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New guests for the cucurbit[8]uril host. Formation of G_2H ternary complexes

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On the basis of the highly stable G_2H (2 : 1) ternary complex formed by two methyl viologen cation radicals inside the cavity of cucurbit[8]uril, we prepared three monocationic 4-phenylpyridinium derivatives: 1-(hydroxyethyl)-4-phenyl-pyridinium (1^+) bromide, 1-(octaethyleneglycol)-4-phenyl-pyridinium (2^+) chloride, and 4-[4-(methoxymethoxy)phenyl] pyridinium (3^+) iodide, as possible guests for 2 : 1 complexation inside cucurbit[8]uril. We also investigated a fourth monocationic guest (4^+), in which a central vinylidene group is inserted to elongate the 4-phenyl-pyridinium residue. Using ^{1}H NMR and UV–Vis spectroscopic data and mass spectrometric data, we obtained unequivocal evidence for the formation of G_2H (2 : 1) ternary complexes in all cases. The stoichiometry of the complexes was further verified by continuous variation (Job) plots, and in some cases, high resolution ESI-MS spectrometric data. Diffusion coefficient measurements, using ^{1}H NMR pulse gradient spin echo techniques, yielded values consistent with the formation and expected structures of the ternary complexes. Copyright © 2012 John Wiley & Sons, Ltd.
Supporting information may be found in the online version of this paper.

Keywords: cucurbituril hosts; host–guest complexes; inclusion complexes; ternary complexes

INTRODUCTION

Cucurbit[8]uril (CB8) is a macrocyclic host formed by the condensation in acidic medium of glycoluril and formaldehyde.[1,2] A member of the cucurbit[*n*]uril family of hosts,[3–11] it is characterized by its ability to bind simultaneously two aromatic guests in its cavity. Kim *et al*. first reported the formation of charge transfer complexes – between a π-donor (dihydroxynaphthalene) and a π-acceptor (methyl viologen) – inside the cavity of CB8.[12] These two guests are obviously different, albeit complementary in their π-donor/acceptor characters. Thus, the corresponding ternary complexes can be classified as GG'H complexes, where G and G' represent the two distinct aromatic guests and H symbolizes the host. Jeon *et al*. also showed that CB8 sharply stabilizes and includes the dimer formed by methyl viologen radical cations,[13] which illustrates a different class of ternary complex (G_2H) with two identical guests. His group has made extensive use of these unique binding properties to design and demonstrate the operation of a number of interesting CB8-based, switchable molecular systems.[6,7] We have used CB8 to mediate the redox-controlled dimerization of dendrimers containing viologen residues[14] and extended this concept to the redox control and size selection of dimeric assemblies formed between two types of dendrimers, containing either (π-acceptor) viologen groups or (π-donor) dialkoxybenzene groups.[15] Recently, Appel *et al*. have shown that CB8 can be used to mediate the formation of supramolecular polymers.[16] Vincil and Urbach also investigated the effects of the number and placement of positive charges on viologen-cucurbit[*n*]uril interactions.[17] This entire body of work relies on the pronounced stabilization of aromatic donor–acceptor charge transfer complexes or viologen radical cation dimers inside the cavity of CB8.

In this work, we propose an expansion of this chemistry and investigate new guests for CB8 inspired by the considerable stability of the ternary complexes that result from two viologen radical cations forming a π–π dimer inside the cavity of CB8. The main idea is shown in Scheme 1. Although methyl viologen forms a stable 1 : 1 complex with CB8, its one-electron reduced form selectively yields a 2 : 1 complex with the same host.[13] As mentioned before, this complex is a clear example of a G_2H complex, in which two identical guests are held inside the host cavity. We reasoned that this ternary (2 : 1 or G_2H) complex derives stabilization from the ion–dipole interactions between the two positive charges on the radical cation dimer and the rims of carbonyl oxygens lining the host cavity portals. Contacts between the aromatic surfaces of the viologen radical cations and between the dimer and the inner surface of the cavity, coupled with hydrophobic forces, also contribute significantly to the stability of the ternary complex. As shown in Scheme 1, we propose to replace the viologen radical cations by two 4-phenyl-pyridinium residues. Each 4-phenyl-pyridinium group provides the same overall charge (+1) as that on the methyl viologen radical cation and a similarly sized aromatic surface. Our hypothesis is that 4-phenyl-pyridinium derivatives will form stable 2 : 1 (G_2H) complexes inside the cavity of CB8 with an overall stability similar to that exhibited by viologen radical cation dimer complexes.

To test this idea, we prepared three monocationic compounds containing the 4-phenyl-pyridinium residue. Their structures are shown in Fig. 1. Guests $\mathbf{1}^+$ and $\mathbf{2}^+$ are simple 4-phenyl-pyridinium derivatives with *N*-substituents of variable length, intended to

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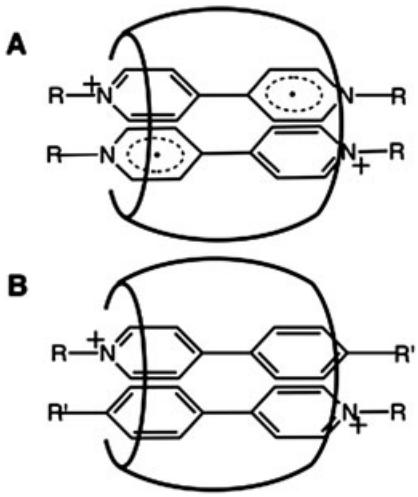

Scheme 1. Schematic comparison of the G_2H ternary complexes formed by CB8 with (A) a viologen radical cation dimer and (B) two identical 4-phenyl-pyridinum guests

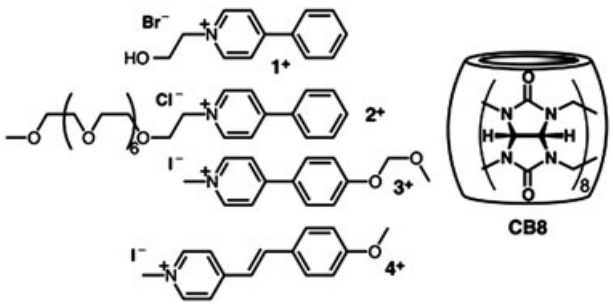

Figure 1. Structures of the cationic guests and the host used in this work

increase their solubility in aqueous solution. Guest $\mathbf{3}^+$ was designed to increase the π-donor character of the 4-phenyl ring by attaching $-OCH_2OCH_3$ as the terminal group. If we assume that, in the CB8 inclusion complex, the positively charged pyridinium rings interact with the host portals, deriving stabilization from ion-dipole forces, each of the 4-phenyl rings should be in close contact with the pyridinium ring on the other guest (see Scheme 1B). Therefore, increasing the π-donor character of the 4-phenyl ring should favor the development of charge transfer interactions and enhance the overall stability of the complex. We also decided to test a structurally related phenyl-vinylidene-pyridinium compound ($\mathbf{4}^+$), which was available to us.

RESULTS AND DISCUSSION

The binding studies between the cationic guests shown in Fig. 1 and the CB8 host were carried out using several experimental techniques. ^{1}H NMR spectroscopy was useful at elucidating the main binding sites and gave us insight into the stoichiometry of the complexes. Electronic absorption spectroscopy was extremely useful, because its higher sensitivity allows the investigation of binding interactions at lower guest/host concentrations than is possible with nuclear magnetic resonance (NMR) spectroscopy. Continuous variation (Job) plots based on UV–Vis data were important to establish the stoichiometry of the complexes and mass spectrometric data were also useful in this regard. Finally, pulse gradient spin echo (PGSE) NMR techniques were used to determine the diffusion coefficients of the various guests, the CB8 host, and the corresponding supramolecular host–guest complexes.

Figure 2 shows the ^{1}H NMR spectrum of guest $\mathbf{3}^+$ in D_2O solution as the concentration of CB8 was increased from 0 to 0.6 equiv. The most noticeable host-induced shifts are experienced by the aromatic protons on the guest, which move upfield, as expected from their inclusion in the cavity of CB8. The N–CH_3 protons also shift upfield by ~0.3 ppm, the O–CH_2–O protons barely shift and the OCH_3 protons experience a small downfield shift. Interestingly, all these host-induced shifts level off and reach saturation values as soon as the concentration of CB8 reaches 0.5 equiv., that is, host additions beyond this level have no further effect on the ^{1}H NMR resonances of the guest. Taken together, this set of experimental data indicates the formation of a G_2H (2 : 1) complex, in which the aromatic residues of the guests are included within the host cavity.

Figure 3 shows similar NMR data obtained with guest $\mathbf{2}^+$. The analysis of the data leads to a similar conclusion, that is, the formation of a G_2H complex, with two $\mathbf{2}^+$ guests bound to CB8 by inclusion of their aromatic units inside the host cavity. However, an important difference between the two complexes is the behavior of the highest field aromatic proton (at ~9.0 ppm), which in the case of guest $\mathbf{2}^+$ undergoes a minimal upfield shift upon addition of CB8. This NMR resonance corresponds to the protons on the carbon adjacent to the pyridinium nitrogen on

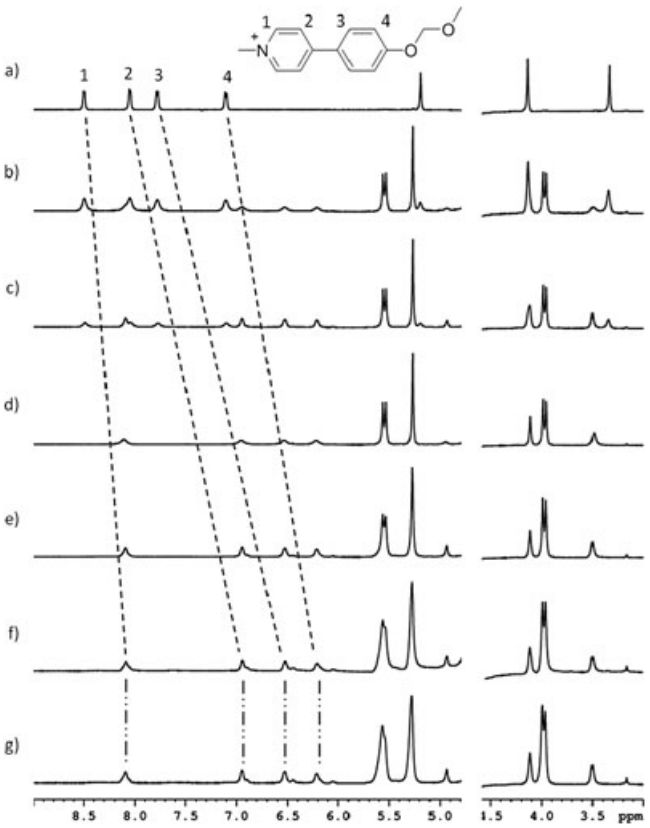

Figure 2. Partial ^{1}H NMR spectra (500 MHz, D_2O) of guest $\mathbf{3}^+$ (1.0 mM) in the absence (a) and in the presence of (b) 0.1 mM, (c) 0.2 mM, (d) 0.3 mM, (e) 0.4 mM, (f) 0.5 mM, and (g) 0.6 mM CB8

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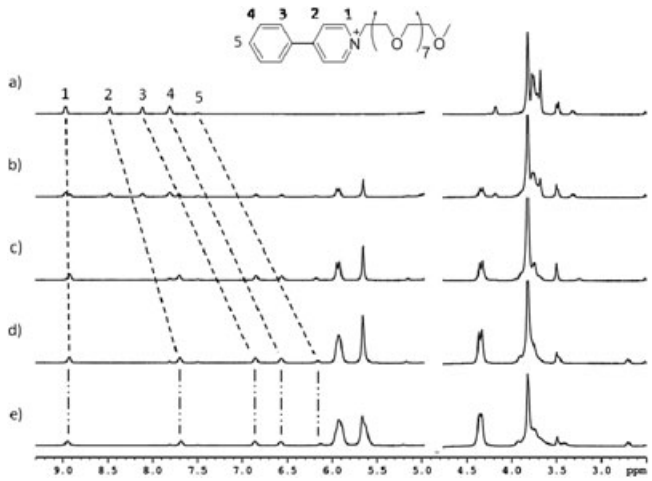

Figure 3. Partial ^{1}H NMR spectra of guest $\mathbf{2}^+$ (1.0 mM) in the absence (a) and in the presence of (b) 0.1 mM, (c) 0.25 mM, (d) 0.5 mM, and (e) 0.75 mM CB8

the guest. The very small upfield shift induced by the presence of CB8 suggests a more shallow inclusion of the aromatic residue of this guest inside the host cavity in the $(\mathbf{2}^+)_2$·CB8 complex as compared with the $(\mathbf{3}^+)_2$·CB8 complex. This difference must be the result of the long ethyleneglycol *N*-substituent chain present in the former guest. The NMR spectroscopic data for the guest $\mathbf{4}^+$ resemble those obtained with guest $\mathbf{3}^+$, suggesting deeper inclusion of the aromatic residue (see Fig. S1). Unfortunately, the simpler guest $\mathbf{1}^+$ was found to be poorly soluble in aqueous solution, which made impossible the collection of suitable NMR spectroscopic data.

The electronic absorption spectrum of $\mathbf{3}^+$ shows two main bands at 225 and 321 nm. In the presence of increasing concentrations of CB8 the intensity of both bands is depressed and the absorption maxima undergo bathochromic shifts (Fig. 4). Similar depressions of the guest's molar absorptivity coefficients have been previously observed with other absorbing guests bound to cucurbituril hosts. In the case of guest $\mathbf{3}^+$, these host-induced effects are more pronounced on the lower energy band at 321 nm. A plot of absorbance (at 321 nm) as a function of the added concentration of CB8 is shown in the inset of Fig. 4. The decreasing absorbance values level off quickly after the addition of 0.5 equiv. of CB8, again suggesting the formation of a G_2H (2 : 1) complex. To further confirm the stoichiometry of the complex, we recorded the corresponding Job plot, which exhibits a very well defined maximum at a molar fraction of guest equal to 0.67 (Fig. 5), providing unequivocal evidence for the expected 2 : 1 stoichiometry in the supramolecular complex. Similar UV–Vis data were obtained with all the other guests, and Job plots confirmed the 2:1 stoichiometry in all cases (see Figs S2–S5).

It is important to note here that these UV–Vis experiments were performed with guest concentrations in the range 1–5 $\times$ 10^{-5} M. The fact that the electronic absorption spectroscopic data show essentially quantitative formation of the G_2H (2 : 1) complexes at these low concentrations indicates that the thermodynamic stability of the complexes is substantial. On the basis of the spectroscopic data, we estimate a minimum value of ~1 $\times$ 10^8 M^{-2} for the equilibrium association constant (K) corresponding to the overall complexation process: $2\,G + H \rightleftarrows G_2H$.

The stability of the complexes led us to attempt their detection in the gas phase using mass spectrometric methods. Cucurbituril complexes are usually stable enough to allow their detection by mass spectrometry and our group has reported a number of examples in recent work.[18] Rauwald *et al*. have developed a method to estimate the stability of cucurbituril inclusion complexes from mass spectrometric data.[19] Using high-resolution electrospray mass spectrometry (ESI-MS) we detected the presence of the $(\mathbf{3}^+)_2$·CB8 complex in the gas phase, at an m/z ratio of 894.8210. The experimental and simulated spectra are shown in the supporting information (Fig. S6). We also detected an intense ESI-MS peak for $(\mathbf{4}^+)_2$·CB8 (Fig. S7). Attempts to obtain ESI-MS evidence for the $(\mathbf{2}^+)_2$·CB8 complex failed, but we could detect a clear peak for the $\mathbf{2}^+$·CB8 1 : 1 complex under matrix-assisted laser desorption ionization mass spectrometry (MALDI MS) conditions (data not shown). Although this is a qualitative result and we cannot discard the possible observation of $(\mathbf{2}^+)_2$·CB8 complex using different mass spectrometric conditions, the relatively easy detection of the $(\mathbf{3}^+)_2$·CB8 and $(\mathbf{4}^+)_2$·CB8 complexes suggest that these two complexes are more stable than $(\mathbf{2}^+)_2$·CB8. This is in qualitative agreement with the NMR spectroscopic results that suggest a more shallow inclusion of the aromatic residues of guest $\mathbf{2}^+$ inside the CB8 cavity.

As discussed before, we also measured diffusion coefficients (D_o's) using NMR PGSE techniques. The recorded values are given in Table 1 and are generally consistent with the formation of 2 : 1 complexes. For instance, the D_o value recorded for the $(\mathbf{3}^+)_2$·CB8 complex is ~10% lower than the value recorded for uncomplexed CB8 and much lower than the value obtained for the free guest ($\mathbf{3}^+$). These findings are consistent with the postulated structure of the 2 : 1 complex, in which the guest aromatic

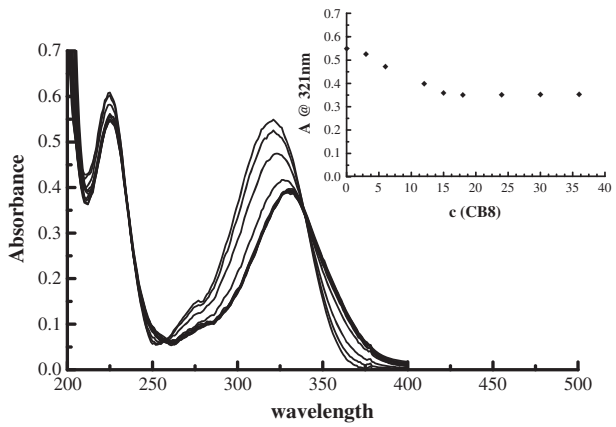

Figure 4. UV-titration guest $\mathbf{3}^+$ (30 μM) upon addition of increasing concentrations of CB8 in aqueous solution

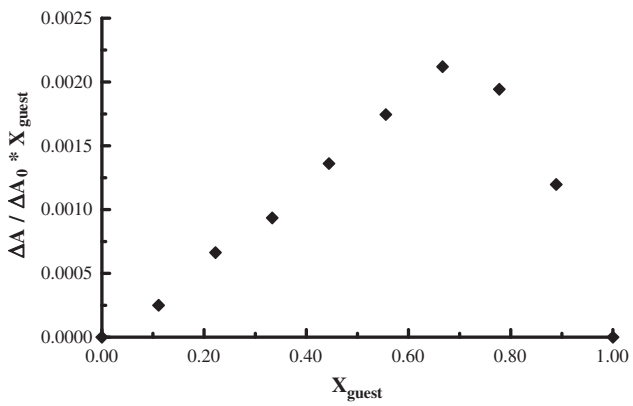

Figure 5. Job-plot of guest $\mathbf{3}^+$ with CB8

Table 1. Diffusion coefficients (D_o's) recorded using ^{1}H NMR PGSE techniques in D_2O solution at 25 °C

Compound	D_o ($cm^2\ s^{-1}$)	Complex	D_o ($cm^2\ s^{-1}$)
CB8	2.63×10^{-6}	—	—
$\mathbf{2}^+$	3.17×10^{-6}	$(\mathbf{2}^+)_2$·CB8	1.64×10^{-6}
$\mathbf{3}^+$	5.56×10^{-6}	$(\mathbf{3}^+)_2$·CB8	2.38×10^{-6}
$\mathbf{4}^+$	5.36×10^{-6}	$(\mathbf{4}^+)_2$·CB8	2.70×10^{-6}

residues are included inside the host cavity. Therefore, the complex is expected to exhibit a molecular volume slightly larger than that of the free host, with the volume increment reflecting the small substituents on the guests that are not included inside the cavity. The D_o value recorded for the $(\mathbf{4}^+)_2$·CB8 complex is identical within experimental error to that of CB8. This is probably a result of the rigid character of guest $\mathbf{4}^+$, which decreases the potential dragging effects of any small groups protruding outside of the CB8 cavity in the 2 : 1 complex. In contrast to these complexes, the $(\mathbf{2}^+)_2$·CB8 complex shows a D_o value significantly lower than that of free CB8, a result of the two long 'PEGylated' chains protruding from the cavity in the 2 : 1 complex.

CONCLUSIONS

We have shown that two new 4-phenyl-pyridinium derivatives ($\mathbf{2}^+$ and $\mathbf{3}^+$) and a related vinylidene compound ($\mathbf{4}^+$) are suitable guests for the formation of G_2H (2 : 1) ternary complexes with the CB8 host. Our experimental results show that these guests form ternary complexes readily at submillimolar concentration levels of the individual components, reflecting the considerable stability of these supramolecular complexes. Somewhat unexpectedly, the ^{1}H NMR data provide experimental evidence for shallower penetration of guest $\mathbf{2}^+$, as compared with guests $\mathbf{3}^+$ and $\mathbf{4}^+$, inside the host cavity. This finding may be attributable to the presence of an oligo(ethyleneglycol) chain attached to the positively charged nitrogen atom. The likely electrostatic repulsions between the chain oxygen atoms and the carbonyl oxygen on the host portal weaken the N^+-portal ion–dipole interactions, leading to less penetration of guest $\mathbf{2}^+$ and increased distance between the nitrogen atom on the guest and the portal entrance on the host. This experimental finding may be of general importance in the design of other guests for inclusion by cucurbit[*n*]uril hosts.

EXPERIMENTAL

Chemicals and experimental techniques

Guests $\mathbf{1}^+$ and $\mathbf{4}^+$ were prepared according to published reports.[20,21]

Synthesis of octaethylene glycol monomethyl ether tosylate

The tosylation reaction was carried out according to the literature procedure[22] reported for polyethylene glycol monomethyl ether. Octaethylene glycol monomethyl ether solution (2.0 mmol, 0.77 mg) in 2.0 mL THF was added to a NaOH solution (2.0 mL, 3.88 M), while keeping the temperature below 5 °C. A solution of TsCl (1.9 mmol, 0.35 g) in 2.0 mL tetrahydrofuran (THF) was added drop-wise over 2.5 h. After stirring for another 4 h, the reaction mixture was poured into water (15 mL) and dichloromethane (15 mL) was added. Following phase separation, the aqueous layer was extracted with dichloromethane (15 mL) three more times and the organic layers were extracted with water (two times) and brine. The organic layer was dried over $MgSO_4$ and filtered. After solvent evaporation the desired compound was obtained as an oil. ^{1}H NMR (CD_2Cl_2, 500 MHz): δ = 2.44 (s, 3H), 3.32 (s, 4H), 3.43-3.68 (m, PEG), 4.11 (s, 2H), 7.37 (d, *J* = 7.46 Hz, 2H), 7.77 (d, *J* = 7.54 Hz, 2H) ppm. HRMS (ESI): calcd for $C_{24}H_{42}O_{11}S$ $[M]^{+[Na]}$ 561.2340; found 561.2358

Synthesis of 1-(octaethyleneglycol)-4-phenylpyridinium (2^+)

The reaction was carried out according to the literature procedure[23] reported for the synthesis of *N*-alkylpyridinium podands. 4-Phenylpyridinium (0.58 mmol, 90 mg) and octaethylene glycol monomethyl ether tosylate (0.72 mmol, 388 mg) were boiled in 5.0 mL of dioxane for 5 h with reflux and the reaction progress was monitored by thin layer chromatography (TLC). Upon completion, the solvent was evaporated. Excess octaethylene glycol monomethyl ether tosylate was removed by reversed phase chromatography. The counter ion (OTs^-) was exchanged to Cl^- by using an ion-exchange resin. The desired 4-phenylpyridinium salt was obtained as a viscous liquid.

^{1}H NMR (D_2O, 500 MHz): δ = 3.42 (s, 3H), 3.57–3.85 (m, PEG), 4.12 (s, 2H), 7.43 (s, 1H) , 7.74 (d, *J* = 3.92 Hz, 2H), 8.05 (d, *J* = 5.5 Hz, 2H), 8.41 (d, *J* = 3.62 Hz, 2H), 8.91 (d, *J* = 3.85 Hz, 2H) ppm. ^{13}C NMR (in D_2O, 500 MHz): δ =68.62($-OCH_3$), 69.53($-OCH_2CH_2O-$), 69.62($-NCH_2-$), 69.79, 71.67, 124.71, 127.95, 129.76, 132.31, 133.68, 144.58, 156.80. HRMS (ESI): calcd for $C_{28}H_{44}O_8N$ $[M]^+$ 522.3061; found 522.3084

Synthesis of 4-[4-(methoxymethoxy)phenyl]pyridinium iodide (3^+)

The precursor pyridine derivative was synthesized using a literature procedure.[24] To a solution of 4-[4-(methoxymethoxy)phenyl]pyridine (0.30 mmol, 65 mg) in acetone (5.0 mL), iodomethane (1.2 mmol, 0.17 g) was added. The reaction mixture was stirred under reflux for 4 h. Afterwards, the mixture was cooled down overnight and the desired phenylpyridinium salt was filtered out and isolated as a yellowish solid.

^{1}H NMR (D_2O, 500 MHz): δ = 3.34 (s, 3H), 4.14 (s, 3H), 5.19 (s, 2H), 7.11 (d, *J* = 8.0 Hz, 2H), 7.78 (d, *J* = 8.2 Hz, 2H), 8.05 (d, *J* = 5.5 Hz, 2H), 8.50 (d, *J* = 5.5 Hz, 2H) ppm. ^{13}C NMR (MeOD, 500 MHz): δ = 46.34($-NCH_3$), 55.22 ($-OCH_3$), 93.91($-OCH_2O-$), 116.98, 123.31, 126.54, 129.50, 144.92, 155.55, 160.99. HRMS (ESI): calcd for $C_{14}H_{16}O_2N$ $[M]^+$ 230.1176; found 230.1196

All electronic absorption spectra were recorded using a 1-cm quartz cuvette. Mass spectrometric data were obtained either with a high-resolution electrospray ionization time-of-flight (ESI-TOF) mass spectrometer or a matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectrometer. Diffusion coefficients were measured by ^{1}H NMR PGSE techniques as previously reported by our group.[25,26]

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