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Supramolecular Assembly of 2,7-Dimethyldiazapyrenium and Cucurbit[8]uril: A New Fluorescent Host for Detection of Catechol and Dopamine

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Abstract: The formation of a highly stable inclusion complex between 2,7-dimethyldiazapyrenium (Me_2DAP^{2+}) and the cucurbit[8]uril host (CB8) was demonstrated by X-ray crystallography; MALDI-TOF mass spectrometry; and ^{1}H NMR, electronic absorption, and emission spectroscopy. The equilibrium association constant was determined to be $8.9(\pm0.2)\times10^5\,L\,mol^{-1}$ from UV-visible data and $8.4(\pm1.5)\times10^5\,L\,mol^{-1}$ from fluorescence data. The Me_2DAP^{2+}·CB8 inclusion complex acted as a host to bind compounds containing aromatic π-donor moieties (D), such as catechol and dopamine. This point was demonstrated by ^{1}H NMR spectroscopy, and electrochemical and emission measurements. Fluorescence detection of the Me_2DAP^{2+}·D·CB8 ternary complexes was evident in aqueous solution and on the surface of silica particles, to which fluorescent diazapyrenium units had been covalently immobilized.

Keywords: charge-transfer complexes · cyclic voltammetry · fluorescence · host–guest systems · sensors

Introduction

Cucurbit[8]uril (CB8), one of the members of the cucurbituril host family, was recently synthesized and first characterized by Kim and co-workers.[1] While the smaller CB hosts, CB6 and CB7, form stable 1:1 complexes by including a single guest molecule at a time, the larger cavity of CB8 has been shown to accommodate two identical[2] or different[3] aromatic guests. So far, much attention has been paid to ternary stable complexes, in which aromatic π-donor–acceptor pairs are stabilized by charge-transfer interactions inside the hydrophobic cavity of CB8. These systems have been used for the preparation of molecular amphiphiles,[3a] molecular loops,[3b,c] supramolecular polymers grown on gold surfaces,[3d] and recognition of aromatic amino acids and neurotransmitters,[3g] in which 4,4′-bipyridinium (viologen) residues have played a prominent role.

We have recently reported that the 2,7-dimethyldiazapyrenium dication (Me_2DAP^{2+}) forms an inclusion complex with CB7.[4] Me_2DAP^{2+} has a larger cross-section than methylviologen (Me_2V^{2+}) and shows significant fluorescence quenching in the presence of electron donors in neutral aqueous solution.[5] Due to their luminescence properties, diazapyrenium derivatives have been investigated as fluorescence probes for the detection of neurotransmitters.[6] Since Me_2DAP^{2+} is structurally and electronically related to Me_2V^{2+} we decided to investigate the formation of ternary inclusion complexes between Me_2DAP^{2+} and electron-rich aromatic guests inside the CB8 cavity (Scheme 1). These ternary complexes may accompany the development of novel fluorescence-based methods for the detection and sensing of catecholamines and related neurotransmitters. Here, we report the results of this investigation.

Results and Discussion

The inclusion complexation of guest Me_2DAP^{2+} by host CB8 was readily detected by ^{1}H NMR spectroscopy[7] (Figure 1). Upon addition of 1.2 equivalents of the host the

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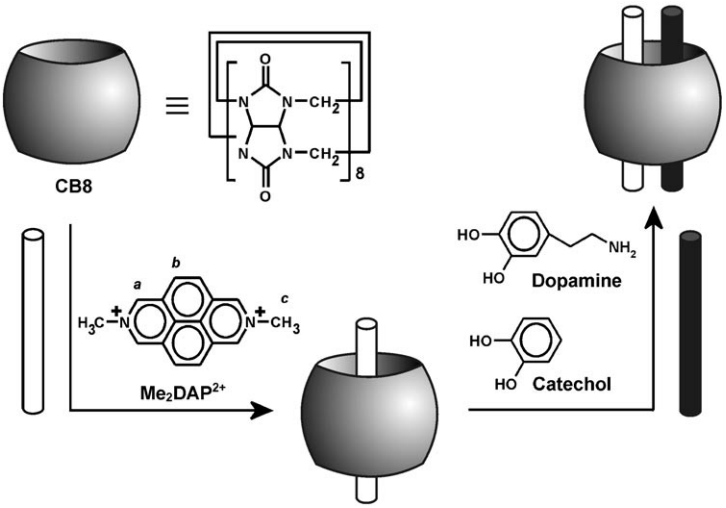


Scheme 1. Formation of binary and ternary inclusion complexes with CB8.

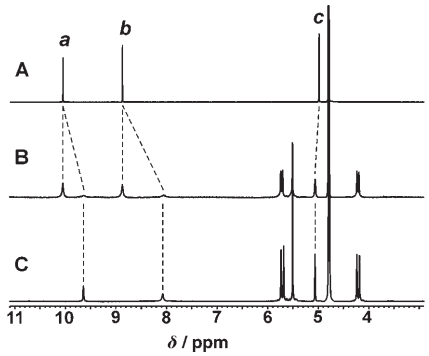


Figure 1. ^{1}H NMR spectra (500 MHz, 0.1 M NaCl/D_2O, sodium phosphate buffer, pH = 7.0) of Me_2DAP^{2+} in the absence (A), and in the presence of 0.5 equivalents (B) and 1.2 equivalents (C) of CB8.

signals *a* and *b* (assigned to the aromatic protons of Me_2DAP^{2+}) exhibit evident upfield shifts of 0.4 and 0.8 ppm, respectively, while the signal corresponding to the terminal methyl protons is displaced downfield by 0.1 ppm. This pattern of complexation-induced shifts is consistent with an inclusion complex in which the aromatic unit of Me_2DAP^{2+} is included inside the hydrophobic cavity of CB8. The formation of a stable 1:1 complex between Me_2DAP^{2+} and CB8 was further supported by observation of a major signal at $m/z = 1563$, corresponding to CB8·Me_2DAP^+, in the MALDI-TOF MS spectrum (see Supporting Information). The construction of a Job plot by using UV-visible spectroscopy (Figure 2) revealed a maximum at $\chi Me_2DAP^{2+} = 0.5$, which also clearly indicates 1:1 stoichiometry between the host and the guest.

The complexation between Me_2DAP^{2+} and CB8 falls within the slow-exchange regime on the NMR timescale. In the presence of 0.5 equivalents of the host, the proton signals of both the bound and free guests are clearly evident (Figure 1B). A similar complexation-induced NMR pattern

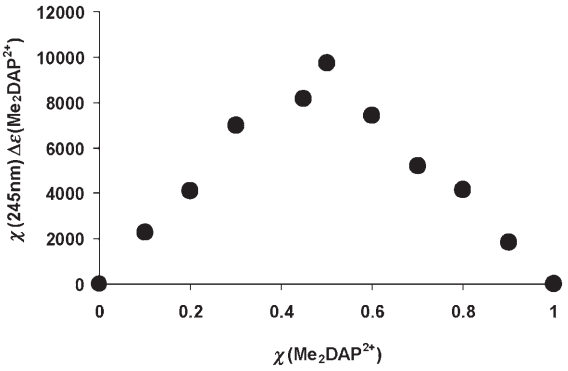


Figure 2. Job plot for CB8·Me_2DAP^{2+} complex ([CB8] + [Me_2DAP^{2+}] = 12 μM) in sodium phosphate buffer, pH 7.0 also containing 0.1 M NaCl.

was previously observed for the tight-fitting complex between Me_2DAP^{2+} and CB7.[4] We obtained good quality single crystals of the CB8·Me_2DAP^{2+} complex and solved the corresponding crystal structure by X-ray diffraction (Figure 3A). X-ray crystallography and molecular modeling of the CB8·Me_2DAP^{2+} complex revealed an elliptical distortion of the CB8 cavity forced by the inclusion of the guest. The energy-minimized structure of the CB8·Me_2DAP^{2+} complex is almost identical to the X-ray structure of the complex in the solid state (Figures 3A and 3B; see also Supporting Information). Both structures show some stretching of CB8; however, this stretching is less pronounced than the distortion of CB7 in the energy-minimized structure of the CB7·Me_2DAP^{2+} complex.[4] This result is indeed consistent with the larger cavity of CB8.

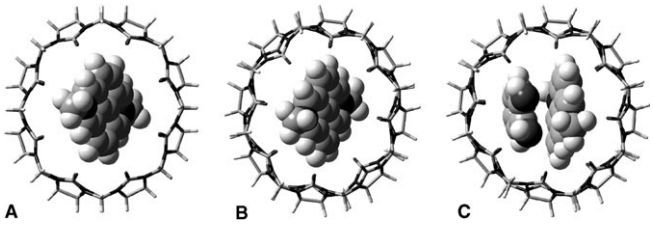


Figure 3. A) Crystal structure, B) energy-minimized structure (AM1) of the CB8·Me_2DAP^{2+} complex, and C) energy-minimized structure (AM1) of the CB8·catechol·Me_2DAP^{2+} complex.

The equilibrium association constant (K) exceeds the maximum value that can be determined by NMR spectroscopy. At the mM concentration levels required for ^{1}H NMR spectroscopic measurements, any NMR parameter sensitive to complexation gives rise to break-point titration curves, which are useless for the determination of binding constants. However, electronic absorption and fluorescence emission spectroscopic techniques can be used for the determination of the K value between Me_2DAP^{2+} and CB8. The band at 245 nm in the electronic spectrum of Me_2DAP^{2+} shows a decreased absorbance upon addition of the host (Figure 4). By fitting the absorbance as a function of the CB8 concentration we obtained a K value for the 1:1 complex of $8.9(\pm 0.2) \times 10^5$ L mol^{-1}.

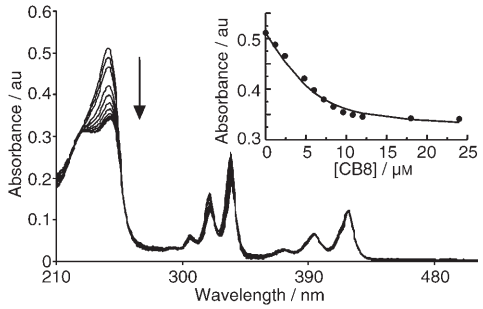


Figure 4. Electronic absorption spectrum of Me_2DAP^{2+} (6 μM) in the presence of increasing CB8 concentrations (0–60 μM, in the direction of the arrow). The inset shows the best fit of the experimental data to the 1:1 binding model.

Due to the fluorescent nature of the guest, emission spectroscopy was also used for the determination of the *K* value. The excitation wavelength was set at 338 nm, which corresponds to an isosbestic point in the set of UV-visible spectra obtained as variable concentrations of the host are added to a solution containing a fixed guest concentration. The fluorescence intensity emitted by Me_2DAP^{2+} was significantly increased by the presence of CB8 (Figure 5). This fluorescence enhancement can be rationalized by the encapsulation of the guest inside the hydrophobic cavity of CB8, which shields the guest from the aqueous environment. The experimental data fit very well to a 1:1 binding isotherm, yielding a *K* value of $8.4(\pm1.5)\times10^5\,L\,mol^{-1}$. The binding constants determined from these two types of spectroscopic data are in excellent agreement. In both cases, the *K* value obtained is more than twofold higher than the equilibrium constant measured for the CB7·Me_2DAP^{2+} complex. In sharp contrast to this finding, the inclusion complex CB8·Me_2V^{2+} is less stable than the complex CB7·Me_2V^{2+}.[8] We suggest that a better fit of Me_2DAP^{2+} inside the CB8 cavity requires significantly less distortion of the host and is responsible for the larger *K* value relative to that of the tight CB7·Me_2DAP^{2+} complex.

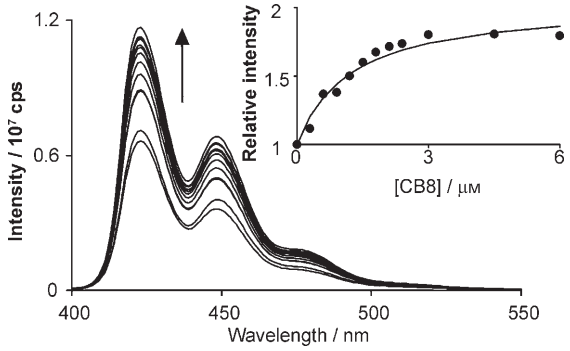


Figure 5. Emission spectrum of Me_2DAP^{2+} (1.5 μM) in the presence of increasing concentrations (0–5 μM, in the direction of arrow, $\lambda_{em}=449$ nm, $\lambda_{exc}=338$ nm) of CB8. The inset shows the best fit of the experimental data to the 1:1 binding model.

The high stability of the CB8·Me_2DAP^{2+} complex suggests its use as a host for a second guest inside the CB8 cavity, giving rise to a CB8·D·Me_2DAP^{2+} ternary complex, in which D stands for a generic π-donor guest. Conceptually, this is equivalent to assembling a receptor for π-donor guests by bringing two components (CB8 and Me_2DAP^{2+}) together by means of molecular recognition. To investigate this possibility, we selected the neurotransmitter dopamine as the second π-donor guest owing to its biological relevance (Scheme 1). In addition, catechol was also used as a simpler model guest.

The formation of a ternary complex in which both dopamine and Me_2DAP^{2+} are included in the CB8 cavity is clearly evident from ^{1}H NMR spectroscopy (Figure 6). Upon addition of one equivalent of CB8 to the 1:1 mixture of both guests, all the aromatic proton signals of dopamine broadened and experienced an upfield shift from 0.1 to 0.3 ppm. At the same time, the aromatic protons of Me_2DAP^{2+} shifted upfield, as described for the inclusion complex CB8·Me_2DAP^{2+} (Figure 1C). Identical ^{1}H NMR spectra were obtained regardless of the addition order of the three components of the ternary complex. These complexation-induced shifts are similar to those previously reported for inclusion of Me_2V^{2+} and 2,6-dihydroxynaphtalene inside CB8.[3d] In a similar experiment, the signals attributed to the catechol protons in the presence of Me_2DAP^{2+} disappear after the addition of the CB8 host, probably because they undergo a significant upfield shift and end up hidden under the CB8 proton signals. This hypothesis was verified by warming up the solution. The catechol proton signals shift downfield and become visible at 90 °C as two broad singlets at approximately $\delta=6.6$ ppm, while these protons exhibit a chemical shift of about $\delta=7.5$ ppm at 90 °C if the same experiment is done in the absence of CB8 (Figure 7 and Supporting Information). The significant upfield shift of the catechol protons in the presence of CB8 verifies the strong catechol–Me_2DAP^{2+} charge-transfer complex formed inside CB8. The charge-transfer interaction between the electron-deficient

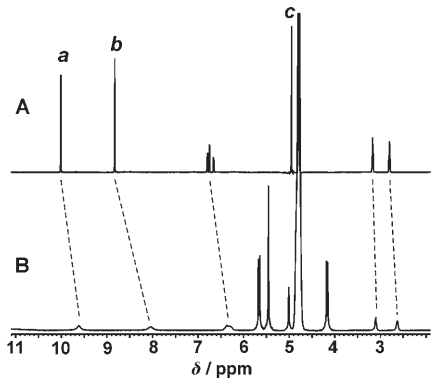


Figure 6. ^{1}H NMR spectra (500 MHz, 0.1 M NaCl/D_2O, sodium phosphate buffer, pH = 7.0 = of 1:1 mixture of Me_2DAP^{2+} and dopamine A) in the absence, and B) in the presence of one equivalent of CB8.

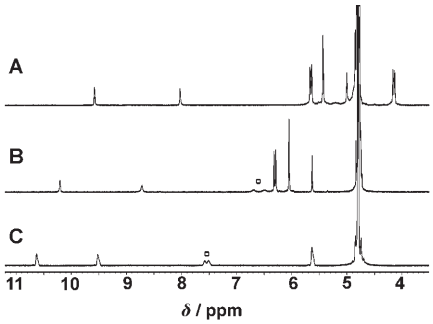


Figure 7. ^{1}H NMR spectra (500 MHz, 0.1 M NaCl/D_2O, sodium phosphate buffer, pH 7.0) of the CB8•catechol•Me_2DAP^{2+} complex at A) 20 °C and B) 90 °C, and C) for a 1:1 mixture of Me_2DAP^{2+} and catechol at 90 °C. "□" labels the catechol protons.

Me_2DAP^{2+} and the electron-rich guest inside the host cavity was also confirmed by the appearance of a broad absorption band at 475 nm in the UV-visible spectrum of these mixtures.

In emission spectroscopic experiments, the fluorescence intensity of Me_2DAP^{2+} significantly increased after addition of one equivalent of CB8. A similar result was previously observed for fluorescent guests included in CB7[9] or cyclodextrins.[10] These findings are probably associated to the protection of the excited state of the included guest from the aqueous environment. In contrast to this, the known fluorescence quenching of Me_2DAP^{2+} by electron-rich guests[5,6] is notably more pronounced when CB8 is present in the solution. In the presence of 1.5 mM dopamine, the relative intensity of the Me_2DAP^{2+} emission band at 449 nm decreases by ~6% compared to a 25% decrease in the presence of 1.5 equivalents of CB8 (Figure 8). More efficient

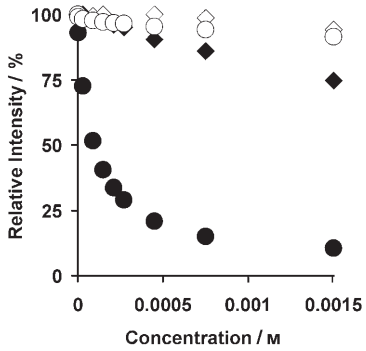
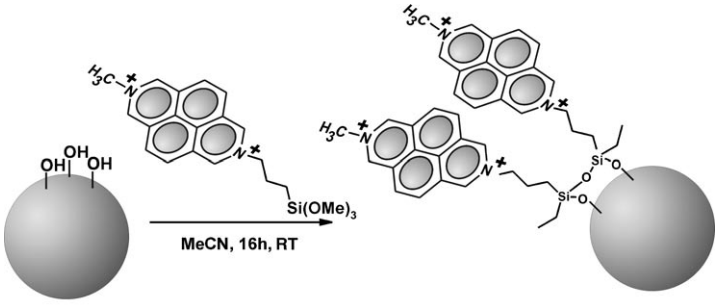


Figure 8. Relative emission intensity of Me_2DAP^{2+} (1.5 μM in phosphate buffer aqueous solution containing 0.1 M NaCl, pH 7.0, 25 °C, λ_{em} = 449 nm, λ_{exc} = 338 nm) in the presence of (◇) dopamine (◆) dopamine and CB8, (○) catechol, and (●) catechol and CB8.

CB8-mediated fluorescence quenching was also observed for catechol under similar conditions. These experiments demonstrate that the presence of CB8 markedly increases the sensitivity of the Me_2DAP^{2+} probe for these aromatic π donors. Increased fluorescence quenching in the presence of the host may be explained by static quenching due to the short lifetime of the excited state of the diazapyrenium dication[11] and the close proximity to the π donor inside the hydrophobic cavity of CB8. The less pronounced fluorescence quenching of Me_2DAP^{2+} by dopamine, relative to that observed with catechol, is probably due to the fact that dopamine is protonated under these experimental conditions.[12] The presence of a positively charged ammonium group on dopamine weakens the charge-transfer interaction with the cationic Me_2DAP^{2+} (Figure 8). On the other hand, catechol is a smaller and simpler guest that fits better as a neighbor of Me_2DAP^{2+} inside the host cavity. In general, the fact that the fluorescence receptor is not completely quenched by any of the two guests even in the presence of the host can be explained by the nonquantitative formation of the ternary complex.

To explore further the sensing ability of the CB8•Me_2DAP^{2+} inclusion complex, we fabricated a fluorescent sensor that incorporates this supramolecular assembly on the surface of silica nanoparticles.[13] A 2,7-diazapyrenium derivative containing a propyltrimethoxysilane group was synthesized and utilized to modify the hydroxylated surface of the silica particles (Scheme 2).[14,15] A loading of approximately 2.5×10^{-4} mmol of DAP^{2+} per mg of coated particles was measured by emission spectroscopy after surface derivatization.



Scheme 2. Modification of silica nanoparticles.

The response of the fluorescent nanoparticles to dopamine and catechol was investigated in the presence and absence[6] of CB8. Resembling the results obtained in solution, the observed level of fluorescence quenching was considerably more pronounced when CB8 was present (Figure 9). Under our experimental conditions, a 1.0 mM concentration of dopamine reduces the emission intensity of the coated nanoparticles to 50% of its initial level, and the same concentration of catechol produces almost complete quenching. Thus, we conclude that the complexation process is at least as effective on the surface of the silica nanoparticles as in the solution phase. These experiments constitute a proof-of-concept for the fabrication of catechol and catecholamine sensors based on their inclusion into CB8•Me_2DAP^{2+} fluorescent complexes.

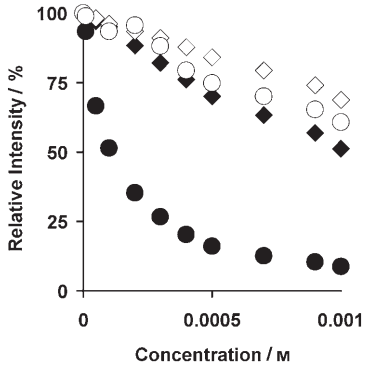


Figure 9. Relative emission intensity of fluorescent silica nanoparticles (0.1 mg mL^{-1}, phosphate buffer aqueous solution containing 0.1 M NaCl, pH 7.0, 25 °C, λ_{em} = 449 nm, λ_{exc} = 338 nm) in the presence of (◇) dopamine, (◆) dopamine and CB8, (○) catechol, and (●) catechol and CB8.

The stability of the charge-transfer complexes inside the CB8 cavity was also investigated using voltammetric techniques. The electrochemical behavior in aqueous solution of Me_2DAP^{2+} is complicated and not well understood at this point, while the electrochemical behavior of MV^{2+} is well known. Therefore, the latter guest was used for electrochemical experimentation. As previously reported[2a] one-electron reduction of Me_2V^{2+} in the presence of CB8 leads to the rapid formation of a 2:1 inclusion complex $(Me_2V^{\bullet+})_2$•CB8. The apparent dimerization constant of $Me_2V^{\bullet+}$ in the presence of CB8 was estimated to be 2×10^7 L mol^{-1}. We observed that the addition of the electron-rich guest into a solution of Me_2V^{2+} and CB8 prevents the dimerization of $Me_2V^{\bullet+}$ inside the CB8 cavity. As shown in Figure 10, upon addition of dopamine the two redox waves corresponding to the $Me_2V^{\bullet+}$ dimer are replaced by two new waves, which we postulate correspond to the formation of a charge-transfer complex inside the CB8 cavity. Note that in the presence of dopamine, reversible waves corresponding to reduction of $(Me_2V^{\bullet+})_2$ as well as Me_2V^{2+}•dopamine are present. This competition between $Me_2V^{\bullet+}$ dimerization and formation of a dopamine•Me_2V^{2+} charge-transfer complex inside the host reflects the considerable stability of this ternary complex, as it successfully competes with the complex between CB8 and the $Me_2V^{\bullet+}$ dimer. Due to the similarities between Me_2DAP^{2+} and Me_2V^{2+}, these experimental results are consistent with the formation of stable charge-transfer complexes between Me_2DAP^{2+} and dopamine (or catechol) inside the cavity of the CB8 host.

In contrast to these findings, the replacement of the charge-transfer complex between Me_2V^{2+} and 2,6-dihydroxynaphthalene from the CB8 cavity by the electrochemically generated $Me_2V^{\bullet+}$ dimer has been recently reported.[16] Comparison of these results with ours, pending additional experimentation, suggests that the selectivity of CB8 for a particular charge-transfer complex may depend strongly on the nature of the π-donor component.

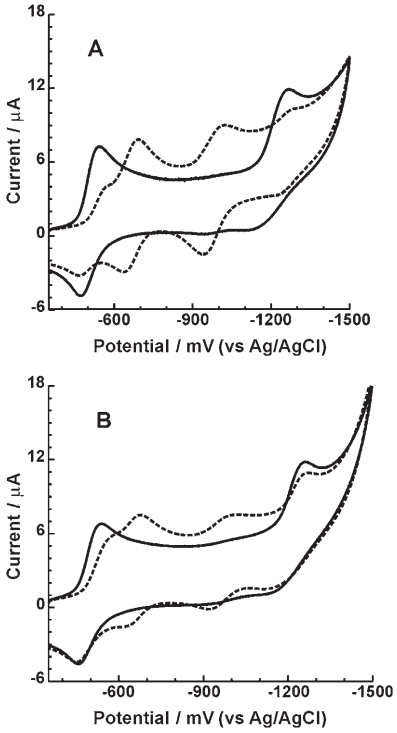


Figure 10. Cyclic voltammograms of 0.5 mM Me_2V^{2+} in phosphate buffer aqueous solution also containing 0.1 M NaCl (pH 7.0, I = 0.1 M) in the presence of one equivalent of CB8 (solid line) and A) 3.0 equivalents of catechol (dashed line) and B) 3.0 equivalents of dopamine (dashed line). Scan rate: 0.100 V s^{-1}.

Conclusion

In summary, the formation of a highly stable inclusion complex between $Me_2DAP^{2+}$and CB8 was confirmed by ^{1}H NMR spectroscopy, MALDI-TOF MS, and X-ray crystallography. In addition, we describe here the formation of novel supramolecular charge-transfer complexes between Me_2DAP^{2+} and catechol (or dopamine) inside the hydrophobic cavity of CB8; these complexes can be used for sensitive fluorescence detection of catecholamine neurotransmitters in solution or in the surface of silica nanoparticles. The presence of CB8 increases considerably the sensitivity for the detection of catechol and dopamine.

Experimental Section

Chemicals were purchased from VWR or Aldrich and were used as received. 3-Iodopropyltrimethoxysilane was purchased from ABCR. Fumed silica (particle size 0.014 μm, surface density = 200 m^2 g^{-1}) was purchased from Aldrich. MeCN was distilled over CaH_2. PhMe was distilled over Na. MALDI-TOF mass spectra were recorded with a Bruker Biflex IV instrument by using α-cyano-4-hydroxy-cinnamic acid as the matrix. NMR spectra were recorded on a Bruker Avance 500 MHz spectrometer. Differential pulse voltammograms were recorded with a CH Instruments 610 A potentiostat, with a glassy carbon working electrode, a platinum wire counter electrode, and a Ag/AgCl reference electrode. The UV-visible spectra were recorded using Shimadzu UV-2101PC spectrophotometer. The emission spectra were recorded using a SpexFluoroMax

spectrophotometer. Binding constants were determined by using well-established procedures.[17] 2,7-Diazapyrene was prepared from naphthalene tetracarboxylic dianhydride following a literature procedure.[14] Me_2DAP^{2+} was prepared as previously reported.[5a] The alkylation of the DAP nucleus with the propyltrimethoxysilane group for surface derivatization was done as reported before.[15] CB8 was prepared following a literature procedure[18] with minor modifications. Molecular modeling computations were run using the AM1 semiempirical method as implemented in the software package Gaussian 98.

Preparation of CB8·Me_2DAP^{2+} complex: Me_2DAP^{2+} (3.6 mg, 7.4 μmol) and CB8 (6.8 mg, 3.7 μmol) were codissolved in water (2 mL). The solution was allowed to stand at room temperature for one week to produce yellow crystals of the CB8·Me_2DAP^{2+} complex. Crystal data for CB8·Me_2DAP^{2+} complex: $[(C_{48}H_{48}N_{32}O_{16})(C_{16}H_{14}N_2)]I_{1.37}Cl_{0.63}\cdot 17H_2O$, $M_r = 2158.07$, orthorombic, space group *Pccn* (No 56), $a = 25.726(5)$, $b = 26.945(5)$, $c = 13.323(3)$ Å, $V = 9235(3)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.552$ g cm^{-3}, $\mu(Mo_{K\alpha}) = 6.41$ cm^{-1}. The X-ray intensity data were measured at 300 K on a Bruker SMART1000 CCD-based X-ray diffractometer system with a Mo-target X-ray tube ($\lambda = 0.71073$ Å). Final block-diagonal-matrix least-squares refinement on F^2 with all 9999 reflections and 576 variables converged to $R1$ ($I > 2\sigma(I)$) = 0.0935, $wR2$ (all data) = 0.3132, and GOF = 1.040. One of the counterions refines well as an iodide ion, and the other can be modeled as 63% Cl^- and 37% I^- occupying the same spatial position. The source of chloride can be traced to residual HCl in the sample of CB8. Positions of all non-hydrogen atoms were derived from direct methods. With all non-hydrogen atoms, except solvent molecules, being anisotropic and all hydrogen atoms in calculated position and riding mode, the structure was refined to convergence by least-squares method on F^2 by using SHELXL-93 incorporated in SHELXTL.PC V 5.03.

CCDC-260316 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.uk/data request/cif.

Acknowledgements

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