Organic LETTERS

Letter

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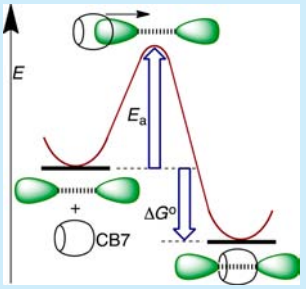
Rotaxane Formation by Cucurbit[7]uril in Water and DMSO Solutions

Sanem Senler, Beijun Cheng, and Angel E. Kaifer*

Center for Supramolecular Science and Department of Chemistry, University of Miami, Coral Gables, Florida 33124-0431, United States

Supporting Information

ABSTRACT: The cucurbit[7]uril (CB7) host forms rotaxane-type complexes with dumbbell-shaped, cationic guests bis(3,5-dimethoxybenzyl)-4,4′-bipyridinium ($\mathbf{1}^{2+}$) and bis(3,5-diethoxybenzyl)-4,4′-bipyridinium ($\mathbf{2}^{2+}$). The kinetics of complex formation is slower with the latter guest because of its bulkier end groups. Rotaxane formation was found to be thermodynamically more favorable and kinetically faster in D_2O than in DMSO-d_6 solution, which highlights the importance of hydrophobic interactions in the assembly of cucurbituril complexes.



The family of cucurbit[*n*]uril (CB*n*) hosts[1−4] can reach very high binding affinities with suitable guests in aqueous media, exceeding the binding affinity of the avidin−biotin host−guest system in optimal cases.[5] In fact, it seems fair to state that CB*n* hosts have shattered the notion that high binding affinity requires at least one component of biological origin, such as aptamers or antibodies. Given this ability to form extremely stable inclusion complexes, it is important to increase our understanding of the key noncovalent forces responsible for the formation of CB*n* complexes. Since hydrophobic forces are important in CB*n* complex formation,[6] it would be interesting to examine these binding phenomena in nonaqueous media. However, the solubility of CB*n* hosts, which is already limited in water, is extremely low in nonaqueous solvents, resulting in a severe paucity of research data in organic media.

Our own group reported that the stable complexes formed between the cucurbit[7]uril (CB7) host and the guests ferrocenylmethyltrimethylammonium or methyl viologen can be precipitated from aqueous solution as their hexafluorophosphate salts and redissolved in dimethyl sulfoxide (DMSO) or acetonitrile solutions.[7] However, we could not determine equilibrium association constants in nonaqueous media because of the very low solubility of the free host. This method was also used by Ramalingam and Urbach to prepare CB8-based rotaxanes.[8] A report on CB7 inclusion complexes of benzylpyridinium cations in DMSO solution sets the corresponding equilibrium association constants (K) at ~1×10^3 M^{-1}.[9] This is considerably lower than the majority of the K values measured with this host, suggesting that hydrophobic forces are important among the interactions responsible for binding.

Looking for a different approach to deal with this problem, we focused on the formation of rotaxanes[10] between the CB7 host and dumbbell guests containing a 4,4′-bipyridinium (viologen) core. By covalently attaching relatively bulky substituents to the two ends of the viologen core, we could prepare dicationic guests, which are soluble in a variety of solvents. Furthermore, rotaxane preparation can be carried out at elevated temperatures, favoring the solubilization of CB7 and leading to its slippage over the guest's bulky end groups to form rotaxane complexes, in which the viologen core is encircled by the host. In this communication, we report our preliminary thermodynamic and kinetic data on the formation of rotaxanes between two viologen-containing, dumbbell-shaped guests ($\mathbf{1}^{2+}$ and $\mathbf{2}^{2+}$) and the CB7 host (Figure 1).

The viologen-containing guests were prepared by quaternization of 4,4′-bipyridine with the corresponding 3,5-substituted benzyl halides. The resulting viologen guests ($\mathbf{1}^{2+}$ and $\mathbf{2}^{2+}$) were fully characterized by ^{1}H and ^{13}C NMR spectroscopic data, as

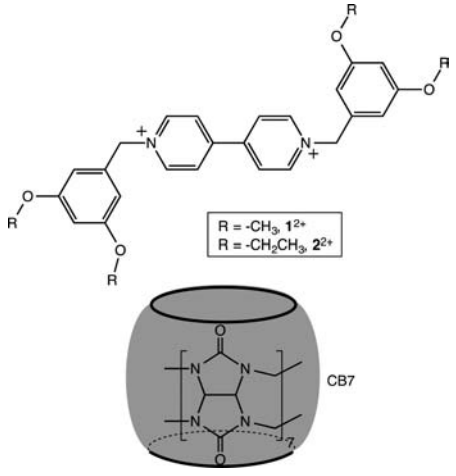


Figure 1. Structures of the CB7 host and guests used in this work.

Received: August 21, 2014
Revised: November 3, 2014
Published: November 10, 2014

dx.doi.org/10.1021/ol502479k | *Org. Lett.* 2014, 16, 5834−5837

well as high-resolution ESI mass spectrometric data. CB7 was prepared using reported procedures,[11] and a published method[12] was used to check its purity periodically. The binding interactions between each of the guests and CB7 were monitored using ^{1}H NMR spectroscopy. For instance, mixing of 0.5 mM $\mathbf{1}^{2+}$ and 0.5 mM CB7 in D_2O solution leads to the rapid formation of the CB7•$\mathbf{1}^{2+}$ complex at room temperature. The corresponding spectra are shown in Figure 2. The presence

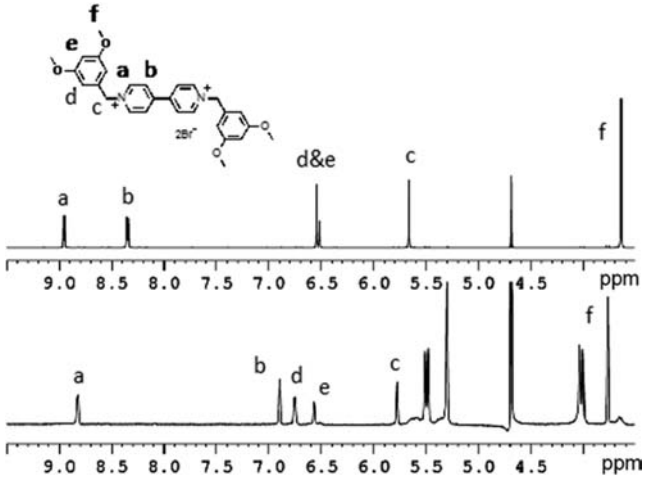


Figure 2. ^{1}H NMR spectra (500 MHz, D_2O) of guest $\mathbf{1}^{2+}$ (0.5 mM) in the absence (top) and in the presence (bottom) of 0.5 mM CB7.

of 1.0 equiv of CB7 leads to a substantial upfield displacement of the signal for the β protons on the bipyridinium group of the guest, which shifts from 8.4 to 6.9 ppm. This pronounced upfield shift constitutes a clear indication that the viologen core is included inside the host cavity[13] and unequivocally reveals the formation of a complex that can be characterized as a pseudorotaxane because of its rapid formation, which also suggests a relatively fast dissociation. In other words, the 3,5-dimethoxybenzyl end groups are not bulky enough to prevent the fast association/dissociation of the complex. According to our ^{1}H NMR spectroscopic data, the CB7•$\mathbf{1}^{2+}$complex is fully formed within ca. 3 min of mixing of the two components, which prevents a full examination of the kinetics of complex formation at the millimolar concentrations used in the NMR experiments. We can estimate a minimum value for the equilibrium association constant (K) of the CB7•$\mathbf{1}^{2+}$complex, by assuming that a maximum of 5% free $\mathbf{1}^{2+}$ can escape detection in the NMR experiments. Therefore, we compute a minimum K value of 8×10^5 M^{-1} at 25 °C ($\Delta G^\circ = -34$ kJ mol^{-1}), which is within the range of values measured for binding of methyl viologen by CB7,[13−15] in excellent agreement with the proposed pseudorotaxane structure of the complex. We also detected the CB7•$\mathbf{1}^{2+}$complex in high-resolution ESI mass spectrometric experiments (see Figure S8). Using competition experiments with a second guest (methyl viologen), we determined the K value between $\mathbf{1}^{2+}$ and CB7 in 50 mM sodium acetate (pD 4.7) as 4.3×10^5 M^{-1} (see Supporting Information). Using UV−vis spectroscopic data, we also verified that in pure water, the CB7•$\mathbf{1}^{2+}$complex forms quantitatively, in agreement with our NMR results in D_2O (Figure S1).

Similar binding experiments conducted in DMSO-d_6 solution yielded very different results. The first difference concerns the kinetic rate of formation of the CB7•$\mathbf{1}^{2+}$ complex, which is much slower than in D_2O solution. The thermodynamic stability of the complex is also different as reflected by the fact that the binding process reaches full saturation when only 47% of the initial concentrations of guest and host have been converted to the complex. From this experimental finding, we calculate a K value equal to 3.4×10^3 M^{-1} at 25 °C ($\Delta G^\circ = -20$ kJ mol^{-1}), which is considerably lower than the value estimated in D_2O solution. While the ^{1}H NMR spectroscopic features of the CB7•$\mathbf{1}^{2+}$ complex (see Figure S5) are similar to those found in aqueous media, indicating its pseudorotaxane structure, the binding affinity is substantially smaller in DMSO solution. This finding suggests the importance of hydrophobic forces in the molecular assembly process for the complex.

The binding between guest $\mathbf{2}^{2+}$ and CB7 offers contrasting behavior. In D_2O solution, the rate of assembly of the complex is much slower than that observed with guest $\mathbf{1}^{2+}$, and it takes several hours to reach full binding saturation. This is a straightforward consequence of the bulkier nature of the substituents on the benzyl groups in guest $\mathbf{2}^{2+}$ relative to $\mathbf{1}^{2+}$, which slows the slipping of the host over the end groups to reach the final binding station, that is, the central viologen unit. However, the final equilibrium situation is identical to that observed with $\mathbf{1}^{2+}$, with quantitative formation of the complex, as detected in NMR spectroscopy. Therefore, the calculated minimum K value is the same for CB7 binding of guest $\mathbf{1}^{2+}$ or $\mathbf{2}^{2+}$, as it should be the case since the residue included by the host is the viologen residue in both cases. The CB7•$\mathbf{2}^{2+}$complex was also detected in high-resolution ESI mass spectrometric experiments (see Figure S9). Finally, NMR spectroscopic examination of the binding interactions between guest $\mathbf{2}^{2+}$ and CB7 in DMSO-d_6 solution leads to the conclusion that binding does not take place, as the spectrum of the guest is unchanged after more than 12 h of exposure to CB7. From the data gathered with guest $\mathbf{1}^{2+}$, it is clear that the kinetic rate of complex formation decreases from water to DMSO solution. Furthermore, CB7 complex formation with $\mathbf{2}^{2+}$ is slower than with $\mathbf{1}^{2+}$ due to the bulkier end groups in the former guest. It seems that both factors combine to substantially slow the rate of complex formation between CB7 and guest $\mathbf{2}^{2+}$ in DMSO solution, to the point that no complex formation was detected in our NMR experiments. Since the thermodynamic driving force for the formation of the CB7 complexes of guests $\mathbf{1}^{2+}$ and $\mathbf{2}^{2+}$ in DMSO solution should be similar, we must conclude that our failure to observe any complex formation between CB7 and $\mathbf{2}^{2+}$ has a kinetic origin.

The rate of complex formation in DMSO between CB7 and guest $\mathbf{1}^{2+}$ can be easily followed by NMR spectroscopy. Proton signals for the CB7 complex and the free guest are simultaneously detected in these experiments, which reveals the slow exchange of the host between guests in the NMR time scale. Integration of these signals permits the calculation of the concentrations of free and bound guests as a function of time (Figure 3). By using the data points collected at the shortest possible times, when the system is still away from equilibrium, and fitting the data to a second-order kinetic model, we can calculate the association rate constant as $k_{ON} = 0.3$ M^{-1} s^{-1} at 25 °C. Similar experiments at 40 °C yield a slightly faster k_{ON} value (0.5 M^{-1} s^{-1}).

While the rate of complex formation in D_2O between CB7 and guest $\mathbf{1}^{2+}$ is too fast to measure by NMR spectroscopy, we can easily monitor complex formation between the host and guest $\mathbf{2}^{2+}$ in this medium. Again, we observe slow exchange of the host between guest molecules in the NMR experiments,

dx.doi.org/10.1021/ol502479k | Org. Lett. 2014, 16, 5834−5837

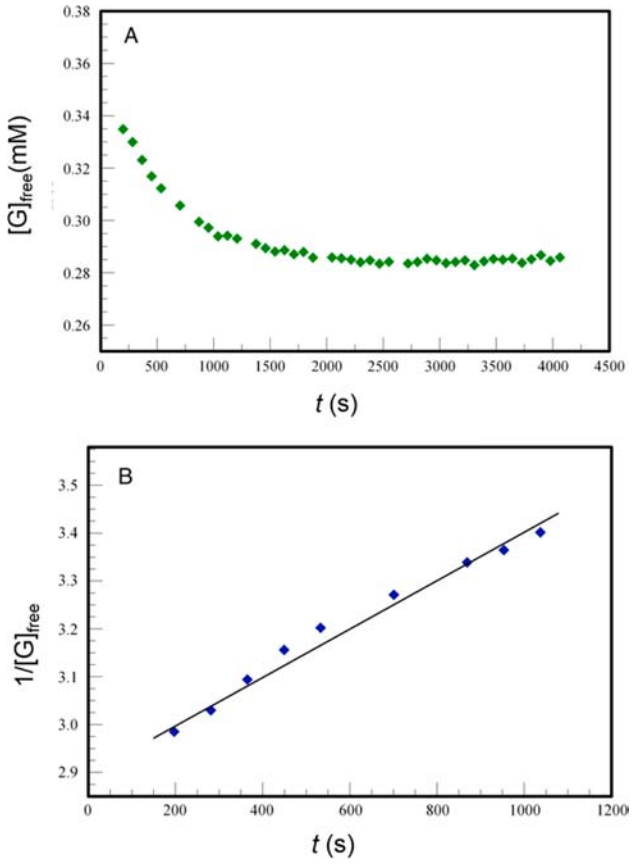


Figure 3. (A) Time dependence of the concentration of free guest $\mathbf{1}^{2+}$ in the presence of 1.0 equiv of CB7 at 25 °C. (B) Time dependence of the reciprocal concentration of the free guest at short times. Initial concentrations: $[\mathbf{1}^{2+}]$ = 0.5 mM, [CB7] = 0.5 mM.

which allowed the calculation of the time-dependent concentrations of free guest and complex, leading to the measurement of the second-order association rate constant as 0.9 M^{-1} s^{-1} at 25 °C. The value determined at 40 °C was 6.4 M^{-1} s^{-1}.

Table 1 summarizes the thermodynamic and kinetic data obtained for these complexes in aqueous and DMSO solution.

Table 1. Thermodynamic and Kinetic Data for the formation of CB7 Complexes with Guests $\mathbf{1}^{2+}$ and $\mathbf{2}^{2+}$ at 25 °C

medium	G	K^a (M^{-1})	k_{ON} (M^{-1} s^{-1})	k_{OFF} (s^{-1})
D_2O	$\mathbf{1}^{2+}$	8×10^5	fast	
D_2O	$\mathbf{2}^{2+}$	8×10^5	0.9	1×10^{-6}
DMSO	$\mathbf{1}^{2+}$	3.4×10^3	0.3	8×10^{-5}
DMSO	$\mathbf{2}^{2+}$	n.o.	n.o.	

[a]The values in D_2O solution are minimum estimates, assuming that a maximum of 5% free guest could go undetected.

A few important points deserve to be highlighted here. First, the equilibrium association constants between CB7 and guests $\mathbf{1}^{2+}$ and $\mathbf{2}^{2+}$ in pure D_2O could not be determined exactly, as the formation of the complexes was essentially quantitative in both cases at the concentrations used in our NMR spectroscopic experiments. However, the minimum value estimated from our experiments (8×10^5 M^{-1}) is perfectly compatible with the range of K values reported for CB7 complexation of methyl viologen.[13−15] We also measured the equilibrium association constant for the CB7•$\mathbf{1}^{2+}$complex in the same medium used by Isaacs and co-workers, 50 mM sodium acetate, and obtained a value of 4.3×10^5 M^{-1}. These findings are completely consistent with the proposed rotaxane structure of the CB7•$\mathbf{1}^{2+}$ and CB7•$\mathbf{2}^{2+}$ complexes (see Figure 4) and reflects the fact

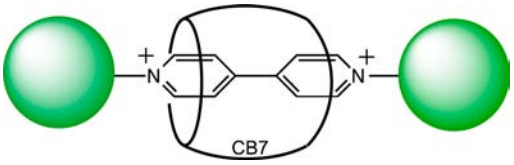


Figure 4. Proposed structure for the complexes between CB7 and the guests $\mathbf{1}^{2+}$ and $\mathbf{2}^{2+}$.

that, in all cases, the CB7 host engulfs the central 4,4′-bipyridinium subunit, deriving similar stabilization for the complex, with relatively small effects due to the nature of the N-substituents attached to the viologen core. Remarkably, the K value for the CB7•$\mathbf{1}^{2+}$ complex in DMSO solution is substantially lower (3.4×10^3 M^{-1}). To the best of our knowledge, this is the first report of the K values for a given CB7 complex in aqueous and nonaqueous solutions. The substantial decrease observed for the stability of the complex in DMSO highlights the importance of hydrophobic interactions as the key driving force for inclusion complex formation in aqueous media. It can be argued that the ion−dipole interactions between the positively charged nitrogens on the viologen subunits and the carbonyl-laced portals of the host would be enhanced in nonaqueous solution because of the lower medium's dielectric constant as compared to aqueous solution. However, our data suggest that any such increase in the strength of the ion−dipole forces is overcome by the decrease in solvophobic interactions inherent to the "transfer" from aqueous to nonaqueous solutions.

Our kinetic data confirm that the bulkier substituents on guest $\mathbf{2}^{2+}$ slow the formation of the CB7 complex, as the host must slide over the 3,5-diethoxybenzyl groups, which are slightly larger than the 3,5-dimethoxybenzyl groups in guest $\mathbf{1}^{2+}$. The size difference between the dimethoxybenzyl and diethoxybenzyl terminal groups is small but certainly just enough to result in substantial differences in the kinetics of association with CB7 of the two guests investigated here. A full kinetic analysis was prevented by experimental limitations in the temperature range that could be explored, as both guests undergo partial decomposition at temperatures above 40 °C. However, our room temperature data indicate that complexation is substantially faster in aqueous media than in DMSO solution. Although ion pairing effects may be stronger in DMSO, faster rotaxane formation in water seems counterintuitive, if we take into account the partial desolvation of the host required for threading of the CB7 by either guest, but is in agreement with the general notion that reactions with larger thermodynamic driving forces tend to be kinetically faster.

Overall, the data collected here indicate that the formation of rotaxane-like complexes via slippage between the CB7 host and the dumbbell-shaped guests $\mathbf{1}^{2+}$ and $\mathbf{2}^{2+}$ is thermodynamically more favorable and kinetically faster in aqueous media than in DMSO solution.

dx.doi.org/10.1021/ol502479k | Org. Lett. 2014, 16, 5834−5837

■ ASSOCIATED CONTENT

Supporting Information

Experimental and synthetic details, mass spectra of guests and complexes, and additional NMR spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: akaifer@miami.edu.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors gratefully acknowledge the U.S. National Science Foundation for the generous support of this research (to A.E.K., CHE-0848637 and CHE-1412455).

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