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Kinetics of Formation of the Host–Guest Complex of a Viologen with Cucurbit[7]uril

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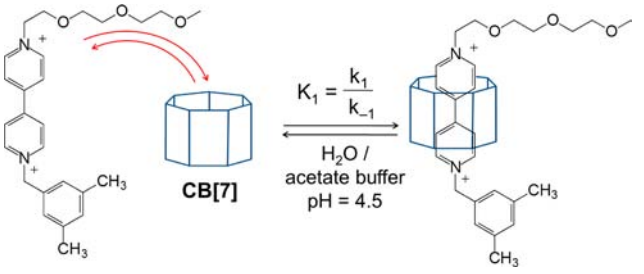
ABSTRACT



Host–guest complexation between the dicationic viologen 1-tri(ethylene glycol)-1′-methyl-*m*-xylyl-4,4′-bipyridinium and cucurbit[7]uril (CB7) was studied at pH = 4.5 in water. The stability constants of the mono- and bis-CB7 adducts were determined at 25 °C by UV–vis spectroscopy. Stopped-flow kinetic experiments were performed to measure the formation and dissociation rate constants of the monoadduct: k_1 = (6.01 ± 0.03) × 10^6 M^{-1} s^{-1} and k_{-1} = 52.7 ± 0.4 s^{-1}, respectively. Possible mechanisms of complexation are discussed in view of the kinetic results.

In recent years, considerable efforts have been made to design and characterize novel supramolecular systems of organic dyes in order to develop technologies such as molecular scale biological probes and sensors.[1,2] Recently, the effect of encapsulation by cucurbit[*n*]urils (*n* = 6, 7, 8) on the photophysical and chemical characteristics of some common fluorescent dyes were investigated in detail.[3−5] The stability and structure of the inclusion complexes of cucurbit[*n*]uril and organic cations[6] including bispyridinium (viologen) derivates[3,7,8] have been extensively studied by experimental (mainly NMR and UV–vis spectroscopic) and theoretical methods.[9]

The molecular mechanism of the association and dissociation of the supramolecular complexes were usually found to comprise several consecutive steps that include structural rearrangemets.[10,11] These steps have been experimentally studied and discussed in the cases of slow reactions, when the system could be conveniently monitored by NMR spectroscopy,[10,11] and recently in the case of fast reactions[12] using stopped-flow spectroflourimetric experiments. Herein we report the fast kinetic study of the formation of the complex of the cucurbit[7]uril (abbreviated as **CB7**; see Figure 1) host with a viologen guest: 1-(methoxy-tri(ethylene glycol))-1′-((3,5-dimethylphenyl)-methyl)-4,4′-bipyridinium dication[13] (abbreviated as **V**, see Figure 1), in a buffered aqueous solution at pH = 4.5.

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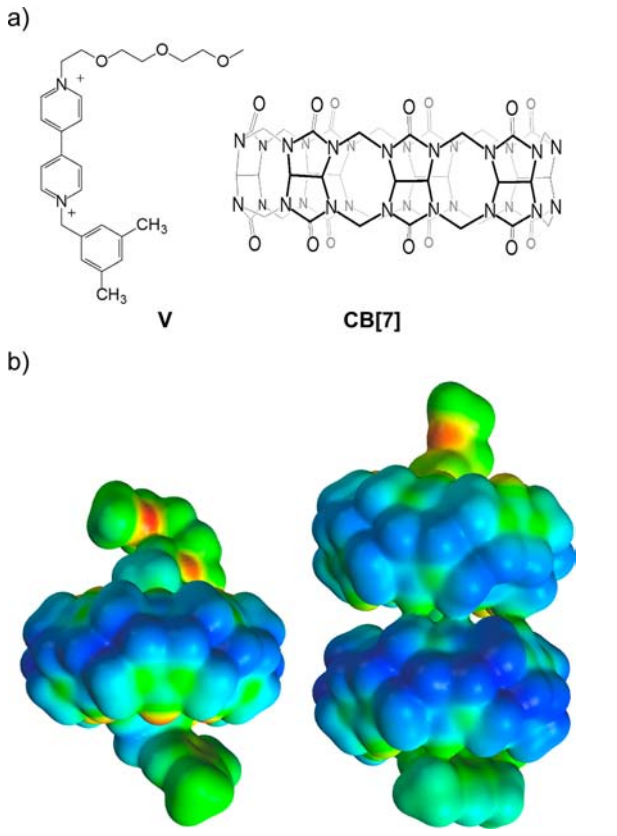

Figure 1. (a) Structure of 1-tri(ethylene glycol)-1′-methyl-m-xylyl-4,4′-bipyridinium dication (**V**) and cucurbit[7]uril (**CB7**). The counterions of **V** are Br^- (not indicated). (b) Potential surface plots of mono-**CB7**-**V** and bis-**CB7**-**V** complexes as calculated by Spartan 08 (AM-1 gas-phase).

Stopped-flow spectroscopy was used for the kinetic measurements, and ensemble spectroscopic studies, including ^{1}H NMR and UV−vis titration experiments, were employed to further characterize the stability of the host−guest system. This guest was chosen in order to probe the rate of association and dissociation of **CB7** as it is forced to pass along the pseudorotaxane tri(ethylene glycol) arm to reach the presumed binding site, the dicationic viologen moiety. The determination of the rate of passage of **CB7** over an extended arm will help inform the design of shuttle rotaxanes or related nanomolecular devices.

Viologen **V** was titrated with **CB7** at pH = 4.5 in aqueous acetate buffer, and the UV−vis spectra were monitored as a function of titrant concentration (Figure 2 and Figure S4 in the Supporting Information (SI)). Two well separated consecutive steps were identified in the spectral observations at $[V]_0 = 12.5\ \mu M$ and $[CB7]_0 = 2.5 - 2000\ \mu M$ (**V**/**CB7** from 1:0.2 to 1:160). At larger concentrations of **CB7** ($> 50\ \mu M$), its contribution to the UV absorption was substantial. Therefore, its molar absorption coefficients were determined in the region of 240−340 nm and taken into account during data evaluation. In order to determine the binding model of **V** with **CB7**, a detailed mathematical analysis of the titration data was carried out with SpecFit/32[14] (see details in the SI).[15−17] In the **V** + **CB7** system, four absorbing components were found, which means two new species besides **V** and **CB7**. The new species were assigned as the 1:1 and 1:2 **V**/**CB7** complexes (**V•CB7** and **V•(CB7)**$_2$, respectively), and the spectroscopic data set was fitted to the 1:0 → 1:1 → 1:2 consecutive complexation model in 100 different wavelengths (from 240 to 340 nm), simultaneously. As seen at a selected wavelength in Figure 2 (top panel), the fitted curve is in good agreement with the experimental points. Consequently, the equilibrium constants were determined to be $K_1 = (1.1 \pm 0.1) \times 10^5\ M^{-1}$ and $K_2 = (1.9 \pm 0.2) \times 10^3\ M^{-1}$ (for the consecutive formation of **V•CB7** and **V•(CB7)**$_2$, respectively). The distribution diagram is found in the SI (Figure S5). Furtheremore, the matrix algebraic fitting approach provided the molar absorbances of both **V•CB7** and **V•(CB7)**$_2$ at each wavelength of data input, enabling the reconstruction of the UV spectra of the adducts as presented in Figure 2 (bottom panel). The formation of the **V•(CB7)**$_2$ type complex is unprecedented. However, the UV−vis titration experiments cannot be described by taking only three absorbing species (**V**, **CB7**, and **V•CB7**) and their equlibria into account, as evident from the deviation of the corresponding simulation (Figure 2, top panel: dashed line) and the measured data. Figure 2 (inset) also demonstrates that the absorbance increases at high $[CB7]_0$ even if its contribution to the overall signal is subtracted. To describe **V•(CB7)**$_2$, we presume that the first **CB7** docks near the more hydrophobic xylyl substituted end of the viologen and the second, more weakly binding **CB7** associates near the ethylene glycol end of the viologen. The gas phase calculated structures shown in Figure 1 can aid in visualizing the steric fit of one or two **CB7** on the viologen, but the actual detailed solution structures will be determined by the additional hydrophobic interactions in these host−guest complexes. The 1:1 complex **V•CB7** was also studied by ^{1}H NMR spectroscopy, utilizing a competitive binding approach described earlier,[18,19] which allowed the indirect measurement of the stability constant (see details in the SI: $K_1 = (6.9 \pm 1.6) \times 10^5\ M^{-1}$). The value of K_1 measured by NMR is reasonably close to that determined by the direct UV−vis titration, considering that the calculations were based on the ^{1}H NMR spectrum of only one equilibrium mixture, which introduced a 1 order of magnitude higher numerical uncertainty compared to the case of the UV−vis titration. The ^{1}H NMR spectrum of a 1.0 mM **CB7** and

(14) SpecFit/32 (from Spectrum Software Associates) is a comprehensive software package designed to evaluate spectroscopic titrations and multiwavelength kinetic data based on user defined chemical models. The mathematics of the software is based on singular value decomposition (matrix algebra).

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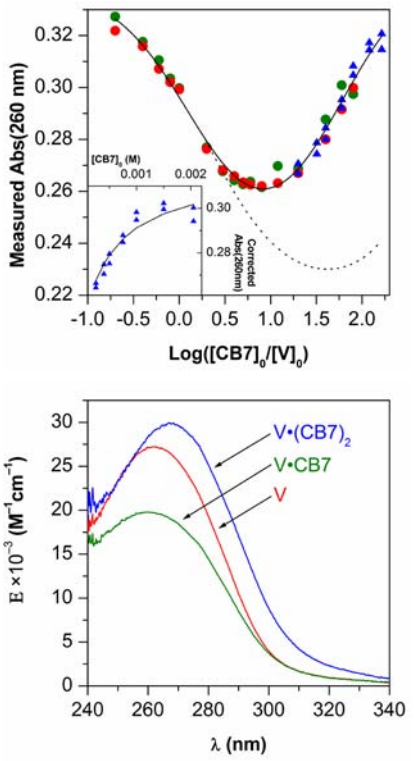

Figure 2. UV−vis titration of **V** with **CB7**. (Top panel) The titration curve measured at 260 nm (dots: parallel experimental points; triangles: experiments at high $[CB7]_0$). Continuous line: fitted curve with the consecutive complexation model (from SpecFit/32). Dotted line: simulation of the absorbance reading taking into account the presence of only **V**, **CB7**, and their 1:1 adduct in an equilibrium system. (Inset) Triangles: the measured absorbance reading is corrected with the contribution of **CB7** at high $[CB7]_0$. Continuous line: fitted curve with the consecutive complexation model (from SpecFit/32). (Bottom panel) UV−vis spectrum of **V** and the derived (reconstructed from SpecFit/32 fit) UV−vis spectra of the 1:1 (**V•CB7**) and the 1:2 complexes (**V•CB7**)$_2$). $[V]_0$ = 12.5 μM, $[CB7]_0$ = from 2.5 to 2000 μM, pH = 4.5 (acetate buffer), T = 25.0 °C.

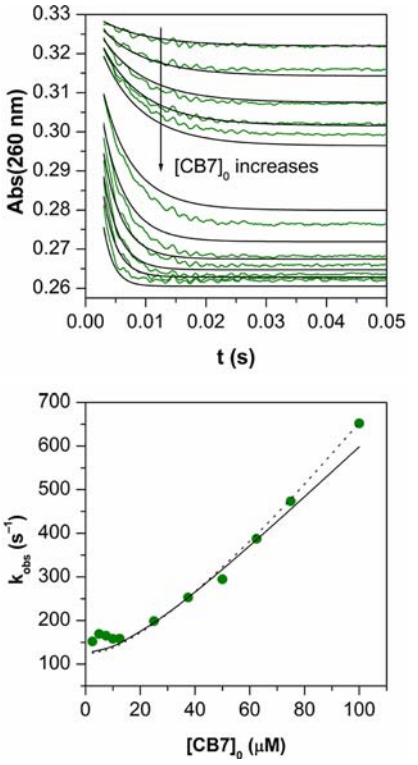

Figure 3. Kinetics of the formation of the 1:1 host−guest adduct of **V** with **CB7**. (Top panel) Single exponential kinetic curves recorded at 260 nm (black lines: result of the global fit with the simple one-step kinetic model). (Bottom panel) The pseudo-first-order rate constants as the function of the **CB7** concentrations. Dots: values for the experimental kinetic curves. Solid line: results of the global fit with the simple one-step kinetic model. Dashed line: results of the global fit with the two-step kinetic model (see details in the SI). $[V]_0$ = 12.5 μM, $[CB7]_0$ = from 2.5 to 100 μM, pH = 4.5 (acetate buffer), T = 25.0 °C.

1.0 mM **V** in unbuffered D_2O (Figure S4a in the SI) exhibited broadened xylyl signals and much less perturbed ethylene glycol signals as would be consistent with the first **CB7** binding near the xylyl capping group. Addition of a second equivalent of **CB7** broadened all hydrogen signals in the capping groups, which would be consistent with a possible second weaker **CB7** binding (Figure S4b). Furthermore, weak signals which indicate the presence of **V•(CB7)**$_2$ were found in the ESI-MS spectrum of the solution of 1 mM **V** and 2 mM **CB7** (Figure S4d and Table S1).

The kinetics and mechanism of the formation of **V•CB7** in water were investigated in detail. The rate of formation of **V•CB7** from **V** and **CB7** is on the millisecond time scale. Therefore, stopped-flow spectrophotometry is required to study the kinetics. **V** (25 μM) was mixed with **CB7** solutions of varying concentrations (from 5.0 to 200 μM). For this concentration range of **V** and **CB7** at pH = 4.5 and 25 °C, formation of the 1:2 complex **V•(CB7)**$_2$ is insignificant (see Figure S5). All the recorded kinetic curves were single exponential and could be fitted to obtain pseudo-first-order rate constants (Figure 3). The simplest one-step kinetic model that describes the stopped-flow data is the following:

$$\begin{array}{lll} 1) & V + CB7 \rightarrow V{\bullet}CB7 & \text{with: } k_1 \\ -1) & V{\bullet}CB7 \rightarrow V + CB7 & \text{with: } k_{-1} \end{array}$$

The differential rate law and the expression of the equilibrium constant for the one-step model are as follows:

$$\frac{d[V]}{dt} = -k_1[V][CB7] + k_{-1}[V\cdot CB7] \quad (1)$$

$$K_1 = \frac{k_1}{k_{-1}} = \frac{[V\cdot CB7]_{Eq}}{[V]_{Eq}[CB7]_{Eq}} \quad (2)$$

where square brackets indicate time dependent actual concentrations, and $[X]_{Eq}$ is the corresponding equilibrium

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concentration under the applied conditions. The integrated rate law is a single exponential expression when the system is close to equilibrium[20] (see details in the SI):

$$[V] = [V]_{Eq} + \frac{\xi[V\cdot CB7]_{Eq}}{\xi + k_1[V\cdot CB7]_{Eq}}\exp(-\xi t) \qquad (3)$$

where:

$$\xi = k_1([V]_{Eq} + [CB7]_{Eq}) + k_{-1}$$

The kinetic curves in Figure 3 were simultaneously (globally) fitted to eq 3 with the nonlinear Levenberg–Marquard least-squares method: to give the rate constants $k_1 = (6.01 \pm 0.03) \times 10^6\ M^{-1}\ s^{-1}$ and $k_{-1} = 52.7 \pm 0.4\ s^{-1}$. The kinetically deduced value of the stability constant ($K_1 = k_1/k_{-1} = 1.15 \times 10^5\ M^{-1}$) is in good agreement with the results of the UV–vis titration.

It is possible to assume that the 1:1 adduct of **V** and **CB7** does not exist as only one stable structure but represents a mixture of isomers, in which case the different forms should be in equilibrium with each other. However, as we mentioned before, the mathematical analysis of the spectral data obtained during the UV–vis titration did not require the introduction of another absorbing species besides **V**, **V•CB7**, and **V•(CB7)**$_2$. Thus, this does not indicate the existence of different isomers of **V•CB7**.[15,17] The kinetic data set was also reinvestigated for evidence to support the occurrence of additional equilibrium processes. The re-evaluation of the kinetic data set according to a kinetic model which incorporates two isomers in equilibrium for **V•CB7** was carried out with the ZiTa software package.[21] The detailed procedures are given in the SI; the calculated rate constants with the two-step model are shown in Figure 3 bottom panel (dashed line). A critical comparison of the two different kinetic models rules out a multistep process which occurs on the stopped-flow time scale (see SI). In other words, the existence of slowly exchanging multiple isomers of **V•CB7** is not supported by the kinetic results.[22] Isomers which exchange in a fast pre-equilibrium are also excluded.[12] The presented methodology cannot rule out the presence of isomers with similar UV–vis spectral properties.

In summary, the formation of a 1:1 complex of viologen **V** with **CB7** is assumed to take place in one step; no evidence was found for a more complicated mechanism of association and dissociation as has been described in the case of analogous host–guest systems.[10,11] This method of kinetic analysis not only provided the association equilibrium constant with high precision but also gave the first direct measurement of the rate of association and dissociation of **CB7** from viologen guests. The rate of **CB7** passage over the extended arm is slower than seen for the inclusion of a compact guest into **CB7**.[12] Analysis of the absorbance spectral data provides evidence for the consecutive formation of 1:1 ($K_1 = (1.1 \pm 0.1) \times 10^5\ M^{-1}$) and 1:2 ($K_2 = (1.9 \pm 0.2) \times 10^3\ M^{-1}$) complexes of **V•CB7** and **V•(CB7)**$_2$.

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Supporting Information Available. Detailed experimental and mathematical procedures, characterization of viologen **V** and its complexes. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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