Electrochemically controlled self-complexation of cyclodextrin–viologen conjugates

Armen Mirzoian and Angel E. Kaifer*

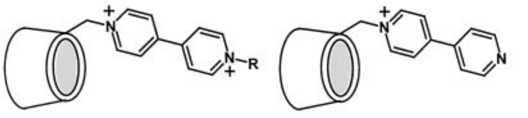
Center for Supramolecular Science and Department of Chemistry, University of Miami, Coral Gables, FL 33124-0431, USA. E-mail: akaifer@umiami.ir.miami.edu

Received (in Columbia, MO, USA) 21st May 1999, Accepted 6th July 1999

Self-complexation of cyclodextrin–viologen conjugates can be controlled electrochemically through changes in the oxidation states of the viologen subunits as well as chemically when competing water-soluble hosts or guests are added to solutions of the conjugates.

The phenomenon of intermolecular self-complexation has attracted considerable interest in supramolecular chemistry.[1,2] A compound must possess suitably located complementary (host and guest) sites to recognize itself and form intermolecular complexes in solution. Depending on the spatial relationship between the host and guest sites of the self-complementary monomer units, different superstructures can be predicted, from cyclic dimers to polymer-like, extended acyclic ones.[3–5] Of course, intramolecular self-complexation is also possible in molecules with enough flexibility.[6] Here we report the first example of electrochemically-driven,[7] intermolecular self-complexation. Specifically, we describe a series of cyclodextrin–viologen conjugates that exhibit remarkable intermolecular self-recognition triggered by the two-electron reduction of their viologen subunits.

We have recently reported on the binding interactions between the hosts β-cyclodextrin (β-CD) and its heptakis(2,6-*O*-dimethyl) analog (DM-β-CD) and a series of viologens (*N*,*N*′-disubstituted 4,4′-bipyridinium derivatives) designed to enhance their water solubility in any of their three oxidation states.[8,9] We have shown that while the oxidized forms of the viologen derivatives are not bound by the CD hosts, the two-electron reduced forms give rise to very stable inclusion complexes.[9] The intermediate one-electron reduced forms are only weakly bound by β-CD. Based on these findings, we reasoned that compounds containing covalently linked β-CD and viologen subunits should undergo self-complexation upon two-electron reduction. Therefore, we prepared the series of cyclodextrin–viologen conjugates $\mathbf{1}^{2+}$–$\mathbf{3}^{2+}$ by alkylation of their precursor $\mathbf{4}^{+}$.[10]



$\mathbf{1}^{+}$ R = Me
$\mathbf{2}^{+}$ R = Et
$\mathbf{3}^{+}$ R = C_5H_{11}

$\mathbf{4}^{+}$

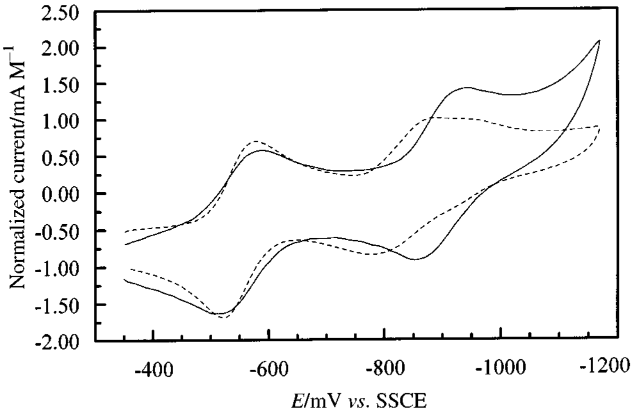


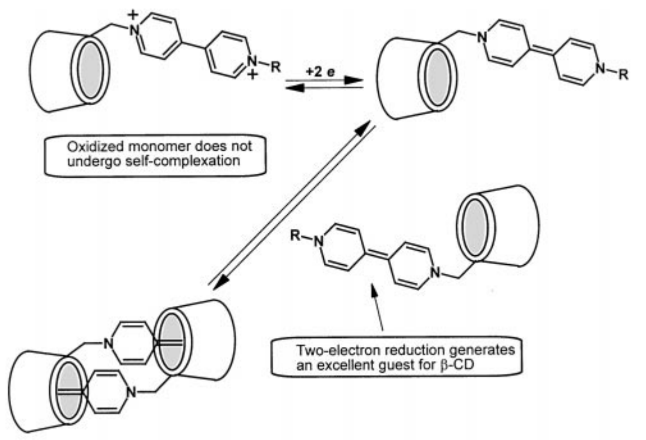
Fig. 1 Normalized cyclic voltammograms ($0.1\ V\ s^{-1}$) of 0.15 (solid line) and 6.7 mM solutions of $\mathbf{2}\cdot Cl_2$ in 0.5 M pH 7 phosphate buffer.

As anticipated, the electrochemical behavior of $\mathbf{1}^{2+}$–$\mathbf{3}^{2+}$ is dominated by the two reversible, one-electron reductions of their viologen residues.[11] Fig. 1 (solid line) shows a typical voltammogram for $\mathbf{2}^{2+}$ in 0.5 M phosphate buffer (pH = 7) solution. Half-wave potential values for $\mathbf{1}^{2+}$–$\mathbf{3}^{2+}$ and $\mathbf{4}^{+}$ are collected in Table 1. In aqueous media the cathodic voltammetric behavior of most viologens is affected by the precipitation on the electrode surface of their more hydrophobic, reduced forms.[12–14] In contrast, the CD–viologen conjugates $\mathbf{1}^{2+}$–$\mathbf{3}^{2+}$ exhibit (at concentrations around 1 mM) two reversible voltammetric reduction waves, free from any precipitation effects, due to the solubilizing effect of the appended CD moieties. On the other hand, we found that the electrochemical behavior of the CD–viologen conjugates is strongly concentration dependent. The second reduction wave of $\mathbf{1}^{2+}$–$\mathbf{3}^{2+}$ broadens and shifts to more positive potentials (Fig. 1, dotted line) at concentrations above 1 mM. In control experiments, other highly water-soluble viologens lacking covalently appended CD residues did not show this type of concentration dependent behavior.[15] Furthermore, the changes observed in the second reduction waves of $\mathbf{1}^{2+}$–$\mathbf{3}^{2+}$ at concentrations above 1 mM are similar to those observed for water-soluble viologens in the presence of added β-CD.[9] We thus conclude that compounds $\mathbf{1}^{2+}$–$\mathbf{3}^{2+}$ undergo intermolecular self-complexation upon two-electron reduction of the viologen subunit (Scheme 1). The intermolecular character of these self-complexation processes is clearly evidenced by the observed concentration dependence. To further verify that the presence in the same molecule of viologen and β-CD subunits is responsible for self-complexation, we performed several experiments using independent guest or host molecules. Fig. 2 shows the voltammetric behavior of a solution containing 7.3 mM $\mathbf{3}^{2+}$ (solid line) clearly

Table 1 Half-wave potentials ($E_{1/2}$) and peak-to-peak splittings (ΔE_p) measured for the cyclodextrin–viologen conjugates in 0.5 M phosphate buffer (pH 7) solution

Cationic compound	$E_{1/2}{}^1$/V (ΔE_p/mV)[a]	$E_{1/2}{}^2$/V (ΔE_p/mV)[b]
$\mathbf{1}^{2+}$	−0.573 (80)	−0.933 (90)[c]
$\mathbf{2}^{2+}$	−0.555 (60)	−0.911 (65)[d]
$\mathbf{3}^{2+}$	−0.524 (65)	−0.934 (75)[e]
$\mathbf{4}^{+}$	−0.908 (70)[f]	—

[a] Half-wave potentials for the first one-electron reduction of the bipyridinium subunit (V^{2+}/V^{+}). The value in parenthesis represents the potential difference between the cathodic and anodic peak potentials measured by cyclic voltammetry at a scan rate of $0.100\ V\ s^{-1}$. [b] Same for the second one-electron reduction of the bipyridinium subunit (V^{+}/V). [c] 1.2 mM. [d] 0.15 mM. [e] 7.3 mM (potential data for the free compound obtained after adding excess of competing guest). [f] 0.22 mM.



Scheme 1

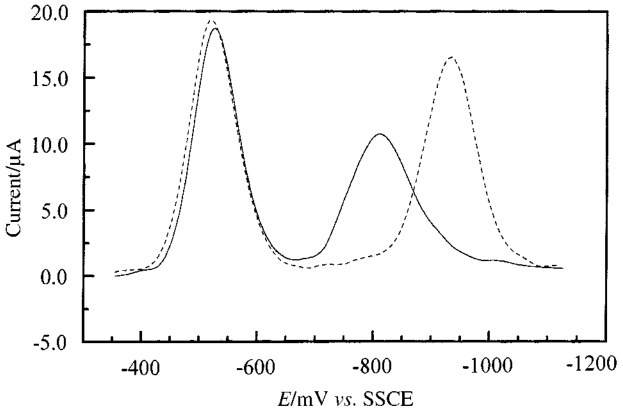


Fig. 2 Square wave voltammograms of a 7.3 mM solution of **3**·Cl_2 in 0.5 M pH 7 phosphate buffer in the absence (solid line) and presence (dotted line) of 8.7 mM adamantane-1-carboxylic acid (ACA). Data recorded using a potential step of 4 mV, pulse amplitude of 25 mV, and frequency of 15 Hz.

exhibiting the broadening and anodic shifting of the second reduction wave which is associated with the self-complexation of the reduced form **3**. Addition of adamantane-1-carboxylic acid, an excellent guest for β-CD hosts,[16] has a profound effect on the second reduction wave (dotted line), which returns to the potential region and to the appearance that it had at concentrations $\leqslant$1 mM. Thus, adamantane-1-carboxylic acid disrupts self-complexation by competing with the reduced viologen subunits for the available CD cavities.

Similarly, voltammograms of the investigated CD–viologen conjugates exhibit large changes in the presence of heptakis(2,6-*O*-dimethyl)-β-cyclodextrin (DM–β-CD). In this case, the addition of the DM–β-CD host leads to a greater anodic shift for the second reduction waves of $\mathbf{1}^{2+}$–$\mathbf{3}^{2+}$, as the added host increases the CD-bound fraction of the reduced viologen subunits (voltammograms not shown). Thus, the observed voltammetric results clearly reveal that the self-complexation of the CD–viologen conjugates upon two-electron reduction (**1**–**3**) can be disrupted by addition of competing CD guests or free CDs. Based on previous electrochemical and spectroscopic studies on the complexation of CD hosts with the viologen guests we estimate the association constant of observed intermolecular complexes to be 10^3 to 10^4 M^{-1}.[17]

A final issue that must be addressed is the mode of assembly exhibited by the CD–viologen conjugates. Are they interacting face-to-face to yield dimeric structures (as shown in Scheme 1) or face-to-tail to produce oligomeric aggregates formed by a larger number of monomers? An unequivocal answer to this question will require additional physicochemical characterization of fully isolated reduced complexes. This task has proven to be a very difficult one due to extreme air sensitivity of the reduced viologen species.[11] Park and coworkers,[10c] however, demonstrated formation of face-to-face dimers in solution upon photochemically-induced, one-electron reduction of related CD–viologen conjugates. Our data also suggest face-to-face dimerization, since face-to-tail complexation should yield bulky insoluble aggregates in solution, which we have never observed, upon two-electron reduction of the viologen moieties. Entropic considerations similarly suggest that formation of small cyclic dimeric complexes is more favorable than aggregation to yield large assemblies.

In summary, we have prepared a series of three CD–viologen conjugates that exhibit concentration-dependent voltammetric behavior. This behavior is clearly indicative of intermolecular self-complexation upon two-electron reduction of the pendant viologen subunits.

The authors are grateful to the National Science Foundation (to A. E. K., CHE-9633434) for the generous support of this work.

Notes and references

1 J. M. Lehn, *Supramolecular Chemistry: Concepts and Perspectives*, VCH, Weinheim, 1995.
2 M. M. Conn and J. Rebek, *Chem. Rev.*, 1997, **97**, 1647.
3 N. Yamaguchi, D. S. Nagvekar and H. W. Gibson, *Angew. Chem., Int. Ed.*, 1998, **37**, 2361.
4 (*a*) D. Metzafos, A. Terzis, A. W. Coleman and C. de Rango, *Carbohydr. Res.*, 1996, **282**, 125; (*b*) A. Ueno, T. Kuwabara, A. Nakamura and F. Toda, *Nature*, 1992, **356**, 136; (*c*) R. C. Petter, J. S. Salek, C. T. Sikorski, G. Kumaravel and F. T. Lin, *J. Am. Chem. Soc.*, 1990, **112**, 3860.
5 P. R. Ashton, I. W. Parsons, F. M. Raymo, J. F. Stoddart, A. J. P. White, D. J. Williams and R. Wolf, *Angew. Chem., Int. Ed.*, 1998, **37**, 1913; J. Bugler, N. A. J. M. Somerdijk, A. J. W. G. Visser, A. van Hoek, R. J. M. Nolte, J. F. J. Engbersen and D. Reinhoundt, *J. Am. Chem. Soc.*, 1999, **121**, 28; P. R. Ashton, I. Baxter, S. J. Cantrill, M. C. T. Fyfe, P. T. Glink, J. F. Stoddart, A. J. P. White and D. J. Williams, *Angew. Chem., Int. Ed.*, 1998, **37**, 1294; J. L. Sessler, A. Andrievsky, P. A. Gale and V. Lynch, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 2782.
6 For a recent example, see: M. B. Nielsen, S. B. Nielsen and J. Becher, *Chem. Commun.*, 1998, 475.
7 For reviews on the use of electrochemical reactions to control host–guest complexation, see: A. E. Kaifer, *Acc. Chem. Res.*, 1999, **32**, 62; P. L. Boulas, M. Gómez-Kaifer and L. Echegoyen, *Angew. Chem., Int. Ed.*, 1998, **37**, 216.
8 A. Mirzoian, PhD Dissertation, University of Miami, 1998.
9 A. Mirzoian and A. E. Kaifer, *Chem. Eur. J.*, 1997, **3**, 1052.
10 Compounds $\mathbf{1}^{2+}$–$\mathbf{3}^{2+}$ were synthesized by reaction of $\mathbf{4}^{+}$ with the corresponding alkyl iodide in DMF. In turn, $\mathbf{4}^{+}$ was prepared by the reaction of mono-6-deoxy(*p*-tolylsulfonyl)-β-CD [ref. 4(*c*)] with excess 4,4′-bipyridine. Compounds $\mathbf{1}^{2+}$–$\mathbf{3}^{2+}$ were isolated as dichloride salts (yields 12–38%) after size exclusion chromatography (Biogel P-2 column) and ion exchange (Amberlite IRA 401). All compounds were characterized by ^1H NMR (400 MHz), UV–VIS spectroscopy and MALDI-TOF mass spectrometry. Compounds $\mathbf{1}^{2+}$ and $\mathbf{2}^{2+}$, as well as related CD–viologen conjugates, have been synthesized previously using different methodology: (*a*) Y. Du, A. Nakamura and F. Toda, *Bull. Chem. Soc. Jpn.*, 1990, **63**, 3351; (*b*) Y. Du, A. Nakamura and F. Toda, *J. Inclusion Phenom.*, 1991, **10**, 443; (*c*) J. W. Park, N. H. Choi and J. H. Kim, *J. Phys. Chem.*, 1996, **100**, 769; (*d*) H. Ikeda, Y. Du, A. Nakamura and F. Toda, *Chem. Lett.*, 1991, 1495; (*e*) J. W. Park, J. H. Kim, B. K. Hwang and K. W. Park, *Chem. Lett.*, 1994, 2075; (*f*) K. K. Park and S. Y. Han, *Tetrahedron Lett.*, 1997, **38**, 4231.
11 C. Bird and A. T. Kuhn, *Chem. Soc. Rev.*, 1981, **10**, 49.
12 A. E. Kaifer and A. J. Bard, *J. Phys. Chem.*, 1985, **89**, 4876.
13 P. A. Quintela and A. E. Kaifer, *Langmuir*, 1987, **3**, 769.
14 P. Quintela, A. Diaz and A. E. Kaifer, *Langmuir*, 1988, **4**, 663.
15 Viologens modified with hydrophilic side chains were used in this experiment along with the highly water soluble methylviologen. See ref. 9.
16 L. A. Godínez, L. Schwartz, C. M. Criss and A. E. Kaifer, *J. Phys. Chem. B*, 1997, **101**, 3376.
17 T. Matsue, T. Kato, U. Akiba and T. Osa, *Chem. Lett.*, 1985, 1825; A. Díaz, P. A. Quintela, J. M. Schuette and A. E. Kaifer, *J. Phys. Chem.*, 1988, **92**, 3537; A. Yasuda, H. Mori and J. Seto, *J. Appl. Electrochem.*, 1987, **17**, 567; M. Kodaka and T. Fukaya, *Bull. Chem. Soc. Jpn.*, 1986, **59**, 2032.

Communication 9/04095A