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Inhibition of C(2)-H Activity on Alkylated Imidazolium Monocations and Dications upon Inclusion by Cucurbit[7]uril

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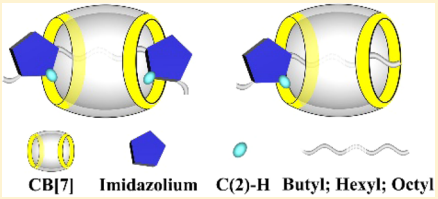
Supporting Information

ABSTRACT: The inclusions of 1-methyl-3-alkylimidazolium cations (ICn^+, n = 4, 6, and 8) and 3,3′-bis(3-(1-methylimidazolium))-1,n-alkane (DICn^{2+}, n = 4, 6, and 8) in the macrocyclic cucurbit[7]uril result in a decrease (up to 25-fold) of the C(2)-H/D exchange rate constants and an increase in the C(2)-H pK_a values (ΔpK_a = 0.34 to 1.45). The alkyl chain lengths were found to play an important role in the extent of C(2)-H activity inhibition, upon complexation with cucurbit[7]uril.



The cucurbit[n]urils (CB[n], where n = 5−8, 10, 14) are a family of macrocyclic host molecules consisting of paired-methylene bridged glycoluril units, whose remarkable binding behaviors toward a variety of guests have attracted significant interest.[1] Among the CB[n] congeners, the CB[7] (Figure 1) has received considerable attention because of both its superior water solubility and its capacity to encapsulate organic molecules of various sizes. Previous examples of the employment of CB[7] include inhibitors or catalysts in chemical and photochemical reactivity,[1,2] molecular drug carriers,[3] hosts for polyaromatic cations[4] and ferrocenes,[5] protectors for organic dyes,[6] macrocyclic receptors for enzymatic activity assays,[7] and hosts for fabricating multifunctional biointerfaces.[8] Moreover, we have previously observed that CB[7] can facilitate a novel switching in the fluorescence behavior of protonated 2-aminoanthracene,[9] as a result of ground-state and excited-state pK_a shifts upon inclusion in the cavity. Similarly, Nau and co-workers also reported a ground-state pK_a shift of another aromatic amine, protonated neutral red, upon inclusion in CB[7].[10] The occurrence of complexation induced pK_a shifts due to encapsulation of various guests by CB[7] has received significant attention during the past decade.[1,11] We have demonstrated that carbon acids also exhibit pK_a shifts upon encapsulation by CB[7].[12] The inclusion of an α,α'-bis(3-(1-methylimidazolium))-p-xylene dication (BMIX^{2+}, Figure 1) in CB[7] significantly inhibited the C(2)-H activity (3.1 pK_a shift) of the imidazolium salt in water through optimized C(2)-H---O═C hydrogen bonding interactions between the guest and the host.[12a] Similarly, we have recently observed that the CB[7] complexation of thiamine and its mono- and diphosphate derivatives also resulted in increases in the pK_a of the C(2)-proton, in a more modest manner.[12b]

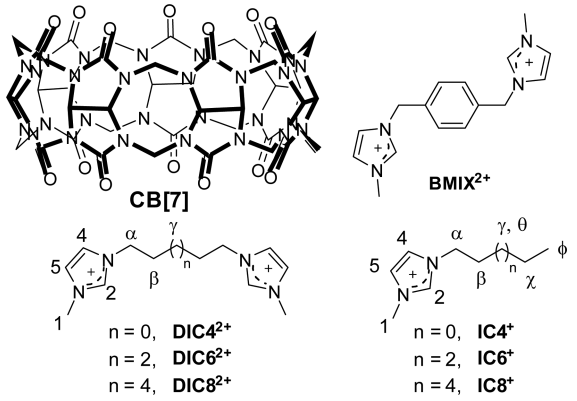


Figure 1. Structures of CB[7], BMIX^{2+}, ICn^+, and DICn^{2+}.

The C(2)-H activity of imidazolium cations[13] is of importance in the development of precursors for carbenes,[14] ionic liquids,[15] and antimalarial drugs.[16] Consequently, it is anticipated that the inclusion of a series of imidazolium cations by CB[7] may have applications in altering and/or controlling the stability of these compounds in aqueous solution, which may thus have implications in the modification of their physical, chemical, and biological properties.

We expanded this research to encompass the complexation between CB[7] and a series of imidazolium based model compounds, including alkylated imidazolium monocations (1-methyl-3-butyl-imidazolium (IC4$^+$), 1-methyl-3-hexyl-imidazolium (IC6$^+$), 1-methyl-3-octyl-imidazolium (IC8$^+$)) and dications (3′-bis(1-methyl-imidazolium)-1,4-butane (DIC4^{2+}), 3,3′-bis(1-methyl-imidazolium)-1,6-hexane (DIC6^{2+}), 3,3′-bis-(1-methyl-imidazolium)-1,8-octane (DIC8^{2+})) (Figure 1). In addition, the effects of encapsulation by CB[7] on the C(2)-H

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activity of these imidazolium cations with different alkyl chain lengths were investigated.

The host–guest interactions of the imidazolium cations ICn^+ and DICn^{2+} (n = 4, 6, and 8) with CB[7] were investigated using ^{1}H NMR spectroscopy in D_2O (containing 0.10 mol dm^{-3} NaCl) solution. All six imidazolium guests formed 1:1 host–guest complexes with their hydrophobic alkyl groups included in the cavity of CB[7]. In the cases of DIC4^{2+}, DIC6^{2+}, DIC8^{2+}, and IC8$^+$, the exchange rates between the free and CB[7]-bound guests were all slow on the ^{1}H NMR time scale. In contrast, the exchange rates between the free and CB[7]-bound IC4$^+$ and IC6$^+$ were both fast on the ^{1}H NMR time scale. The slow-exchange ^{1}H NMR spectrum (Figure 2 for DIC6^{2+}; Figures S1, S3, S4 for DIC4^{2+}, DIC8^{2+}, and IC8$^+$) displays separate proton resonances corresponding to both the free and bound DIC6^{2+} molecules in the presence of 0.3 equiv of CB[7]. In the presence of 1.2 equiv of CB[7], the three resonances of the hexyl protons (Hα, Hβ, Hγ) in the ^{1}H NMR spectrum have migrated significantly upfield, indicating that the hexyl group is included in the hydrophobic cavity. Meanwhile, the two imidazolium protons (H4 and H5) as well as the C(2)-proton of its inclusion complex have only moved upfield in a modest fashion from those of the free guest, indicative of their positions in the shallow area of the cavity of CB[7]. The resonance of the methyl protons (H1) have moved downfield, indicating that the methyl group is likely situated outside of the cavity of CB[7], where it is deshielded by the carbonyl groups that line the portals.

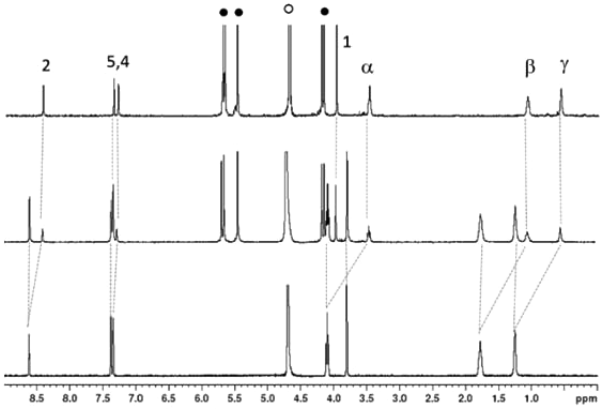

Figure 2. ^{1}H NMR spectra of DIC6^{2+} guest in the absence (bottom) and presence of 0.3 equiv (middle) and 1.2 equiv of CB[7] (top). The CB[7] and HOD peaks are labeled as (●) and (○), respectively.

Instead, the representative fast-exchange ^{1}H NMR spectrum (Figure 3 for IC6$^+$, Figure S2 for IC4$^+$) shows only one set of ^{1}H NMR resonances for IC6$^+$ in the presence of 0.3 equiv of CB[7]. Similar to those of DIC6^{2+}, in the presence of 1.2 equiv of CB[7], the hexyl group and the C(2)-proton were included within the cavity of CB[7], whereas the methyl group (H1) is also likely situated outside of the cavity of CB[7].

In addition to ^{1}H NMR spectroscopy, Job plots (continuous variation UV–visible absorption), and electrospray ionization mass spectrometry (ESI-MS) measurements were employed to further confirm the 1:1 binding stoichiometry of these supramolecular complexes. The Job plots, with a maximum absorbance change at a mole ratio of 0.5, are consistent with the conclusions from ^{1}H NMR spectra, as the representative Job plots (Figure 4 for DIC6^{2+} and IC6$^+$, others Figures S11–S12)

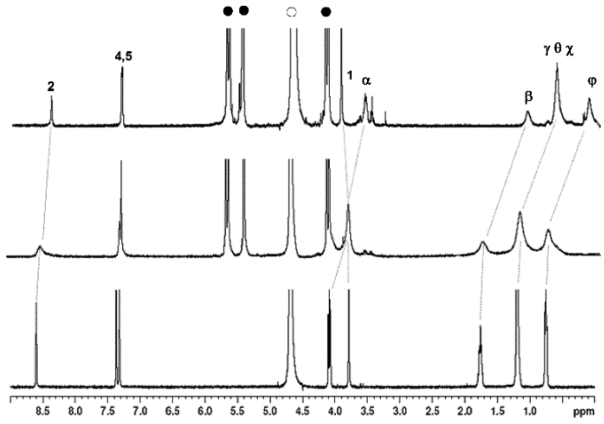

Figure 3. ^{1}H NMR spectra of IC6$^+$ guest in the absence (bottom) and presence of 0.3 equiv (middle) and 1.2 equiv of CB[7] (top). The CB[7] and HOD peaks are labeled as (●) and (○), respectively.

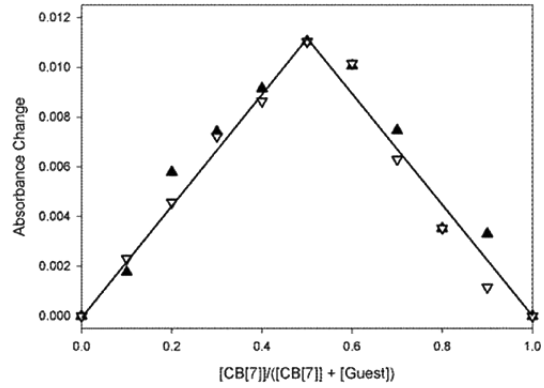

Figure 4. Job plots of the complexations of IC6$^+$ (▽) and DIC6^{2+} (▲) by CB[7].

are indicative of a 1:1 binding stoichiometry between the host and the guests. The 1:1 binding stoichiometry was also supported by the mass spectra, all of which showed singly and/or doubly charged peaks with m/z values corresponding to the inclusion complexes (Figures S5–S10).

As was the case with the BMIX^{2+} guest, it was not possible to calculate the stability constants directly by using either ^{1}H NMR or UV–visible titrations of the imidazolium cations with CB[7], because of their high binding affinities. Instead, ^{1}H NMR competition experiments were carried out by using a reasonably strong binding guest with a known stability constant with CB[7] as a competitive binding agent (3-(trimethylsilyl)-propionic-2,2,3,3-d_4 acid).[17] Using a limiting amount of CB[7], with excess amounts of the competitor and the imidazolium cation, the stability constants for the six complexes were calculated (Figures S13–S18) and are presented in Table 1.

The IC4$^+$ has been studied previously with CB[n] molecules, with host–guest complexes observed with CB[6],[18] CB[7], and CB[8].[19] With CB[7], Biczók and co-workers have reported stability constants of 6.9 × 10^6, 2.0 × 10^7, and 1.1 × 10^7 dm^3 mol^{-1}, for IC4$^+$, IC6$^+$, and IC8$^+$, respectively, determined by ITC measurements, and slightly lower values using competitive fluorescence methods. Our values, using competitive NMR measurements, with host and ICn^+ guest concentrations much higher than those used for fluorescence and ITC measurements, are larger. The $K_{CB[7]}$ values for the present series of cations and dications with CB[7] demonstrated an increase

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Table 1. C(2)-H/D Exchange Rate Constants, pK_a Values, and CB[7] Host−Guest Stability Constants for the Monocationic and Dicationic Imidazolium Guests

imidazolium cation	10^2 k_{DO} (dm^3 mol^{-1} s^{-1})	pK_a	ΔpK_a	10^9 K_{CB} (dm^3 mol^{-1})
IC4$^+$	2.188 ± 0.150	23.04 ± 0.03	0.34 ± 0.09	1.04 ± 0.13
{IC4·CB[7]}$^+$	1.007 ± 0.138	23.38 ± 0.06		
DIC4^{2+}	5.876 ± 0.135	22.61 ± 0.01	0.70 ± 0.08	1.37 ± 0.17
{DIC4·CB[7]}$^{2+}$	1.187 ± 0.190	23.31 ± 0.07		
IC6$^+$	2.669 ± 0.486	22.96 ± 0.08	1.38 ± 0.09	4.54 ± 0.55
{IC6·CB[7]}$^+$	0.109 ± 0.003	24.34 ± 0.01		
DIC6^{2+}	3.723 ± 0.342	22.81 ± 0.04	1.45 ± 0.12	11.6 ± 1.4
{DIC6·CB[7]}$^{2+}$	0.134 ± 0.024	24.26 ± 0.08		
IC8$^+$	2.142 ± 0.197	23.05 ± 0.04	0.66 ± 0.10	2.11 ± 0.25
{IC8·CB[7]}$^+$	0.471 ± 0.065	23.71 ± 0.06		
DIC8^{2+}	3.998 ± 0.458	22.78 ± 0.05	0.86 ± 0.17	18.6 ± 2.3
{DIC8·CB[7]}$^{2+}$	0.569 ± 0.153	23.64 ± 0.12		
BMIX^{2+}[a]	12.00 ± 1.000	22.30 ± 0.50	3.10 ± 1.00	4.30 ± 0.80
{BMIX·CB[7]}$^{2+}$[a]	0.009 ± 0.001	25.4 ± 0.50		

[a]From ref 12a.

with the charge on the guest, as it would be anticipated that higher stability constants between CB[7] and the bis-(imidazolium) cations than the monoimidazolium cations. We have observed a similar range of $K_{CB[7]}$ values (10^8−10^{10} dm^3 mol^{-1}) for dications R(CH$_2$)$_n$R^{2+} (n = 4, 6, and/or 8) with R = isoquinolinium,[20] 4-pyridinium,[21] and trimethylammonium.[22] Interestingly, the stability constants maximize at IC6$^+$ and DIC8^{2+}, for the monocations and dications respectively, likely due to the favorability of having six to eight methylene groups within the cavity.

Complexation with CB[7] can influence the behavior of the guest in various ways. In the case of the BMIX^{2+} dication, we have previously reported the inhibition of its C(2)-H activity, demonstrated by slowing-down of C(2)-H/D exchange, as well as a pK_a shift, upon complexation with CB[7].[12a] By employing the same methodologies, the first-order rate constants, the second-order rate constants, and the pK_a values of these imidazolium cations in the absence and presence of CB[7] were all evaluated.

The H/D exchange in the absence and presence of CB[7] was monitored via ^{1}H NMR spectroscopy (400 MHz). The first-order rate constants for H/D exchange of these imidazolium cations in the absence and presence of CB[7] at different pD environments were determined from the semi-logarithmic plots of the reaction progress R against time (Figures S19−S24).[13] Under these conditions, the second-order rate constants k_{DO} for the DO$^-$ catalyzed deuterium exchange of the imidazolium cations C(2)−proton, in the absence and presence of CB[7], can be obtained from a linear fit of log k_{ex} against pD (eq 1) for the deuterium exchanges of eq 1 by using the data of first-order rate constants k_{ex} and pD values (Figure S25).

$$\log k_{ex} = \log(k_{DO}K_W/\gamma_{OL}) + \mathrm{pD} \quad (1)$$

The second-order rate constants for C(2)-H/D exchange were determined in the absence and presence of CB[7] from the y-axis intercepts, and these values are listed in Table 1. The values of k_{DO} are very similar for the monocations (2×10^2 dm^3 mol^{-1} s^{-1}), with the dications exhibiting rate constants ($(4-6) \times 10^2$ dm^3 mol^{-1} s^{-1}) approximately double those of the corresponding monocations. The values observed for the monocations are very similar to the value of 2.47×10^2 dm^3 mol^{-1} s^{-1} for the 1,3-dimethylimidazolium (I = 1.0 M (KCl)), and the different aliphatic chain lengths should have no effect on the exchange rate constants. The higher values for the DICn^{2+} dications, as well as BMIX^{2+}, reflects the presence of two sites for exchange.

The second-order rate constants for the C(2)-H/D exchange of all imidazolium cations decreased upon complexation with CB[7]. The decreases were more significant for the IC6$^+$ and DIC6^{2+} guests than either the IC4$^+$/DIC4^{2+} or IC8$^+$/DIC8^{2+} sets of guests. Accordingly, the C(2)-H pK_a values for these imidazolium cations in the absence and presence of CB[7] were estimated based on the second-order rate constants k_{DO}.[13] Similarly, the values of pK_a for the imidazolium guests increase upon CB[7] complexation, with the largest changes observed for DIC6^{2+} and IC6$^+$, reflective of the changes in the H/D exchange rate constants.

The proposed mechanism for the inhibition of the C(2)-H activity involves the C−H---O═C hydrogen bond formation between the imidazolium cations and the carbonyl portals of CB[7]. The binding mode and geometry play crucial roles in defining optimal hydrogen bonding interactions, which may ultimately influence the reactivity of the C(2)−proton. For both the monocation and dication series, the pK_a shifts vary moderately with the polymethylene chain length. The different lengths of the alkyl chain lead to noticeable differences in binding geometries between the hydrophilic imidazolium C(2)-H and the carbonyl oxygens of CB[7] portals. Generally, the most significant pK_a shifts exhibited by both DIC6^{2+} and IC6$^+$ may be attributed to the hexyl chain providing better binding geometry for optimal C(2)-H---O═C bonding between the imidazolium and CB[7] than is available for the imidazolium cations bearing shorter butyl and longer octyl chains. To provide further evidence, the energy-minimized structures of these complexes were determined from *ab initio* calculations (via the HF method using the 3-21G** basis set; see Supporting Information).[23] As illustrated in Figure 5, only in the case of DIC6^{2+} and IC6$^+$ is the imidazolium moiety located directly in front of the carbonyl portals to facilitate the formation of the optimal hydrogen bonding. Meanwhile, in the cases of both DIC4^{2+} and IC4$^+$ (Figure S26) the C(2)-H is somewhat pulled inside the carbonyl portals and therefore is restricted for optimal hydrogen bonding. Finally, in the cases of DIC8^{2+} and IC8$^+$ (Figure S26), the C(2)-H interaction with the portal oxygens is too flexible. The hydrogen bond lengths and angles predicted by these energy minimized structures may

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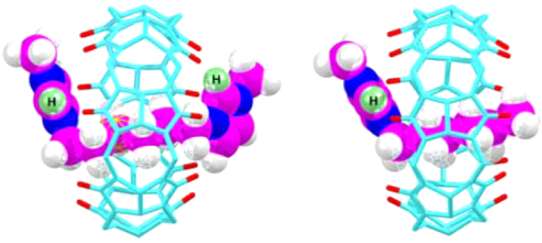

Figure 5. Energy-minimized structures (HF/3-21G** basis set) of $\{DIC6{\cdot}CB[7]\}^{2+}$ (left), $\{IC6{\cdot}CB[7]\}^{+}$ (right).

also support this assumption. The distances between the C(2)−hydrogen of $DIC6^{2+}$ (or $IC6^{+}$) and the carbonyl oxygens are all in the range of 2.26 to 2.35 Å, while the C−H···O bond angles vary from 142.3° to 148.8°. The hydrogen bonds between the other alkylated imidazolium cations and CB[7] (Supporting Information) have either larger distances between C(2)-H and the carbonyl oxygens or smaller C−H···O angles.

The increase in pK_a of $BMIX^{2+}$ is larger than those of the alkylated imidazolium cations examined in this article. This might be attributed to the optimal length and the rigidity of the hydrophobic xylene linker. Once the xylene group is encapsulated, the two imidazolium rings are anchored to the portals to form hydrogen bonding interactions between the C(2)-proton and the CB[7] portal oxygens. Meanwhile, the rigid xylene linker prevents the imidazolium rings from swinging around to break the hydrogen bonding, in contrast to the flexible alkyl chains of the guests reported herein.

In conclusion, the antimalarial drugs and ionic liquid/carbene precursor imidazolium salts form very stable complexes with CB[7] in aqueous solution. Upon complexation, the C(2)-H/D exchange rates of these guests are greatly slowed down and the acidity of these carbon acids decreases accordingly. The lengths of the alkyl chain play an important role in the binding geometry, thus influencing the strength of hydrogen bonding between C(2)-H and CB[7] carbonyl oxygens, and the associated C(2)-H activity. Our findings might be employed in the design and fabrication of activity-controllable imidazolium based compounds of both biomedical and material interest.

■ EXPERIMENTAL SECTION

The 1D ^{1}H NMR spectra were recorded using a 400 M NMR spectrometer. The UV−visible spectra were all acquired on a diode array UV−visible spectrometer using quartz cells with a 1.0 cm path length. The ESI-MS spectra were acquired using a Single Quadrupole MS spectrometer equipped with an ESI/APcI multiprobe. The modeled structures of the host−guest complexes were calculated via energy minimizations using the Gaussian 03 (Revision C.02) program at the High Performance Virtual Computing Laboratory (HPVCL) at Queen's University.[23] 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**.

The C(2)-H/D exchange reactions were followed by ^{1}H NMR spectroscopy, and the reaction progress, R, was calculated from the integration of the C(2)−proton with an internal reference of the methylene protons (4H) at zero time and time t, according to the equation $R = (I_{2H})_t/(I_{2H})_0 = (I_{2H})_t/2$.[24] The first-order rate constants were determined from the slopes of the linear semilogarithmic plots of the reaction progress against the reaction time ($\ln R = -k_{ex}t$).

Materials. The acetate and phosphate buffer solutions (total buffer concentration of 0.050 mol dm^{-3} 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 and sodium phosphate (Aldrich), respectively. The ionic strength was adjusted to 0.20 mol dm^{-3} using NaCl. Each imidazolium cation was mixed with CB[7] in a 1:1.2 (imidazolium salt: CB[7]) molar ratio in buffered D_2O and sonicated for 20 s after mixing.

Synthesis of CB[7] and the Imidazolium Salts. Cucurbit[7]uril was synthesized via the method reported by Day and co-workers.[25] The imidazolium salts were synthesized according to a literature method.[26]

3,3′-Bis(1-methyl-imidazolium)-1,4-butane Dibromide ([DIC4]-Br_2). 1-Methylimidazole (1.0 g, 12 mmol) was reacted with 1,4-dibromobutane (0.71 mL, 6.0 mol) in 25 mL of anhydrous THF under reflux for about 18 h. The oily product was layered out of solvent by adding ether, and an orange oil was collected by decanting the supernatant out of the reaction vessel and then washed with ether three times. Yield: 1.7 g (yield 75%). ^{1}H NMR (D_2O, 400 MHz) δ 8.63 (s, 2H), 7.36 (d, 2H, J = 1.5 Hz), 7.33 (d, 2H, J = 1.5 Hz), 4.14 (br, 4H), 3.78 (s, 6H), 1.79 (br, 4H) ppm. Lit.[27] ^{1}H NMR (D_2O, 400 MHz) δ 7.39 (d, J = 11.5 Hz, 4H), 4.18 (s, 4H), 3.82 (s, 6H), 1.83 (s, 4H) ppm. HRMS (ESI/TOF-Q) m/z: $[M+Br]^+$ calcd for $C_{12}H_{20}N_4Br$ 299.0871; found 299.0885.

3,3′-Bis(1-methyl-imidazolium)-1,6-hexane Dibromide ([DIC6]-Br_2). 1-Methylimidazole (0.50 g, 6.0 mmol) was reacted with 1,6-dibromohexane (0.46 mL, 3.0 mmol) in 15 mL of anhydrous THF under reflux for about 18 h, after cooling in an ice−water bath, and the white precipitate was filtered and washed with THF and ether three times, respectively, and dried in a vacuum oven. Yield: 0.70 g (58%). Mp 26−27 °C; ^{1}H NMR (D_2O, 400 MHz) δ 8.62 (s, 2H), 7.38 (s, 2H), 7.34 (s, 2H), 4.10 (t, 4H, J = 7.1 Hz), 3.80 (s, 6H), 1.77 (br, 4H); 1.25 (br, 4H) ppm. Lit.[27] ^{1}H NMR (D_2O, 400 MHz) δ 7.36 (d, J = 14.8 Hz, 4H), 4.10 (t, 4H, J = 7.1 Hz, 4H), 3.80 (s, 6H), 1.78 (s, 4H); 1.26 (s, 4H) ppm. HRMS (ESI/TOF-Q) m/z: $[M + Br]^+$ calcd for $C_{14}H_{24}N_4Br$ 327.1184; found 327.1177.

3,3′-Bis(1-methyl-imidazolium)-1,8-octane Diiodide ([DIC8]I_2). 1-Methylimidazole (1.0 g, 12 mmol) was reacted with 1,8-diiodooctane (1.2 mL, 6.0 mol) in 25 mL of anhydrous THF under reflux for about 18 h. Cooling the reaction mixture in an ice−water bath yielded an off-white precipitate, which was filtered, washed three times with THF and ether, respectively, and dried in a vacuum oven. Yield: 2.8 g (yield 88%). Mp 92−93 °C; ^{1}H NMR (D_2O, 400 MHz) δ 8.61 (s, 2H), 7.38 (s, 2H), 7.34 (s, 2H), 4.09 (t, 4H, J = 7.2 Hz), 3.80 (s, 6H), 1.77 (m, 4H); 1.22 (m, 4H) ppm. (Lit.[28] ^{1}H NMR (90% H_2O/10% D_2O, 600 MHz) δ 8.59 (2H), 7.35 (2H), 7.31 (2H), 4.06 (4H), 3.77 (6H), 1.73 (4H), 1.18 (4H) ppm. HRMS (ESI/TOF-Q) m/z: $[M + I]^+$ calcd for $C_{16}H_{28}N_4I$ 403.1359; found 403.1365.

1-Methyl-3-butyl-imidazolium Iodide ([IC4]I). A solvent-free sonochemical preparation method was used to synthesize the [ICn]X imidazolium salts.[26b] 1-Methylimidazole (0.82 mL, 10 mmol) was mixed with 1-iodobutane (1.26 mL, 11 mmol) and sonicated for 2 h, to produce a light yellow oil. This product was washed with ether three times and dried in an oven. The final product was obtained as a light yellow oil in a yield of 1.5 g (56%). ^{1}H NMR (D_2O, 400 MHz) δ 8.61 (s, 1H), 7.37 (s, 1H), 7.32 (s, 1H), 4.09 (t, 2H, J = 7.2 Hz), 3.78 (s, 3H), 1.72 (d, 2H, J = 7.1 Hz), 1.21 (q, 2H, J = 7.1 Hz), 0.82 (t, 3H, J = 7.2 Hz) ppm. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.15 (s, 1H), 7.79 (s, 1H), 7.71 (s, 1H), 4.17 (t, 2H, J = 7.2 Hz), 3.85 (s, 3H), 1.76 (qn, 2H, J = 7.4 Hz), 1.23 (qn, 2H, J = 7.4 Hz, 0.88 (t, 3H, J = 7.4 Hz) ppm. (Lit.[29] ^{1}H NMR (DMSO-d_6, 250 MHz) δ 9.20 (s, 1H), 7.80, (s, 1H), 7.70 (s, 1H), 4.20 (t, 2H), 3.87 (s, 3H), 1.87 (m, 2H), 1.25 (m, 2H) 0.85 (t, 3H) ppm). HRMS (ESI/TOF-Q) m/z: $[M]^+$ calcd for $C_8H_{15}N_2$ 139.1235; found 139.1241.

1-Methyl-3-hexyl-imidazolium Bromide ([IC6]Br). 1-Methylimidazole (0.82 mL, 10 mmol) was mixed with 1-bromohexane (1.54 mL, 11 mmol) and sonicated for 4 h. The colorless oil product was washed three times with ether and dried in an oven. 1.7 g (69%). ^{1}H NMR (D_2O, 400 MHz) δ 8.60 (s, 1H), 7.37 (d, 1H, J = 1.5 Hz), 7.32 (d, 1H, J = 1.5 Hz), 4.09 (t, 2H, ^3J = 7.1 Hz), 3.79 (s, 3H), 1.76 (qn, 2H, J = 6.7 Hz), 1.19 (br, 6H), 0.75 (t, 3H, ^3J = 6.9 Hz) ppm. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.34, 7.60, 7.44, 4.30, 4.11, 1.89, 1.29, 0.85 ppm. Lit.[30] ($CDCl_3$, 60 MHz) δ 8.41 (s, 1H), 7.54 (s, 1H), 7.33 (s,

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1H), 4.03 (t, 2H), 3.66 (s, 3H), 1.93−1.11 (m, 8H), 0.81 (t, 3H). HRMS (ESI/TOF-Q) m/z: $[M]^+$ calcd for $C_{10}H_{19}N_2$ 167.1548; found 167.1551.

1-Methyl-3-octyl-imidazolium Bromide ([IC8]Br). 1-Methylimidazole (0.82 mL, 10 mmol) was mixed with 1-bromooctane (1.9 mL, 11 mmol) and sonicated for 5 h. A yellow oily product was washed with ether three times and dried in an oven. 1.5 g (yield: 55%). ^{1}H NMR (D_2O, 400 MHz) δ 8.59 (s, 1H), 7.36 (d, 1H, J = 1.6 Hz), 7.32 (d, 1H, J = 1.6 Hz), 4.08 (t, 2H, J = 7.1 Hz), 3.78 (s, 3H), 1.75 (qn, 2H, J = 7.2 Hz), 1.17 (m, 10H), 0.75 (t, 3H, J = 6.6 Hz); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.42 (s, 1H), 7.54 (s, 1H), 7.39 (s, 1H), 4.31 (t, 2H, J = 7.4 Hz, 4.13 (s, 3H), 1.91 (qn, 2H, J = 7.1 Hz), 1.32−1.24 (m, 10H), 0.86 (t, 3H, J = 6.8 Hz) ppm. (Lit.[30] ^{1}H NMR ([C_8mim]Cl, $CDCl_3$, 400 MHz) δ 10.33 (s, 1H), 7.59 (s, 1H), 7.37 (s, 1H), 4.16 (t, 2H, J = 7.4 Hz, 3.97 (s, 3H), 1.75 (m, 2H), 1.10 (m, 10H), 0.70 (t, 3H, J = 7 Hz) ppm.) HRMS (ESI/TOF-Q) m/z: $[M]^+$ calcd for $C_{12}H_{23}N_2$ 195.1861; found 195.1853.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01853.

^{1}H NMR spectra and titrations (including competitive binding), ESI mass spectra, Job plots, H/D exchange kinetic plots, energy-minimized structures (including atomic coordinates and absolute energies), H-bonds length and angles, and the full citation of ref 24 (PDF)

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Notes

The authors declare no competing financial interest.

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