ^{1}H NMR spectroscopy. At a pD value of ~3.9 (DOAc/OAc- buffer), for instance, 83% of the C(2)-protons underwent exchange with deuterium after ~100 min in the absence of CB[7]. In the presence of 1.1 equiv.CB[7], only ~30% of the C(2)-H/D exchange was detected after approximately the same length of time. The first-order rate constants for H/D exchange of the C(2)-proton in the BTX^{2+} dication in the absence and presence of CB[7] at different pD environments were determined from the plots of reaction progress lnR ($R = I_t/I_0$, where I is the integration of the C(2)–H proton resonance, using Hα as a non-exchanging integration reference) against time (Figure 6). From the linearity of the plots it appears that the two thiazolium C(2)-protons underwent exchange independently of one another with similar rate constants. Under these conditions, the second-order rate constants k_{DO} for the DO^- catalysed 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 (Figure 7). The second-order rate constants for C(2)-proton deuterium exchange were determined from the y-axis intercepts of the linear fits. The value of 9.8 x 10^6 M^{-1} s^{-1} for BTX^{2+} in the absence of CB[7] may be compared with the literature value of 8.4 x 10^6 M^{-1} s^{-1} for the

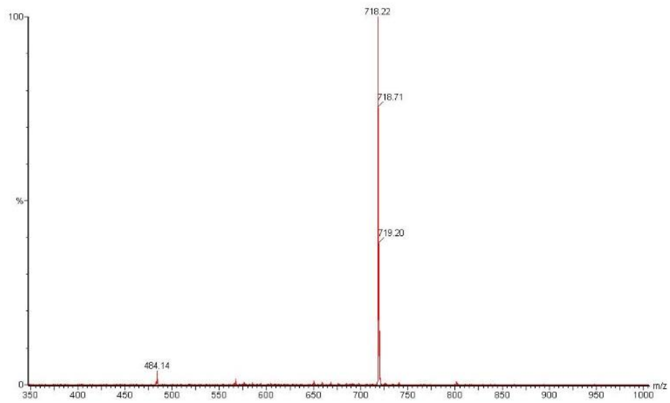

Fig. 5. ESI-MS spectrum of $\{CB[7]{\cdot}BTX\}^{2+}$.

H/D exchange of the C(2)-proton on the thiazolium ring of thiamine.[25] I n the presence of CB[7], the exchange rate constant is reduced to 2.1 x 10^6 M^{-1} s^{-1} from the linear fits. The pK_a values of the BTX^{2+} cation in the absence and in the presence of CB[7] were estimated to be 18.4 and 19.1, respectively, based on the second-order rate constants k_{DO} and with k_{DO}/k_{HO} = 2.4, K_W = 1.00 x 10^{-14}, and k_{HOH} = 1 x 10^{11} s^{-1} for the reverse protonation of the carbene by solvent water.[21]

In comparison with our previously reported pK_a shift of 3.1 observed for a $BIMX^{2+}$ dication, it is noticeable that CB[7] has a more significant effect on decreasing the acidity of imidazolium cations than thiazolium cations through host-guest complexation. The second order rate constant of 1.2 x 10^3 M^{-1} s^{-1} for the $BIMX^{2+}$ dication[15] compared 9.8 x 10^6 M^{-1} s^{-1} for BTX^{2+}, in very good agreement with the 3.5 orders of magnitude increase in the H/D reactivity predicted by Haake *et al.* in going from an imidazolium to a thiazolium acid center.[14] The complexation by CB[7] resulted in a decrease of 3 orders of magnitude in the exchange rate constant for $BMIX^{2+}$, while the decrease for BTX^{2+} is less than five-fold.

The reasons for such differences in ΔpK_a and $k/k_{CB[7]}$ are not clear at this point, although the inhibition of C(2)-H/D exchange for both imidazolium and thiazolium cations is generally proposed to be attributed to hydrogen bond formation between C(2)-proton and CB[7] portal oxygen atoms through the formation of stable host-guest complexes.

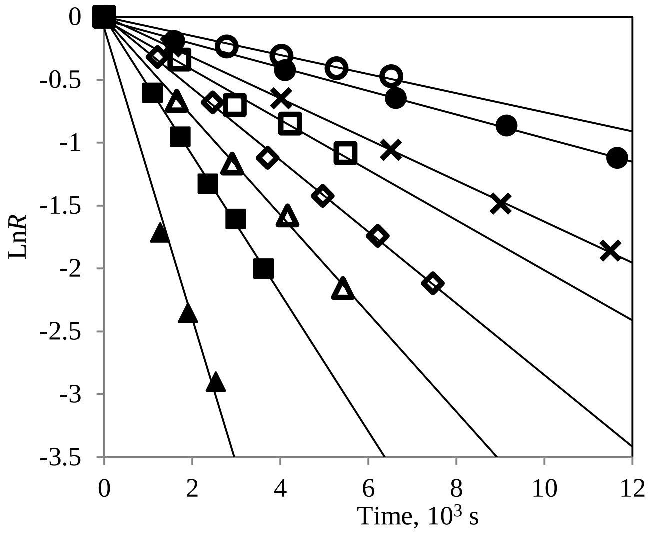

Fig. 6. Semilogarithmic plot of ln$R$ versus time for the C(2)-proton deuterium exchange for BTX^{2+} (2 mM) at pD = 3.96 (×), 4.26 (◊), 4.54 (■), and 4.81 (▲), and for $(BTX\text{-}CB[7])^{2+}$ (2 mM) at pD = 4.31 (○), 4.45 (●), 4.71 (□) and 5.06 (Δ).

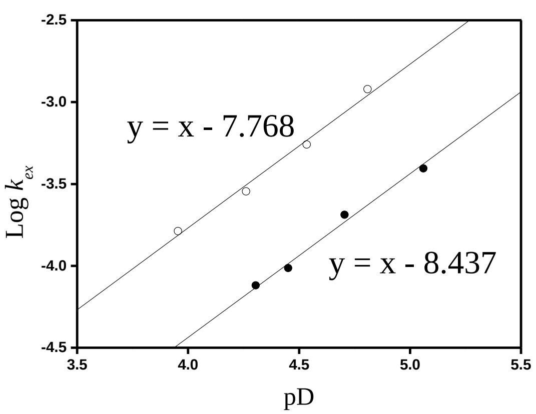

Fig. 7. Plots of logk_{ex} against pD for the deuterium exchanges of the C(2)-protons on BTX^{2+} (○, 2 mM) and $\{CB[7]\cdot BTX\}^{2+}$ (●, 2 mM) in D_2O at 25 °C.

4. Conclusions

The α,α'-bis(thiazolium)-*p*-xylene dication exhibits high-affinity complexation with CB[7], with an complexation-induced inhibition of the C(2)-H/D exchange reactivity. This host-guest complexation of thiazolium has the potential to be employed in the stabilization of thiazolium-based drugs such as antimalarial bis(thiazolium) dications and other thiamine based drugs. In addition, this complexation may be used to tune the reactivity/stability of a range of other thiazolium carbon acids, which are often employed as *N*-heterocyclic carbene precursors in catalytic organic and organometallic chemistry. We are currently working along these lines.

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Notes and references

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Electronic Supplementary Information (ESI) available: 1D and 2D NMR spectra, and HPLC chromatogram of the guest, DOSY and NOESY NMR spectra of the host-guest complex, binding constant calculations, first-order kinetic plots, UV-visible spectra from continuous titration, and energy-minimized structures and tables of atom coordinates. See DOI: 10.1039/b000000x/.

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