LETTER

NJC
www.rsc.org/njc

# Tight inclusion complexation of 2,7-dimethyldiazapyrenium in cucurbit[7]uril†

**Vladimir Sindelar, Mabel A. Cejas, Françisco M. Raymo and Angel E. Kaifer***

*Center for Supramolecular Science and Department of Chemistry, University of Miami, Coral Gables, FL 33124-0431, USA. E-mail: akaifer@miami.edu*

***Received (in St Louis, MO, USA) 6th October 2004, Accepted 6th December 2004***
***First published as an Advance Article on the web 17th January 2005***



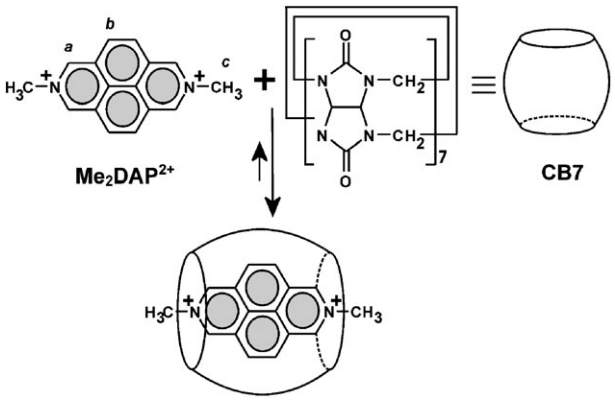
**The dicationic guest 2,7-dimethyldiazapyrenium is bound inside the host cucurbit[7]uril, forming a very stable inclusion complex in which the host undergoes structural distortions to accommodate the guest.**

The host binding properties of cucurbit[*n*]urils constitute a very active topic of research.[1] The current interest in this area sprung from the seminal report by Kim and co-workers[2] on the preparation and isolation of the larger cucurbit[*n*]urils ($n \geq 7$). Day and coworkers have also made important contributions to the preparation and isolation of large cavity cucurbiturils.[3] Our group has focused considerable research interest on the host properties of cucurbit[7]uril (CB7). We have shown that this host forms highly stable inclusion complexes with methylviologen,[4] other viologen derivatives,[5] organometallic cations[6] and bis(pyridinium)-1,4-xylylene[7] derivatives. All these guests exhibit one or more positive charges, which can develop favorable ion-dipole interactions with the rims of carbonyl oxygens on the cavity openings, and a hydrophobic core that fits well inside the host cavity. Therefore, the high thermodynamic stability of the inclusion complexes, with typical association equilibrium constants ($K$) over $10^5$ l mol$^{-1}$ in aqueous solution, is the result of a combination of ion-dipole and hydrophobic forces. Here we report the host–guest inclusion complexation between CB7 and the dicationic guest 2,7-dimethyldiazapyrenium ($Me_2DAP^{2+}$, Scheme 1). Having a maximum width of 6.8 Å (measured perpendicularly to the N–N axis), this guest represents the largest known molecule that has been included inside the host CB7 cavity.

The formation of an inclusion complex between CB7 and $Me_2DAP^{2+}$ is clearly evident from $^1$H NMR spectroscopy (Fig. 1). Upon addition of 1.2 equiv. of CB7 the resonances corresponding to the aromatic *a* and *b* protons of the guest exhibit an upfield shift of *ca.* 0.1 and 0.6 ppm, respectively. At the same time the signal of the $CH_3$ protons experiences a downfield shift of *ca.* 0.1 ppm. An upfield displacement of the aromatic protons together with a downfield shift of the terminal aliphatic protons was previously described as a result of inclusion complexation between CB7 and simple viologen derivatives (dimethylviologen and diethylviologen).[4,5] Similarly, our results indicate the formation of an inclusion complex between CB7 and $Me_2DAP^{2+}$. The diazapyrenium unit is included inside the CB7 cavity, while the positively charged nitrogen atoms interact with the polar portals on the host (Scheme 1). The formation of a stable inclusion complex was also confirmed by the observation of a dominant peak corresponding to an $m/z$ ratio of 1396, which is consistent with the $[CB7 \cdot Me_2DAP]^+$ species in MALDI-TOF MS experiments (see Electronic supplementary information, ESI).

In contrast to the viologen derivatives,[4,5] the complexation between CB7 and $Me_2DAP^{2+}$ is slow on the NMR timescale, probably due to the tight fit of the guest molecule while encapsulated inside the host (see ESI for energy-minimized structures of the complex $CB7 \cdot Me_2DAP^{2+}$). Signals corresponding to protons on the free and bound guests are present after addition of 0.5 equiv. of CB7 (spectrum B in Fig. 1). The free guest proton resonances disappear when the concentration of CB7 exceeds 1 equiv. When the CB7 concentration is less than 1 equiv. the differences between the host and complex concentrations are too small to be accurately determined from the NMR spectra. This precludes the determination of the association equilibrium constant by NMR spectroscopy at mM concentration levels. However, two different techniques, electronic absorption and fluorescence spectroscopies, can be used for the quantitative determination of the $K$ value between CB7 and $Me_2DAP^{2+}$.[8] In the UV-Vis spectrum the diazapyreniun dication shows intense absorption bands that are affected in the presence of CB7 (Fig. 2). A decrease in intensity of the absorption band at 245 nm with increasing concentration of the host was easily fitted to a 1 : 1 binding model to determine the equilibrium constant,[9] which was found to be $(2.9 \pm 0.2) \times 10^5$ l mol$^{-1}$, $\varepsilon = 8.65 \times 10^5$ M$^{-1}$ cm$^{-1}$. The stoichiometry of the complex was also verified to be 1 : 1 by constructing the corresponding Job plot (see ESI).

The fluorescence intensities in the emission spectrum of $Me_2DAP^{2+}$ were found to increase significantly upon addition of CB7 (Fig. 3).[10] This finding probably reflects the shielding of the guest from the aqueous environment while included inside the host cavity.[11–13] The fluorescence enhancement was accompanied by a red shift of the emission maximum from 448 nm in the absence of the host to 454 nm in the presence of 5 μM of the




**Scheme 1**

† Electronic supplementary information (ESI) available: MALDI-TOF mass spectrum, Job plot and energy-minimized structural views of the complex. See http://www.rsc.org/suppdata/nj/b4/b418017h/

DOI: 10.1039/b418017h

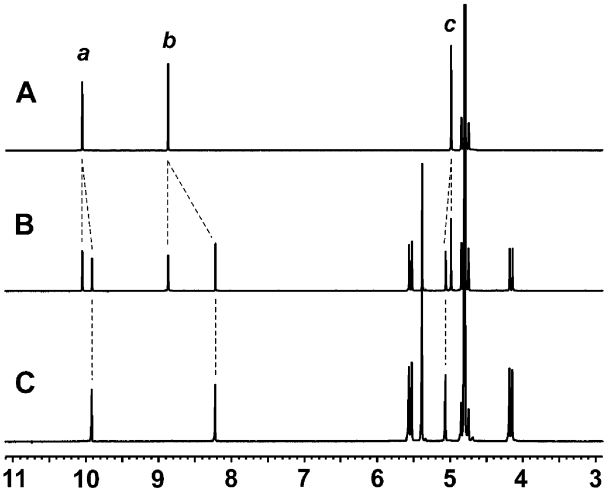



**Fig. 1** $^1$H NMR spectra (400 MHz, 0.1 M NaCl in $D_2O$, sodium phosphate buffer, pH = 7.0) of $Me_2DAP^{2+}$: in the absence (A) and in the presence of 0.5 (B) and 1.2 (C) equiv. of CB7.

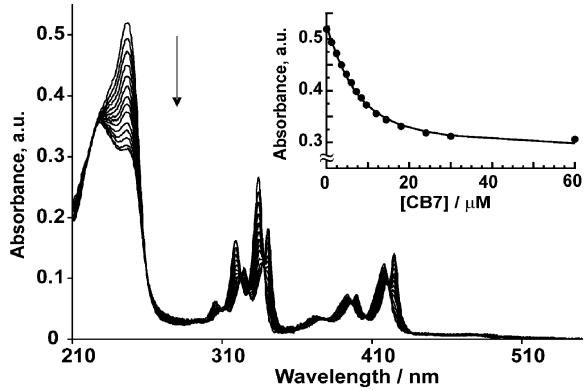



**Fig. 2** Electronic absorption spectrum of 6 μM $Me_2DAP^{2+}$ in the presence of increasing CB7 concentrations (0–60 μM, increasing in the direction of the arrow). The inset shows the best fit of the experimental data to the 1 : 1 binding model.

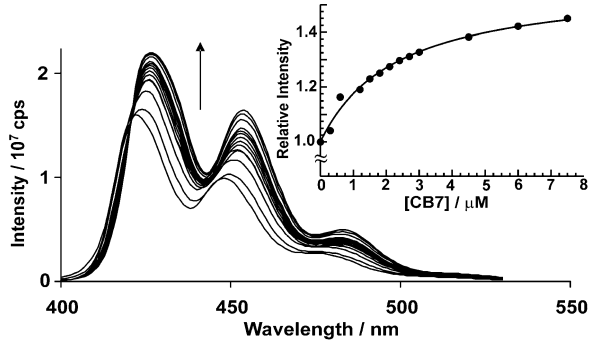



**Fig. 3** Emission spectrum of 1.5 μM $Me_2DAP^{2+}$ in the presence of increasing concentrations of CB7 (0–7.5 μM, increasing in the direction of arrow, $\lambda_{em}$ = 449 nm and $\lambda_{exc}$ = 338 nm). The inset shows the best fit of the experimental data to the 1 : 1 binding model.

host. The fitting of the relative fluorescence enhancement as a function of the concentration of CB7 afforded an equilibrium association constant for the 1 : 1 complex of $(4.4 \pm 0.1) \times 10^5$ l mol$^{-1}$, in good agreement with the value obtained from UV-Vis data.

The internal diameter of the CB7 cavity goes from 5.4 Å, at both carbonyl portals, to 7.3 Å in the equatorial plane of the molecular host.[1] The maximum width of the $Me_2DAP^{2+}$ guest is 6.8 Å, measured as the largest H–H distance perpendicular to its N–N axis. These dimensions clearly suggest that inclusion of $Me_2DAP^{2+}$ requires some stretching of the CB7 host and a departure from $D_{7h}$ symmetry. This point was verified computationally using the Gaussian molecular modeling program (AM1 semi-empirical method). Energy minimization of the inclusion complex (using the reported crystal structure of the host as a starting point for the computation) leads to the structure shown in Fig. 4 (additional views of the inclusion complex are shown in the ESI). The anticipated cavity distortion is clearly visible, with the cross section of the cavity departing from a circular shape and adopting an elliptical configuration. We should note here that this cavity distortion is not detected in the NMR spectrum of the complex, suggesting fast spinning (on the NMR timescale) of the included guest. The equilibrium association constant for this inclusion complex is higher than that observed for the methylviologen · CB7 inclusion complex ($\sim 6.8 \times 10^4$ l mol$^{-1}$) in a similar medium.[14] This finding suggests that the necessary structural distortion of the host is more than compensated by stronger hydrophobic forces between the aromatic moiety of the guest and the inner surface of the cavity. The ion-dipole interactions between the positively charged nitrogens and the carbonyl portals remain essentially unchanged in both complexes. The superior binding properties of diazapyrenium units with respect to bipyridinium analogs have also been described by Stoddart and co-workers.[15]

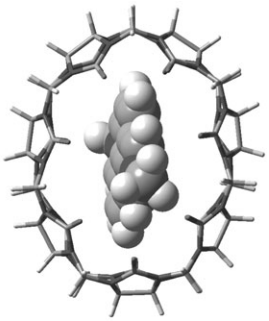


**Fig. 4** Energy-minimized structure of the CB7 · $Me_2DAP^{2+}$ complex (AM1). The cross section of the host undergoes an elliptical distortion to accommodate the guest.

In summary, we described here the formation of a tight and highly stable inclusion complex between the macrocyclic host CB7 and the guest $Me_2DAP^{2+}$. The presence of the complex was confirmed by $^1$H NMR spectroscopy and MALDI-TOF MS. The equilibrium constants determined from absorption and emission spectroscopy are in good agreement and show a strong host–guest interaction.

## Acknowledgements

The authors are grateful to the National Science Foundation for the generous support of this work (to AEK, CHE-0240295 and to FMR, CHE-0237578).

## References

1 J. W. Lee, S. Samal, N. Selvapalam, H.-J. Kim and K. Kim, *Acc. Chem. Res.*, 2003, **36**, 621.
2 J. Kim, I.-S. Jung, S.-Y. Kim, E. Lee, J.-K. Kang, S. Sakamoto, K. Yamaguchi and K. Kim, *J. Am. Chem. Soc.*, 2000, **122**, 540.
3 A. Day, A. P. Arnold, R. J. Blanch and B. Snushall, *J. Org. Chem.*, 2001, **66**, 8094.
4 (*a*) W. Ong, M. Gómez-Kaifer and A. E. Kaifer, *Org. Lett.*, 2002, **4**, 1791; (*b*) See also: H.-J. Kim, W. S. Keon, Y. H. Ko and K. Kim, *Proc. Natl. Acad. Sci. USA*, 2002, **99**, 5007.
5 K. Moon and A. E. Kaifer, *Org. Lett.*, 2004, **6**, 185.
6 W. Ong and A. E. Kaifer, *Organometallics*, 2003, **22**, 4181.
7 V. Sindelar, K. Moon and A. E. Kaifer, *Org. Lett.*, 2004, **6**, 2665.

8 All measurements were done at 25 °C in phosphate buffer aqueous solution (pH = 7.0) also containing 0.1 M NaCl.
9 K. A. Connors, *Binding Constants*, Wiley, New York, 1987, Ch. 4.
10 The isosbestic point at 338 nm was taken as the excitation wavelength.
11 F. Simon, F. C. J. M. van Veggel and D. N. Reinhoudt, *Chem. Commun*., 1999, 2229.
12 B. D. Wagner, N. Stojanovic, A. I. Day and R. J. Blanch, *J. Phys. Chem. B*, 2003, **107**, 10741.
13 B. D. Wagner, A. C. Sherren and M. A. Rankin, *Can. J. Chem*., 2002, **80**, 1210.
14 W. Ong and A. E. Kaifer, *J. Org. Chem*., 2004, **69**, 1383.
15 P. R. Ashton, S. E. Boyd, A. Brindle, S. J. Langford, S. Menzer, L. Perez-Garcia, J. A. Preece, F. M. Raymo, N. Spencer, J. F. Stoddart, A. J. P. White and D. J. Williams, *New J. Chem*., 1999, **23**, 587.