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Synthesis and Redox Properties of Methylbipyridinioalkyl (Viologen)-modified β–Cyclodextrins at the Secondary Face

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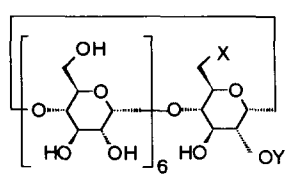
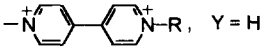
Abstract. Viologens linked to the secondary face of β-CD *via* aliphatic chains, which show several desirable properties for an artificial redox enzyme, are prepared. Their redox behaviors and stability are compared with viologens directly bonded to the primary side of β-CD. © 1997 Elsevier Science Ltd.

β-Cyclodextrin (β-CD) derivatives have drawn great amount of interest as enzyme mimics and building blocks for supramolecular structures and functional units.[1] Our continued interest in utilization of viologens (1,1'-dialkyl-4,4'-bipyridinium) as electron-transfer catalysts (ETC) in reductive transformation of organic compounds[2,3] prompted us to synthesize viologen-appended β-CDs to combine the recognition properties of β-CD with the ETC properties of viologens. Alkyl viologen-modified β-CDs at the primary side **1** have been prepared by reacting the 6-monoiodo-β-CD[4] or 6-monotosyl-β-CD[5,6] with 1-alkyl-4,4'-bipyridinium ion. Toda et al.[4] showed that ethyl viologen-modified β-CD undergoes the Rose Bengal-sensitized photochemical reduction *ca.* 3 times more efficiently than dimethyl viologen (MV^{2+}). In previous papers, we reported that the two-electron reduction product of methyl viologen-modified β-CD **1a** is stabilized in water *via* intramolecular interaction of the viologen moiety with β-CD cavity,[5] and dimerization of one-electron reduction products of **1b-d** is facilitated by inclusion of the alkyl chain of a molecule into the β-CD cavity of the counter molecule.[6]

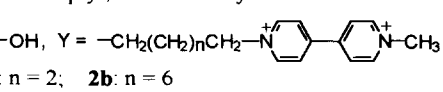
The secondary hydroxyl side of β-CD is more open than the primary side and it is generally known that the secondary side is more important for binding guest molecules and catalytic activities of β-CD.[1] Here, we describe the synthesis of the viologens linked to one of the secondary hydroxyl groups of β-CD *via* aliphatic chains, mono-2-O-[4-(1-methyl-4-pyridinio)-1-pyridinio]alkyl-β-CD **2**.[7] Their redox behaviors and stability are compared with viologen derivatives directly bonded to the primary side, mono-6-deoxy-6-[4-(1-alkyl-4-pyridinio)-1-pyridinio]-β-CD **1**, and MV^{2+} in the presence and absence of β-CD.



1: X =  , Y = H

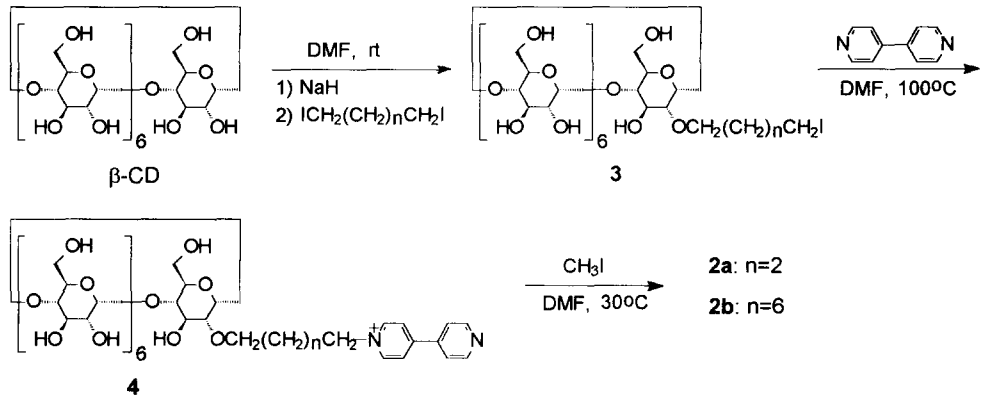
1a: R = methyl; **1b**: R = hexyl

1c: R = heptyl; **1d**: R = octyl

2: X = −OH, Y = 

2a: n = 2; **2b**: n = 6

2 was prepared as shown in Scheme **1**: dried β-CD was dissolved in DMF, to which equimolar amount of NaH was added and the mixture was stirred overnight until the solution became clear.[8] To this solution was added equimolar amount of ω,ω'-diiodoalkane and stirred at rt for 5 h. The product **3** was precipitated by addition of acetone and then purified by gel filtration chromatography using Sephadex G-15. **3** was reacted with ten molar excess of 4,4'-bipyridine in DMF at 100 °C for 24 h. The reaction mixture was concentrated to one fifth of the volume and the product **4** was precipitated by addition of acetone and then purified by cation exchange chromatography using Sephadex CM C-25.[9] Methylation of **4** using ten molar excess of methyl iodide in DMF at 30 °C for 24 h, followed by precipitation of the product through the addition of acetone and then purification by cation exchange chromatography[9] provided **2** in overall yield of 3-4 % starting from β-CD. **2** and **4** were characterized by nmr and FAB MS data.[10] a large downfield chemical shift of C2 of the substituted glucose unit in ^{13}C nmr spectra of **2** was observed as reported by Rong and D'Souza.[8]



Scheme 1

To compare the capability of these viologen-modified β-CDs as ETC, we investigated the redox properties of **1** and **2** and the reactivity of their reduced products electrochemically. Cyclic voltammograms of **1** and **2** showed two reversible 1-e$^-$ redox processes, which are similar to that of MV^{2+}.[2] The redox potentials of viologen moieties were found to depend on the position of its substitution on β-CD and the length of the linking aliphatic chain (for **2**) or terminal alkyl group (for **1**) (Table 1). The reactivity of reduced viologens was studied spectroelectrochemically. Constant-potential electrolysis of 1.0 mM viologen solution in 110 μm thin layer cell at -0.8 V *vs* Ag electrode yielded the monomer-dimer mixture of 1-e$^-$ reduction product of **1** or **2**. The apparent dimerization constants of the 1-e$^-$ reduced viologens ($V^{+\cdot}$) were calculated from the resolved spectra of the monomer and the dimer by a procedure reported previously.[6] The results are included in Table 1. The viologens directly bonded to the primary side of β-CD, **1** show strong tendency of dimerization and the first reduction potential becomes less negative (viologens are more easily reduced and thus $V^{+\cdot}$ is less potent reductant) as the terminal alkyl chain is longer. These indicate that $V^{+\cdot}$ is stabilized by dimerization. On the other hand, the viologens linked to the secondary side of β-CD *via* aliphatic chains, **2** exhibit only slightly enhanced dimerization and a little loss of reducing ability of $V^{+\cdot}$, compared to $MV^{+\cdot}$.

Two-electron reduced viologens V^0 are potent reductants having the reduction potential comparable to that of coenzyme NADH. One of the limitations for using this species as ETC is transformation of V^0 to inert

Table 1. Redox Potentials (E) of Viologens, Dimerization Constants (K_D) of One-electron Reduced Viologens, and the Relative Stability of Two-electron Reduced Viologens in Water at 25 °C.

Viologens	E/V (vs SCE)[a]		K_D/M^{-1}	Stability of 2-e⁻ Reduced Viologen	
	First	Second		Rel. Decomp. Rate	(k x 10^3/min^{-1})[c]
MV^{2+}	-0.67	-1.00	(500)[b]	1.00	7.0
MV^{2+} + 10 mM β-CD	-0.67	-1.00	500	0.34	2.4
1a	-0.64	-0.93	(100)[b]	0.30	(2.1)[d]
1b	-0.58	-0.93	(4.0×10^4)[b]	-	-
1c	-0.50	-0.97	(8.9×10^5)[b]	-	-
1d	-0.48	-0.98	(6.8×10^6)[b]	0.0016	0.011
2a	-0.63	-0.94	1100	0.061	0.43
2b	-0.60	-0.93	760	0.011	0.077

[a] Measured at scan rate of 100 mV/s and the values are the average of cathodic and anodic peak potentials. [b] Ref. 6. [c] Pseudo-first order rate constants for reactions of V° with H_2O to produce inert species. Estimated from the reported result of **1a**. [d] Ref. 5

species by reacting with water.[5] To compare the stability of V°, we generated V° by electrolysis of the afore-mentioned solutions in thin layer cell at -1.1 V and followed the concentration of viologens spectroscopically.[12] During continuous electrolysis, the concentration of V° decreased, following first order kinetics (data not shown), presumably due to the reaction of V° with water. From the relative decomposition rates of V° under the constant electrolysis condition and the reported rate constant of V° of **1a** with water,[5] we estimated the rate constants for the reaction of the 2-e⁻ reduced products of other viologens with water (see Table 1).

It is clear from the table that **2** has several desirable properties as an artificial redox enzyme with chiral binding site for substrates: unlike **1b-d**, attachment of β-CD causes only a slight loss in the reducing power of the reduced viologens, the one-electron reduction products show much less tendency of dimerization, and the β-CD cavity is available for substrate binding as the viologen moiety is linked *via* aliphatic chains.[7] Also, the 2-e⁻ reduction products are well protected against reaction with water and thus can be used with high efficiency for reduction of the substrates. Though **1a** also shows little tendency of dimerization, the 2-e⁻ reduction product of **1a** reacts with water 5 - 27 times faster than those of **2**. Studies on the utilization of **2** as chiral artificial redox enzyme are in progress.

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7. It was shown that bipyridinium moiety of ethyl viologen-modified β-CD at primary side locates on the top of the cavity.[4] Similar conformation may be expected for derivatives at secondary side if the bipyridinium ion is directly bonded to β-CD. This may inhibit the guest binding from the secondary side. The aliphatic linkages in **2** may give enough room for the guest binding from the secondary side.
8. Rong, D.; D'Souza, V. T. *Tetrahedron Lett.* **1990**, *31*, 4275-4278.
9. Eluent was water and then 0.02 M phosphate buffer (pH 7.2) with 0.0 - 0.3 M NaCl gradient. The products at these stages contains large amounts of salts which were removed by filtration after selective solubilization of the products in DMF.
10. ^{1}H nmr spectra in D_2O (they are recorded on a Bruker AM 300 or AMX 500 spectrometer, and the chemical shifts are reported in δ relative to the residual solvent at 4.65): **2a**[11] 9.00 (d, 2H, J=6.6, H^a), 8.91 (d, 2H, J=6.6, H^d), 8.42 (d, 2H, J=6.6, H^b), 8.39 (d, 2H, J=6.6, H^e), 5.06 (d, 1H, J=3.3, $H1^A$), 5.0-4.85 (m, 6H, H1), 4.70 (-CH_2N^+, overlapped with the solvent peak), 4.36 (s, 3H, CH_3N^+), 3.95-3.6 (m, 30H, H3, H5, H6, -OCH_2), 3.6-3.3 (m, 14H, H2, H4), 2.15-2.0 (m, 2H, -$\underline{CH_2}CH_2N^+$), 1.65-1.5 (m, 2H, -$OCH_2\underline{CH_2}$-); **2b**[11] 9.03 (d, 2H, J=5, H^a), 8.94 (d, 2H, J=6, H^d), 8.48 (d, 2H, J=5, H^b), 8.42 (d, 2H, J=6, H^e), 5.15-4.85 (m, 7H, H1), 4.71 (-CH_2N^+, overlapped with the solvent peak), 4.38 (s, 3H, CH_3N^+), 4.1-3.2 (m, 44H, H2, H3, H4, H5, H6, -OCH_2), 2.1-1.85 (m, 2H, -$\underline{CH_2}CH_2N^+$), 1.7-1.45 (m, 2H, -$OCH_2\underline{CH_2}$-), 1.45-1.05 (m, 8H, -$OCH_2CH_2\underline{(CH_2)_4}CH_2CH_2N^+$); **4a**[11] 8.92 (d, 2H, J=6.6, H^a), 8.65 (d, 2H, J=5, H^d), 8.23 (d, 2H, J=6.6, H^b), 7.78 (d, 2H, J=5, H^e), 5.1-4.8 (m, 7H, H1), 4.70 (-CH_2N^+, overlapped with the solvent peak), 4.0-3.25 (m, 44H, H2, H3, H4, H5, H6, -OCH_2), 2.15-1.95 (m, 2H, -$\underline{CH_2}CH_2N^+$), 1.65-1.4 (m, 2H, -$OCH_2\underline{CH_2}$-); **4b**[11] 8.96 (d, 2H, J=6.6, H^a), 8.85 (d, 2H, J=5, H^d), 8.42 (d, 2H, J=6.6, H^b), 8.28 (d, 2H, J=5, H^e), 5.1-4.8 (m, 7H, H1), 4.70 (-CH_2N^+, overlapped with the solvent peak), 4.05-3.2 (m, 44H, H2, H3, H4, H5, H6, -OCH_2), 2.05-1.85 (m, 2H, -$\underline{CH_2}CH_2N^+$), 1.65-1.35 (m, 2H, -$OCH_2\underline{CH_2}$-), 1.35-1.05 (m, 8H, -$OCH_2CH_2\underline{(CH_2)_4}CH_2CH_2N^+$).

    ^{13}C nmr spectra in D_2O: **2a**[11] 152.8^c, 152.5^f, 149.0^d, 148.2^a, 129.7^b, 129.3^e (bipyridyl carbons), 104.5 (C1), 102.6 ($C1^A$), 84.1 ($C4^A$), 83.7 (C4), 82.9 ($C2^A$), 75.7, 74.6, 74.4, 73.8 (C2, C3, C5, -OCH_2), 64.4 (-CH_2N^+), 62.8 (C6), 51.0 (CH_3N^+), 30.3(-$\underline{CH_2}CH_2N^+$), 28.3 (-$OCH_2\underline{CH_2}$-); **2b**[11] 152.8^c, 152.1^f, 149.0^d, 148.0^a, 129.7^b, 129.4^e (bipyridyl carbons), 104.5 (C1), 102.6 ($C1^A$), 84.1 ($C4^A$), 83.7 (C4), 82.9 ($C2^A$), 75.8, 74.6, 74.4, 73.8 (C2, C3, C5, -OCH_2), 64.5 (-CH_2N^+), 62.8 (C6), 51.1 (CH_3N^+), 34.1, 33.5, 31.1, 28.3, 27.6, 24.4 (-$OCH_2\underline{(CH_2)_6}CH_2N^+$).

    FAB MS data gave 1345.4930 for **4a** (calcd for $C_{56}H_{85}O_{35}N_2$ 1345.4933), 1401.5532 for **4b** (calcd for $C_{60}H_{93}O_{35}N_2$ 1401.5559), 1360.5175 for **2a** (calcd for $C_{57}H_{88}O_{35}N_2$ 1360.5168), 1416.5763 for **2b** (calcd for $C_{61}H_{96}O_{35}N_2$ 1416.5794).
11. *a*, *b* and *c* denote the α, β and γ atoms of the pyridine ring connected to the linking alkyl chain, and *d*, *e* and *f* represent the α, β and γ atoms of the terminal pyridine ring, respectively. Peak assignments are made by ^{1}H COSY, HMBC, and HMQC spectra.
12. The electrogenerated V^0 is also reoxidized to $V^{+\cdot}$ by the reaction with water,[5] and thus the fraction of V^0 was 11 - 40 % and the remaining was $V^{+\cdot}$ monomer and dimer, during electrolysis.

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