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Solvent Effects on the Redox-Dependent Binding Properties of a Viologen-Based Receptor for Neutral Organic Molecules

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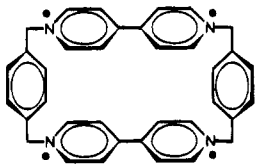
Cyclic voltammetry of a viologen-based cyclophane receptor, VH, in water, 10% acetonitrile/water, and acetonitrile is described. Minimal electrolyte was necessary in order to prevent precipitation of the reduced VH in aqueous solutions. Shifts in the half-wave potential of the first viologen reduction are observed in the presence of various substituted benzenes. The direction and magnitude of the shifts are explained in terms of two competing factors: (i) the change in the electron donor–acceptor character of the host that occurs upon reduction and (ii) the change in the hydrophobic/hydrophilic character of the host upon reduction. The first factor promotes binding of acceptor-substituted guests to the reduced host and donor-substituted guests to the oxidized host. The second factor promotes binding of all the guests to the reduced host in aqueous solution. Large potential shifts are observed when both factors work in the same direction.

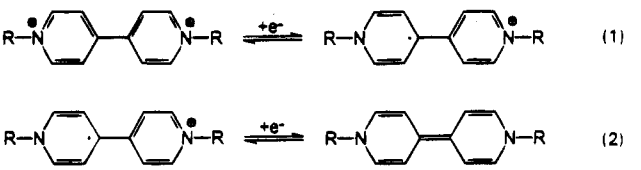
A redox-dependent receptor is a receptor that undergoes a reversible redox process that changes the binding properties of the receptor. Such receptors have several potential applications in analytical chemistry. For example, they could function as the primary components in electrochemical sensors, providing both substrate recognition and a means for electrochemical detection. Redox-dependent receptors could also be utilized in membrane separation systems that employ a potential gradient to effect selective transport across the membrane.

In previous reports, we have described some of the redox-dependent binding properties of the viologen-based receptor, VH, in acetonitrile.[1,2] VH, originally prepared and studied by Stoddart



VH

and co-workers,[3] binds benzene-size aromatics in the cavity between the 4,4′-bipyridiniums,[3–6] commonly known as viologens. Like other viologens, the viologens in VH undergo two reversible reductions, first to a stable radical cation and then to a neutral quinoid structure, eqs 1 and 2.[1,2,4] Although not much change in



the size or shape of the binding cavity is expected upon reduction, we reasoned that the changes in charge and electronic structure which do occur would alter the binding properties of VH, and, indeed, this turned out to be the case.

Although numerous redox-dependent receptors for ionic species have been described,[7] VH is one of only a few redox-dependent receptors for neutral compounds which have been reported to date.[7,8] Of these, it is the only example where binding strength changes in a straightforward and predictable manner upon reduction/oxidation. In our previous work, we showed that the oxidation state which is preferred by a particular substrate or guest molecule in acetonitrile can be predicted on the basis of the ability of the guest to interact with the positive charges on VH and on electron donor–acceptor considerations. Specifically, benzene derivatives with ethoxy ether side chains that interact with the positively charged sites bind more strongly to the oxidized VH^{4+} form, which has a greater positive charge. This was determined from the negative shift in the half-wave potential of the first viologen reduction in the presence of these guests. Smaller but still significant shifts are observed with guests which do not specifically interact with the positive charges. In these cases, the preferences are controlled by electron donor–acceptor considerations. Donor-substituted guests, which bind more strongly to the relatively electron poor VH^{4+}, cause negative shifts in the observed half-wave potential of the $VH^{4+/2+}$ couple. In contrast, acceptor-substituted guests, which bind more strongly to the reduced VH^{2+} form, cause positive shifts in the half-wave potential.

(1) Fonseca, R. J.; Colina, J. T.; Smith, D. K. *J. Electroanal. Chem.* **1992**, *340*, 341.
(2) Smith, E. A.; Lilienthal, R. R.; Fonseca, R. J. *Anal. Chem.* **1994**, *66*, 3013.
(3) Odell, B.; Reddington, M. V.; Slawin, A. M. Z.; Spencer, N.; Stoddart, J. F.; Williams, D. J. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1547.
(4) Anelli, P. L.; Ashton, P. R.; Ballardini, R.; Delgado, M.; Gandolfi, M. T.; Goodnow, T. T.; Kaifer, A. E.; Philp, D.; Pietraszkiewicz, M.; Prodi, L.; Reddington, M. V.; Slawin, A. M. Z.; Spencer, N.; Stoddart, J. F.; Vicent, C.; Williams, D. J. *J. Am. Chem. Soc.* **1992**, *114*, 193.
(5) (a) Goodnow, T. T.; Reddington, M. V.; Stoddart, J. F.; Kaifer, A. E. *J. Am. Chem. Soc.* **1991**, *113*, 4335. (b) Philp, D.; Slawin, A. M. Z.; Spencer, N.; Stoddart, J. F.; Williams, D. J. *J. Chem. Soc., Chem. Commun.* **1991**, 1584. (c) Cordova, E.; Bissell, R. A.; Spencer, N.; Ashton, P. R.; Stoddart, J. F.; Kaifer, A. E. *J. Org. Chem.* **1993**, *58*, 6550.
(6) Bernardo, A. R.; Stoddart, J. F.; Kaifer, A. E. *J. Am. Chem. Soc.* **1992**, *114*, 10624.
(7) Beer, P. *Adv. Inorg. Chem.* **1992**, *39*, 79.
(8) Seward, E. M.; Hopkins, R. B.; Sauerer, W.; Tam, S.-W.; Diederich, F. *J. Am. Chem. Soc.* **1990**, *112*, 1783.

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In this paper, we explore the influence of solvent on the redox-dependent binding properties of VH. Solvent typically has a strong influence on binding in organic host–guest systems.[9,10] Indeed, solvation forces are often the primary driving force for binding in these systems. This is particularly true in aqueous solution, where the unfavorable solvation of an apolar guest and apolar binding site strongly promote binding. Since viologens become more hydrophobic upon reduction, the solvation properties of the binding site in VH will change considerably in aqueous solution, and this could lead to large changes in binding strengths.

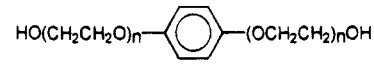
Unfortunately, it is not straightforward to investigate the electrochemistry of VH in aqueous electrolyte for the very reason that it would be interesting to do so. The increased hydrophobicity of the radical cation promotes precipitation of the radical onto the electrode surface, leading to distorted voltammograms which can not be simply interpreted in terms of binding equilibria. The tendency to precipitate is much greater for VH than for simpler viologens, making it nearly impossible to observe undistorted voltammograms in aqueous electrolyte solution.

Bernardo et al. avoided this difficulty by exchanging the viologen host into a Nafion film coated on an electrode surface.[6] This allowed them to examine the undistorted voltammetry of VH in the presence of different guests in aqueous solution. However, the interior of a Nafion film is a considerably different environment than water, so their results do not necessarily reflect the influence of solvation forces which we wish to explore. In addition, although the Nafion approach will be useful for practical applications such as sensors or membrane separation systems, it increases the complexity of the experimental system, making it more difficult to extract fundamental information regarding the redox-dependent binding.

We took another approach to solving the precipitation problem which avoids the added complexity of a surface-modified electrode system. By using microelectrodes, we have studied the voltammetry of VH in water, with minimal electrolyte. Under these conditions, no distortion is observed, and the electrochemistry can be examined in the presence of different guests. In many cases, we observe a positive shift in the redox potential in the presence of the guests, implying stronger binding to the reduced form of the host. The positive shift is consistent with solvation-controlled binding, since the reduced VH^{2+} state is more hydrophobic and is therefore less favorably solvated by water than the VH^{4+} state. The observation that even guests which give negative potential shifts in acetonitrile give positive shifts in water underscores the significance of solvation forces in this system.

EXPERIMENTAL SECTION

Compound Preparation. VH was prepared and purified as described in the literature.[3] ^1H NMR and ^{13}C NMR of the purified product agreed with the reported chemical shifts. The initial PF_6^- salt was converted to the chloride salt by dissolving in acetonitrile and adding excess tetraethylammonium chloride. Methylviologen (MV) was prepared by reacting excess methyl iodide with 4,4′-bipyridine in acetonitrile. The resulting iodide salt was converted to the PF_6^- salt by adding excess NH_4PF_6 to an aqueous solution of the iodide. The PF_6^- salt was converted to the chloride as described above. 1,4-Bis[2-(2-hydroxyethoxy)ethoxy]benzene (**1b**) was prepared and purified according to the literature procedure.[4]



1a n = 1, **1b** n = 2

All other guest compounds were purchased from commercial sources and further purified as follows. 1,4-Diaminobenzene, 1,2-diaminobenzene, and 1,2-dihydroxybenzene were sublimed in vacuo. 1,4-Dihydroxybenzene was recrystallized from acetonitrile under N_2.

Electrochemical Studies. The microelectrode experiments were performed using a Pine Instrument Co. RDE4 bipotentiostat with a Kipp and Zonen $X-Y$ chart recorder. Both the electrochemical cell and the potentiostat were placed in a copper mesh faraday cage to reduce signal noise. For the nonmicroelectrode experiments, a PAR Model 173 potentiostat connected to a PAR Model 175 universal potential programmer was used. All electrochemical measurements were made under Ar or N_2 in a one-compartment cell with a Pt or Au disk working electrode (2 mm or 25 μm diameter) and a Pt wire counter electrode. A SCE reference electrode was used for the aqueous experiments, and a $Ag/AgNO_3$ reference electrode was used for the acetonitrile work.

Water from a Millipore Milli-Q water purification system was used for aqueous electrochemical experiments. HPLC-grade acetonitrile was used for the nonaqueous experiments. For the 100% acetonitrile experiments, the acetonitrile was passed through a small column of activated alumina directly into the electrochemical cell. Tetrabutylammonium hexafluorophosphate, previously recrystallized 3 times from 95% ethanol and dried in vacuo for 24 h at 70 °C, was used as the electrolyte in the nonmicroelectrode experiments.

Binding Constant Measurements. Binding constants for all guests with VH^{4+} were estimated from NMR data using the following procedure. A D_2O or 10% CD_3CN/D_2O solution which contained a known concentration of VH (~0.5 mM) and a known concentration of guest (0.3–1.0 mM) was prepared, and its ^1H NMR spectrum was recorded (Chem Magnetics 200 MHz FT NMR spectrometer). Enough guest was then added to the NMR tube to increase the concentration to ~10 mM, and another NMR was recorded. Finally, the guest concentration was increased to ~20 mM, and a final NMR was recorded. With most guests, little change in chemical shift (<3%) was observed between the 10 and 20 mM guest solutions, indicating saturation binding. To calculate the binding constant, we measured the change in chemical shift in hertz (ΔHz) of the VH^{4+} xylyl protons in the VH solution containing a low concentration of guest relative to a VH^{4+} solution with no added guest. The methylene VH^{4+} protons were used as an internal standard for this calculation since they did not shift significantly with added guest. These data were then plugged into the 1:1 NMR binding isotherm, eq 3,[11] where [G] is taken to

$$\Delta\mathrm{Hz} = \frac{\Delta\mathrm{Hz}_{max} K[\mathrm{G}]}{1 + K[\mathrm{G}]} \qquad (3)$$

be the total guest concentration in the original solution, ΔHz is the change in chemical shift in hertz in the original solution, and

(9) Diederich, F. *Cyclophanes*; Royal Society of Chemistry: London, 1991; Chapter 7.

(10) (a) Smithrud, D. B.; Diederich, F. *J. Am. Chem. Soc.* **1990**, *112*, 339. (b) Smithrud, D. B.; Wyman, T. B.; Diederich, F. *J. Am. Chem. Soc.* **1991**, *113*, 5420.

(11) Connors, K. A. *Binding Constants*; John Wiley: New York, 1987; Chapter 5.

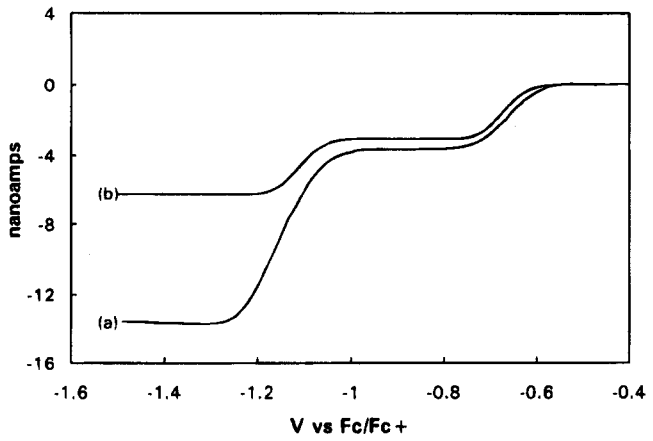


Figure 1. Voltammograms of 0.5 mM VH in acetonitrile with (a) no electrolyte and (b) 100 mM NBu_4PF_6. Other conditions: 25 μm Pt disk electrode, 50 mV/s scan rate.

ΔHz_{max} is the change in chemical shift in hertz in the 20 mM guest solution. (With benzonitrile and nitrobenzene, it did not appear that saturation binding had been reached at 20 mM, so instead the average ΔHz_{max} observed for all the other guests was used for the ΔHz_{max} of these two guests.) Since the [G] term in eq 3 represents the free guest concentration and not the total guest concentration, this calculation gives only an initial estimate of K. An iterative procedure was used to get a better estimate of K. First, the initial K was used to calculate the free guest concentration at a given value of G_{tot} and H_{tot} using eq 4. This value of [G]

$$[G] = \frac{KG_{tot} - KH_{tot} - 1 + \sqrt{(KH_{tot} - KG_{tot} + 1)^2 + 4KG_{tot}}}{2K} \quad (4)$$

was then plugged back in to eq 3 to get a better estimate of K, and the new K was used to recalculate [G]. The process was repeated until the values of K and [G] converged. We estimate that the resulting K values have an error on the order of 35% as a result of large uncertainties in the host and guest concentrations, due to the small amounts of material used. Three replicate measurements were made with **1a** in D_2O, and the resulting experimental value, 11 000 ± 3400 (90% confidence limits), agrees with the error analysis.

RESULTS

Cyclic Voltammetry of VH in Acetonitrile with No Electrolyte. Microelectrodes were required for this work because the larger currents at "normal"-size electrodes (millimeter diameter), coupled with high solution resistance without electrolyte, lead to large IR drops and the accompanying distortion in the voltammetry. The low currents at micrometer-size electrodes minimize the IR drop, making it possible to do voltammetry in quite resistive media.[12] However, use of microelectrodes does not eliminate another complication of removing the electrolyte, i.e., with no electrolyte and a charged species like VH, migration effects cannot be conveniently ignored as they typically are.

The effect of migration is illustrated in Figure 1, which shows voltammograms of VH at a 25 μm diameter Pt disk electrode in acetonitrile with no electrolyte present and with excess electrolyte. Both voltammograms show the expected sigmoidal-shaped waves characteristic of microelectrodes at slow scan rates. The two reduction waves at −0.66 and −1.10 V are for the first and second reductions of VH. At high electrolyte concentrations, the limiting current after the second viologen reduction is approximately twice that after the first viologen reduction, consistent with both reduction processes involving equal number of electrons (in this case, two). However, at lower electrolyte concentrations, the limiting current after the second reduction is more than twice that of the first reduction, and both currents are greater than that observed in the presence of electrolyte.

The observed changes in the voltammetry with different electrolyte concentrations can largely be explained by migration effects. Qualitatively, reduction of the cationic host makes the region near the electrode surface relatively negatively charged compared to the bulk. This creates a potential field which pulls in more VH^{4+} from the bulk, leading to enhanced mass transport and enhanced currents compared to the excess electrolyte situation, where diffusion is the only form of mass transport. The effect is even greater at the potential of the second reduction, because there is a greater charge differential between the surface region and the bulk.

Amatore has derived a series of equations for predicting the expected current enhancements for charged species when no electrolyte is present.[13] These equations predict the observed current fairly well in several real systems.[13,14] For the first reduction of VH, the equations predict that the limiting current without electrolyte will be 1.35 times greater than the limiting current in the presence of a large excess of electrolyte. This is reasonably close to the observed value of 1.26 (from Figure 1). However, for the second reduction, Amatore's equations predict an enhancement of 5.0 in the absence of electrolyte, whereas the observed enhancement is only 2.2. Qualitatively similar results were observed by Norton and White for MV under the same experimental conditions.[15] They showed that the smaller than expected current for the second reduction could be explained by consideration of the comproportionation reaction between MV^{2+} and MV^0. The large favorable equilibrium constant ($K = 8.5 \times 10^6$) means that at potentials where MV^0 is produced at the electrode, there is mainly MV^+ in the diffusion layer, so the electric field is not as great as expected and the migration current is less. We assume that a similar explanation holds for VH, since the equilibrium constant for the comproportionation would also be large ($K = 2.7 \times 10^7$ from the difference in the $E_{1/2}$'s).

Cyclic Voltammetry of VH in Water with No Electrolyte. Unlike in acetonitrile, we are not able to observe the effect of electrolyte in water, nor are we able to observe a difference in limiting current between the first and second reductions. This is because either adding excess electrolyte or scanning into the second reduction leads to highly distorted voltammetric waves, as shown in Figure 2. The large stripping peaks observed on the return scan are definitive evidence for precipitation of the reduced species under these conditions. However, the key point for the present study is that, without electrolyte, we are able to at least scan through the first reduction with no evidence of precipitation onto the electrode surface. Under these conditions, the steady state wave is broader than that observed for the first reduction in

(12) Wightman, R. M.; Wipf, D. O. In *Electroanalytical Chemistry, Vol. 15*; Bard, A. J., Ed.; Marcel Dekker: New York, 1989; pp 308–316.

(13) Amatore, C.; Fosset, B.; Bartelt, J.; Deakin, M. R.; Wightman, R. M. *J. Electroanal. Chem.* **1988**, *256*, 255.

(14) Lee, C.; Anson, F. C. *J. Electroanal. Chem.* **1992**, *323*, 381.

(15) Norton, J. D.; White, H. S. *J. Electroanal. Chem.* **1992**, *325*, 341.

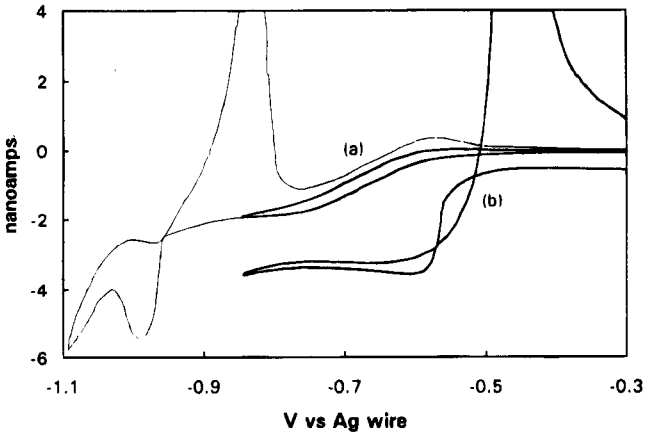


Figure 2. Voltammograms of 0.5 mM VH in water with (a) no electrolyte and (b) 100 mM KCl. Other conditions: 25 μm Pt disk electrode, 50 mV/s scan rate.

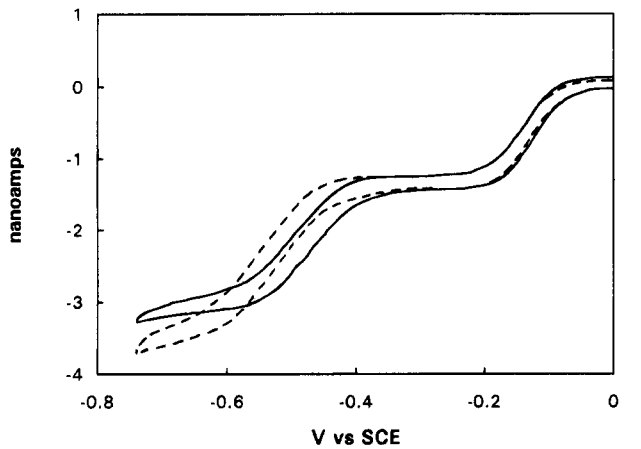


Figure 3. Voltammograms of 0.5 mM VH and 1 mM $Ru(NH_3)_6Cl_3$ in water with no electrolyte. Dashed line, no guest. Solid line, +10 mM **1b**. Other conditions: 25 μm Pt disk electrode, 50 mV/s scan rate.

acetonitrile in the presence of excess electrolyte, suggesting that some IR drop is occurring. However, for most of the work, we also added 1 mM $Ru(NH_3)_6Cl_3$ as an internal potential reference. With the additional ions present, the IR drop is minimal since the log plot slope in this case (Figure 3) is identical to that observed in acetonitrile with excess electrolyte.

Potential Shifts in the Presence of Guest Molecules. Upon addition of suitable guest molecules to an aqueous solution of VH, significant shifts in the $VH^{4+/2+}$ redox potential are typically observed. This is illustrated in Figure 3 with **1b** as the guest molecule. The solid line is the voltammogram observed for 0.5 mM VH^{4+} and 1 mM $Ru(NH_3)_6^{3+}$ in water. The reduction at −0.13 V is for the $Ru^{3+/2+}$ couple, and that at −0.51 V is for the $VH^{4+/2+}$ couple. Upon addition of 10 mM **1b** (solid line in Figure 3), the $E_{1/2}$ of $Ru^{3+/2+}$ remains the same, but the $E_{1/2}$ of $VH^{4+/2+}$ shifts positive by 34 mV. The fact that the Ru potential does not shift upon addition of the guest, along with the fact that no shift is observed for 1 mM MV under the same experimental conditions (Table 1), suggests that this shift is due to binding of **1b** in VH and not to experimental artifacts such as changes in liquid junction potentials or solution resistance.

Interestingly, the potential shift observed upon addition of **1b** to the aqueous solution of VH^{4+} is in the direction opposite that observed in 0.05 M NBu_4PF_6/MeCN. In the latter solvent system, a negative shift of −49 mV is observed upon addition of 10 mM

Table 1. Observed Shifts in Half-Wave Potential (in mV) for the First Viologen Reduction in the Presence of Different Guests under Different Solvent Conditions

			$\Delta E_{1/2}$ $VH^{4+/2+}$		
			10 mM guest		
entry	guest	$\Delta E_{1/2}$ $MV^{2+/+}$, 10 mM guest, H_2O	H_2O	10% MeCN/ H_2O	100 mM guest, MeCN[a]
1	**1a**	−2	+41	0	−35
2	**1b**	+2	+34	−3	−80
3	1,4-dihydroxybenzene	−2	+20	−27	−21
4	1,2-dihydroxybenzene	0	−23	−47	−34
5	phenol		−13	−36	
6	1,4-diaminobenzene	−1	+10	−22	−42
7	1,2-diaminobenzene	0	−13	−36	−45
8	aniline	−4	−6	−13	−34
9	benzene	+4	0	−6	−13
10	cyanobenzene	+2	+60	+40	+11
11	nitrobenzene	*b*	+87	+55	+10

[a] With 0.05 M NBu_4PF_6. [b] Potential obscured by guest electrochemistry.

1b. Analysis of the dependence of the potential shift on **1b** concentration indicates that the binding constant of **1b** with VH^{4+} in 0.05 M NBu_4PF_6/MeCN is 4000 M^{-1}, while the binding constant of **1b** with VH^{2+} is essentially 0 M^{-1}, within experimental error.[2] The strong binding of **1b** to VH^{4+} in acetonitrile is largely due to the favorable electrostatic interaction between the ethoxy ether side chains and the positive charges on the viologens. Reduction to VH^{2+} decreases the charge, and this evidently weakens the interaction to a level where binding does not occur. The opposite behavior observed for VH in water indicates that in this solvent, not only does **1b** bind to VH^{2+} but the binding is stronger than that to VH^{4+}!

As shown in Table 1, a number of other benzene derivatives show similar behavior similar to that of **1b**. Consider first the oxygen-substituted guests, entries 1−5. These guests all cause the $E_{1/2}$ of $VH^{4+/2+}$ to shift negative in acetonitrile, but, like **1b**, **1a** and 1,4-dihydroxybenzene (hydroquinone) both cause a positive shift in water. In contrast, 1,2-dihydroxybenzene (catechol) and phenol both cause negative shifts in water. With all the guests, the shift moves in a negative direction in 10% acetonitrile/water. With **1a,b**, this results in essentially no shift in 10% acetonitrile/water, but with 1,4-dihydroxybenzene, the shift becomes negative, and with 1,2-dihydroxybenzene and phenol, the shift becomes even more negative. Interestingly, both of these guests give a larger negative shift in 10% acetonitrile/water than they do in pure acetonitrile with 10 times more guest. Under the same conditions (no electrolyte, 10 mM guest), the potential shift observed with 1,2-dihydroxybenzene in 10% acetonitrile/water is −47 mV, compared to −17 mV in pure acetonitrile.

We also examined three amino-substituted benzenes, entries 6−8. Like the oxygen guests, these all give negative shifts in acetonitrile, as expected on the basis of donor−acceptor considerations. Smaller shifts are observed with these guests in water than with the oxygen-substituted guests. However, the trends observed with the amino guests are exactly the same as those observed with the hydroxy guests: a positive shift with the 1,4-substituted guest, a negative shift with the 1,2-substituted guest, and a smaller negative shift with the monosubstituted guest. Again, the shifts become more negative in 10% acetonitrile.

As might be expected, the largest positive shifts are observed with the two guests that also give positive shifts in acetonitrile,

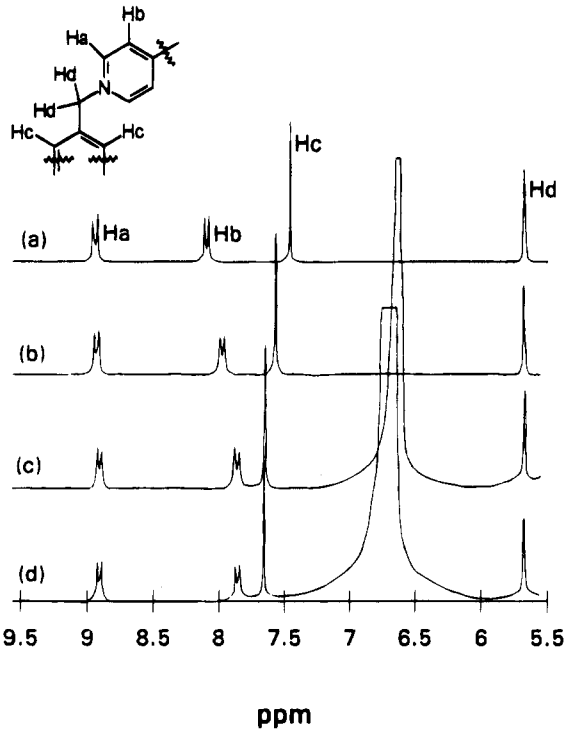


Figure 4. ^{1}H NMR spectra of VH in D_2O in the presence of (a) 0, (b) 0.3, (c) 10, and (d) 20 mM 1,2-dihydroxybenzene.

benzonitrile, and nitrobenzene. The shift with nitrobenzene is most impressive: 90 mV with only 10 mM added guest! Like the other guests, with both of these guests, the shift is less positive in 10% acetonitrile and even less positive in pure acetonitrile.

With all the guests, blank experiments were run in water with MV. No significant shift in the $E_{1/2}$ of MV was observed with any of these guests, indicating that the shifts observed with VH are, indeed, due to binding in the cavity and not to other experimental artifacts, such as changes in liquid junction potentials or solution pH.[16]

NMR Studies. Although we suspected strong binding in aqueous solution, we were initially surprised to find that addition of more guest to aqueous solutions of 0.5 mM VH and 10 mM **1a,b** caused no further changes in $E_{1/2}$, indicating saturation binding at these concentrations.[17] This conclusion was confirmed by NMR studies, which suggest that most of the guests give saturation binding under the conditions of the electrochemical experiments.

Figure 4 illustrates typical results with ^{1}H NMR spectra of a 0.5 mM D_2O solution of VH in the presence of 0, 0.3, 10, and 20 mM 1,2-dihydroxybenzene. Upon addition of guest, definite downfield shifts are observed in the xylyl protons (H_C) of VH and upfield shifts in the inner bipyridinium protons (H_B). Much smaller changes are observed in the outer bipyridinium protons (H_A), and there is essentially no change at all in the methylene protons (H_D). All these changes are completely consistent with binding of the guest in the central cavity of the host. The xylyl protons of VH fall in the deshielding region of the aromatic system of the guest and therefore move downfield, whereas the bipyridinium H_B protons fall in the shielding region of the guest and, as a result, move upfield. Smaller changes would be expected for the bipyridinium H_A protons, since they lie intermediate between the shielding and deshielding regions of the guest, and no change would be expected for the methylene protons, since they are pointing away from the binding cavity and should have little interaction with the guest.

Upon increasing the guest concentration from 0.3 to 10 mM, increased shifts are observed in the host protons, but no further changes are observed upon doubling the concentration to 20 mM. Similar results are observed for **1a,b** and all the other hydroxy- and amino-substituted guests in both D_2O and 10% CD_3CN/D_2O. This is good evidence that, for these guests, saturation binding occurs at 0.5 mM VH and 10 mM guest, the conditions of the voltammetric measurements.

The fact that we observe saturation binding and therefore know the maximum change in chemical shift allows us to use data such as those shown in Figure 4 to make a rough estimate of binding constants. The details of the calculations are described in the Experimental Section, and the results are tabulated in Table 2 under K_{ox}. Bernardo et al. report a value (from a UV/vis titration) of 3850 M^{-1} for VH with 1,2-dihydroxybenzene in pH 7 (0.3 M) phosphate buffer.[6] This is considerably smaller than the value of 22 000 M^{-1} we estimate from the NMR in D_2O. It is doubtful that the buffer system would have that large an effect, so it is possible that we are overestimating the binding constants, perhaps by assuming too low a value for the maximum change in chemical shift. Nonetheless, we believe it likely that the relative order of binding strengths is correct, and additional understanding can be gathered by examining the trends in the estimated K_{ox}'s.

Table 2. Estimated Binding Constants for Both Oxidized and Reduced VH with Various Guests in Water and 10% Acetonitrile/Water

		H_2O		10% $MeCN/H_2O$	
entry	guest	K_{ox} (M^{-1})[a]	K_{red} (M^{-1})[b]	K_{ox} (M^{-1})[a]	K_{red} (M^{-1})[b]
1	**1a**	11 000	260 000	3 300	3 300
2	**1b**	25 000	350 000	6 200	4 900
3	1,4-dihydroxybenzene	40 000	190 000	3 900	480
4	1,2-dihydroxybenzene	22 000	3 600	5 500	140
5	phenol	9 700	3 500	3 600	220
6	1,4-diaminobenzene	4 000	8 700	2 000	360
7	1,2-diaminobenzene	960	350	1 240	80
8	aniline	7 800	4 900	3 800	1 400
9	benzene	700	700	480	300
10	cyanobenzene	300	32 000	120	2 700
11	nitrobenzene	220	199 000	100	7 500

[a] Binding constants in the oxidized form estimated from ^{1}H NMR data, as described in the Experimental Section. Measurements made in D_2O or 10% CD_3CN/D_2O. [b] Binding constants in the reduced form are estimated from K_{ox} and $\Delta E_{1/2}$ in Table 1, as described in the text.

(16) Since the solutions are unbuffered, the addition of some of the guests will cause small changes in solution pH. For example, addition of 10 mM 1,2-diaminobenzene causes a pH change from 7.2 to 7.5, and addition of 10 mM 1,4-diaminobenzene causes a pH change from 7.2 to 8.6. (Both values measured with a pH electrode.) However, since protons are not directly involved in the viologen reduction, these changes should not have a direct effect on the viologen electrochemistry. The lack of a potential shift with MV indicates that there is also no indirect effect.

(17) At lower guest concentrations, the $E_{1/2}$ does shift with increasing guest concentration. In our earlier work (ref 2), we were able to use this type of information to determine K_{ox} and K_{red}. We are not able to do this in this case because, given the magnitude of the binding constants measured with NMR, we should be in the regime where, at <1 equiv of guest, we see two CV waves, one for bound and one for unbound host. (see ref 18.) Unfortunately, we cannot observe this, because the waves are too close together. Simple spreadsheet calculations indicate that we would need at least a 120 mV difference in $E_{1/2}$ in order to observe a clear inflection in the steady state CV wave, and the largest difference we observe is only 90 mV.

In many respects, these trends agree with our expectations, although there are some interesting surprises. To begin, it appears that the OR- and NH_2-substituted guests bind more strongly to VH^{4+} than benzene, benzonitrile, and nitrobenzene, as expected on the basis of donor–acceptor considerations. However, since N is generally considered a stronger π-donating substituent than O, we would have guessed that the NH_2 guests would bind more strongly than the OH guests. In fact, the opposite is true in most cases. This may reflect the importance of an electrostatic interaction between the heteroatom on the guest and the H's on the bipyridinium ring. These H's, which have partial positive charge, would interact more strongly with O than with N, since the former has more negative charge character due to the greater electronegativity of O.

Another unexpected result is the sensitivity to substitution patterns. Under most circumstances, both 1,2-dihydroxybenzene and 1,2-diaminobenzene bind substantially more weakly than their respective 1,4-isomers. This may be attributed to the increased water solubility of the more polar 1,2-isomers. Another intriguing possibility is that it is an entropic effect. The 1,2-isomers may be locked more tightly in the binding cavity than the 1,4-isomers, making binding more entropically unfavorable with the ortho isomers.

DISCUSSION

By combining the K_{ox}'s estimated from the NMR data with the $\Delta E_{1/2}$'s in Table 1, and assuming the latter to be the maximum shifts, the binding constants to the reduced host, K_{red}, can also be estimated by using eq 5.[18] These data, tabulated in Table 2,

$$\Delta E_{1/2,max} = (29.6\ \text{mV})\ \log(K_{red}/K_{ox}) \qquad (5)$$

cannot be taken quantitatively due to the uncertainty in the estimated binding constants. However, the relative order of binding strength is likely correct, giving an overall qualitative view of the redox-dependent binding.

In general, there are three factors which can promote binding in a host–guest system.[9] One is favorable interactions between the host and guest. This is determined by the stereoelectronic complementarity of host and guest. The other two factors are related to solvation. One is the release of solvent molecules from the surface of the binding cavity into bulk solution upon binding of a guest in the cavity, and the other is the release of solvent molecules from the surface of the guest into bulk solution upon binding. The last two factors should be favorable from both enthalpic and entropic standpoints for apolar guests and an apolar binding site in water.[10]

The second solvation factor, release of solvent molecules from the guest, depends only on the guest, and it therefore will not vary with oxidation state of the host and cannot directly affect redox-dependent binding. However, it can affect the magnitude of the binding constants and, through them, the magnitude of the observed potential shift at a given guest concentration. This factor undoubtedly contributes substantially to the strong binding which is observed in water, since the guests are relatively apolar and are not solvated particularly well by water. On average, the estimated K_{ox}'s decrease by 54% on going from water to 10% acetonitrile/water, and this is likely due to the better solvation of the guests by the acetonitrile.

The other important solvation factor promoting host–guest binding is the release of solvent molecules from the binding cavity into bulk solution. This should always be a favorable process for an apolar binding site in water. How favorable it is will depend on the hydrophobic/hydrophilic character of the binding site, and this can vary with oxidation state of the host and, therefore, can directly affect the redox-dependent binding. Since the viologen host becomes more hydrophobic on reduction, this factor will always promote binding to the reduced host and will tend to cause a positive shift in redox potential with any hydrophobic guest.

The estimated binding constants of the donor-substituted guests decrease by an average of 67% on going from oxidized to reduced VH in 10% acetonitrile/water, whereas in pure water they *increase* by an average of 490%. We attribute the generally stronger binding of the reduced host in water to the poor solvation of the biradical cavity by water. Again, the acetonitrile molecules solvate the reduced cavity more effectively, and so the binding is weaker in the presence of acetonitrile. An alternate way to look at this is that the acetonitrile also acts as a guest and, due in part to its large concentration, competes favorably with the benzene derivative for the reduced cavity.

The other factor promoting binding, favorable interactions between the host and guest, is determined by the stereoelectronic complementarity of host and guest. This will vary depending on the oxidation state of the host. As discussed earlier, this factor explains the observed potential shifts in acetonitrile quite nicely. Specifically, the shifts with all the guests agree with predictions based on electron donor–acceptor considerations. The larger shifts observed with **1a,b** are due to the additional strong electrostatic interaction between the ethoxy ether side chains and the positive charge on the host.

For the acceptor-substituted guests, benzonitrile and nitrobenzene, the two factors discussed above both promote binding to the reduced host, so its not surprising that these guests give the largest magnitude potential shifts in water. With the donor-substituted guests, the two factors pull in opposite directions, resulting in smaller shifts. The direction of the shift indicates which factor wins out. In the case of **1a,b**, 1,4-dihydroxybenzene, and 1,4-diaminobenzene, the solvation factor is apparently stronger, because positive shifts are observed. With aniline and benzene, the two forces balance each other out in water, because almost no shift is observed. However, with 1,2-dihydroxybenzene, 1,2-diaminobenzene, and phenol, host–guest interactions are more important than the hydrophilic/hydrophobic state of the binding site, because negative potential shifts are observed.

Why are there these differences between the donor-substituted guests? Although we have framed the argument that host–guest interaction considerations should favor binding to the oxidized host for donor guests, there are also interactions with the reduced biradical host, and it would seem that differences in these interactions must explain the differences between the donor guests. The general trend that the 1,4-isomers bind more strongly than the 1,2-isomers is even more pronounced in the reduced state, resulting in negative potential shifts for the ortho guests. One possible explaination for this is that the delocalized radical interacts more favorably with the less polarized, more polarizable π-system of the completely symmetric para isomers. It is perhaps significant that the different potential shifts of the 1,4-oxygen-

(18) Miller, S. R.; Gustowski, D. A.; Chen, Z.-H.; Gokel, G. W.; Echegoyen, L.; Kaifer, A. E. *Anal. Chem.* **1988**, *60*, 2021.

substituted guests, **1a,b** and 1,4-dihydroxybenzene, appear to be due almost entirely to differences in K_{ox}. The π-systems of all three guests should have similar electronic structures, and this results in K_{red}'s that are identical within experimental error.

CONCLUSIONS

The data presented in this paper clearly demonstrate the significant role solvent plays in redox-dependent binding. Changes in both magnitude and direction of potential shift are observed with VH and the same guests in water, 10% acetonitrile/water, and acetonitrile. These changes are consistent with increased overall binding in water and with relatively stronger binding to the reduced host in water. The latter observation is most easily explained by the change in hydrophobic/hydrophilic character of the host. The increased hydrophobicity of the reduced host promotes binding of the guest. However, although this factor is clearly very important in determining which oxidation state is preferred, our results also show that it does not overwhelm electron donor–acceptor considerations. The largest potential shifts are observed when both solvation forces and donor–acceptor forces pull in the same direction. When they pull in opposite directions, sometimes the solvation factor wins, and sometimes the donor–acceptor factor wins.

Designing redox-dependent receptors for neutral molecules is inherently a more challenging task than designing receptors for ionic compounds. Since reduction or oxidation typically involves a change in charge, receptors for ionic compounds can rely on the perturbation of a strong electrostatic interaction to alter the binding properties. Receptors for neutral guests must rely on the perturbation of weaker interactions to alter the binding properties. Nevertheless, our work with the viologen host clearly shows that redox-dependent binding with neutral guests is possible. Furthermore, we have now demonstrated three general ways in which binding control can be achieved: (i) by using changes in electron donor–acceptor character, (ii) by perturbation of strong ion–dipole interactions, and (iii) by altering the solvation properties of the binding site. By designing redox-dependent host–guest systems where multiple factors work in the same direction, significant binding differences and large potential shifts should be possible with neutral guests.

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