rings form an angle of 15.3° and the distance between their centers is 4.1 Å, similar to the expected van der Waals separation for phenyl groups.[38] Intermolecular, "graphitic" phenyl ring stacking of this type has been observed in several other phosphine complexes,[39] but no striking intermolecular packing features were observed for this structure.

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Supplementary Material Available: Supplementary Table I (characterization data for SO_2 adducts) and a listing of structure factor amplitudes (34 pages). Ordering information is given on any current masthead page.

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A Theoretical Model for the Effects of Solvent and Protein Dielectric on the Redox Potentials of Iron-Sulfur Clusters

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Abstract: A theoretical model for the effects of solvent and protein dielectric on the redox potentials of iron-sulfur clusters is formulated to account for observed differences between the potentials of synthetic analogues and proteins. Each of the redox processes is considered to be accompanied by a change in the charge on the iron-sulfur cluster such that the free energy change will in part be dependent on the difference in charging energies associated with the interaction of a cluster with its environment. The model also considers that the electrostatic interactions within a cluster are dependent on the macroscopic dielectric of its environment and thus affect the free energy change for a redox process. The results of calculations based on the difference in the electrostatic free energy changes associated with a redox process are consistent with observed differences in the redox properties of the analogues and the proteins.

Most recent research[1-4] on iron-sulfur proteins has been directed toward describing the detailed structure of the iron-coordination centers. Chemical,[5] spectroscopic,[1-4] and x-ray structural analyses[6-11] have indicated that these proteins are characterized by three types of coordination centers consisting of one, two, and four iron atoms coordinated to inorganic sulfide and/or the thiolate groups of cysteine residues. The description of these centers has been augmented by the elegant syntheses[12-16] of iron-sulfur cluster complexes which are close structural representations of the three redox centers in the proteins. It is anticipated that all such research will provide an understanding of the redox properties of the proteins and the relationship of protein structure to the intrinsic properties of the iron-sulfur coordination centers. Each of the iron-sulfur centers in proteins is characterized by two redox states coupled by a single electron transfer reaction. Redox potentials of −0.057 V[17] (rubredoxin), −0.42 V[18,19] (plant ferredoxin), and −0.40 V[19] (bacterial ferredoxin) correspond to iron-sulfur proteins with one, two, and four iron atoms centers, respectively. Redox potentials of the synthetic complexes in nonaqueous solutions exhibiting corresponding reactions are up to 0.85 V[14] more negative than the proteins and synthetic

Table I[a]

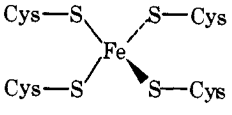
Iron cluster redox reaction	$\Delta G°_{Redox}$ (V) ϵ_{DMF}	ϵ_{H_2O}	$\Delta(\Delta G°_{redox})$
(a) $[Fe(S\text{-}Cys)_4]^-/[Fe(S\text{-}Cys)_4]^{2-}$	0.260	0.122	0.138
(b) $[Fe_2S_2(S\text{-}Cys)_4]^{2-}/[Fe_2S_2(S\text{-}Cys)_4]^{3-}$	0.290	0.136	0.159
(c) $[Fe_4S_4(S\text{-}Cys)_4]^{2-}/[Fe_4S_4(S\text{-}Cys)_4]^{3-}$	0.234	0.110	0.124

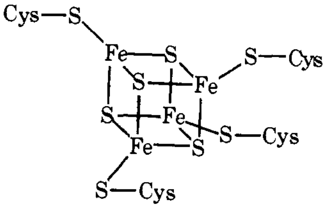
[a] Values of r used to calculate $\Delta G°$ values correspond to (a) average Fe–S bond distance in a synthetic analogue,[16] (b) the average calculated distance between a thiolate sulfur and the two iron atoms,[14] and (c) the calculated distance between the cubic body center and the thiolate sulfur.[12,13]

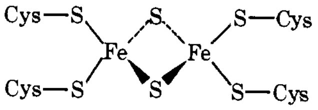
complexes in aqueous solution.[20] In addition it is found that the bacterial ferredoxins and the high-potential (HP) iron proteins containing equivalent four iron centers exhibit different redox reactions.[21] It is not understood what factors contribute to such large differences although the influence of H bonding has been suggested to account for differences in redox properties among proteins.[22] Thus the property of the proteins most relevant to their function has not been adequately explained. In this report we wish to present a theoretical model which indicates an additional contribution of the cluster environment to the observed differences between the redox potentials of the synthetic iron–sulfur cluster complexes and the proteins.

Formulation of Model and Computational Results

Structures of the three iron coordination centers in proteins are represented below. Redox reactions of the clusters in three types of proteins are described by the following equations:







$$[Fe(S\text{-}Cys)_4]^- + e^- = [Fe(S\text{-}Cys)_4]^{2-} \qquad (1)$$

$$[Fe_2S_2(S\text{-}Cys)_4]^{2-} + e^- = [Fe_2S_2(S\text{-}Cys)_4]^{3-} \qquad (2)$$

$$[Fe_4S_4(S\text{-}Cys)_4]^{2-} + e^- = [Fe_4S_4(S\text{-}Cys)_4]^{3-} \qquad (3)$$

Evidence for these as well as other redox reactions corresponding to the full range of possible redox states has been reported[14,23,24] for the synthetic analogues. The charge on a complex in a given redox state corresponds to the sum of the formal valences of ferric and ferrous ions, inorganic sulfide, and the cysteinyl thiolate groups. The one-electron transfer reaction may be associated with a change in valence of one of the iron atoms from +3 to +2 thus increasing the negative charge on the cluster. The corresponding redox potentials are dependent on the differences between the free energies of the oxidized and reduced states (eq 4)

$$-nFE_0 = \Delta G°_{\text{iron-cluster}} - \Delta G°_{\text{hydrogen}} \qquad (4)$$

Differences between the redox potentials of the clusters in the natural and synthetic systems may in part be related to the difference between their aqueous and nonaqueous environments. Water is characterized by a relatively high dielectric constant while the solvents acetonitrile, DMF, and Me_2SO used to characterize the redox properties of most of the synthetic complexes have much lower dielectric constants. One factor which contributes to $\Delta G°_{\text{iron-cluster}}$ that is dependent on the environment of the cluster may be identified as the difference in charging energies between the redox states. Consider that the cluster complexes may be approximated by charged spheres. The molar electrostatic free energy change involved in charging a sphere of radius r immersed in a continuum of uniform dielectric ϵ is given by the Born equation[25] (eq 5)

$$\Delta G°_{el} = \frac{Nz^2e^2}{2r}\frac{1}{\epsilon} \qquad (5)$$

A charging energy may be associated with each of the redox states of a cluster where z represents the charge on the cluster. Thus the free energy change for a redox process includes the difference in charging energies between the two redox states as given by eq 6

$$\Delta G°_{redox} = \frac{Ne^2}{2r\epsilon}(z^2_{red} - z^2_{ox}) \qquad (6)$$

assuming that the value of r is equivalent for each of the redox states. Free energy changes for a redox process in polar (P) and nonpolar (N) dielectrics may be represented as (eq 7 and 8)

$$\Delta G°_{redox} = \frac{Ne^2(z^2_{red} - z^2_{ox})}{2r}\frac{1}{\epsilon_P} \qquad (7)$$

$$\Delta G°_{redox} = \frac{Ne^2(z^2_{red} - z^2_{ox})}{2r}\frac{1}{\epsilon_N} \qquad (8)$$

Differences between the redox potentials of proteins and synthetic clusters in water and synthetic clusters in nonaqueous solutions may then in part be related to the differences in charging energies for the redox processes as given by eq 9

$$\Delta(\Delta G°_{redox})_{N\text{-}P} = \frac{Ne^2}{2r}(z^2_{red} - z^2_{ox})\left(\frac{1}{\epsilon_N} - \frac{1}{\epsilon_P}\right) \qquad (9)$$

Table I indicates the magnitude of the free energy changes associated with the iron-cluster redox reactions described by eq 1-3 in dimethylformamide and water.

A second factor which contributes to the $\Delta G°_{\text{iron-cluster}}$ that may be related to the environment is the electrostatic free energy change within the cluster accompanying the one electron redox reaction. Electrostatic contributions to the free energy change correspond to the electrostatic potential-energy change for the reduction of a cluster. As a first approximation point charges having values equal to the formal valencies of iron and sulfur may be used to characterize the average distribution of charges in a cluster. The electrostatic potential energy (U) corresponding to the interaction of two charged species is in general given by eq 10

$$U = \frac{kqq'}{4\pi\epsilon_0 Dd} \qquad (10)$$

where k is a proportionality constant, q and q' are the charges on the two species, ϵ_0 is the permittivity of free space, D is the dielectric constant of the medium between the charges, and d is the distance between point charges. The electrostatic potential energy of the iron–sulfur cluster complex in a given oxidation state is equal to the sum of the interactions of all charges. The electrostatic potential energy of the oxidized state of a cluster may be given by (eq 11)

$$\frac{4\pi\epsilon_0 D}{k}U_{ox} = \sum_{i\neq j}^{ox}\frac{q_iq_j}{2d_{ij}} \qquad (11)$$

Likewise, the electrostatic potential energy of the reduced state is given by eq 12

$$\frac{4\pi\epsilon_0 D}{k}U_{red} = \sum_{i\neq j}^{red}\frac{q_iq_j}{2d_{ij}} \qquad (12)$$

Table II

Iron cluster redox reaction	$\Delta U_{\mathrm{Redox}}$ (V)[a] ϵ_{DMF}	$\epsilon_{\mathrm{H_2O}}$	$\Delta(\Delta U_{\mathrm{redox}})$
$[Fe(S\text{-}Cys)_4]^-/[Fe(S\text{-}Cys)_4]^{2-}$	5.574	5.313	0.261
$[Fe_2S_2(S\text{-}Cys)_4]^{2-}/[Fe_2S_2(S\text{-}Cys)_4]^{3-}$	6.368	6.069	0.299
$[Fe_4S_4(S\text{-}Cys)_4]^{2-}/[Fe_4S_4(S\text{-}Cys)_4]^{3-}$	5.318	5.069	0.249

[a] Values of d_{ij} used to calculate $\Delta U_{\mathrm{redox}}$ were derived from reported[12-16] bond distances for the synthetic iron-sulfur cluster analogues. $D_E{}^N$ and $D_E{}^P$ were calculated from the Kirkwood-Westheimer equation[26] using values of $D_i = 1$ and $X^{1/2} = 0.5$ and the macroscopic dielectric constants (ϵ) of DMF and H_2O.

The electrostatic potential energy change for the redox reaction is given by (eq 13)

$$\frac{4\pi\epsilon_0 D}{k}\,\Delta U_{\mathrm{redox}} = \sum_{i\neq j}{}_{\mathrm{red}}\frac{q_iq_j}{2d_{ij}} - \sum_{i\neq j}{}_{\mathrm{ox}}\frac{q_iq_j}{2d_{ij}} \tag{13}$$

The molar electrostatic potential energy change is then given by (eq 14)

$$\Delta U_{\mathrm{redox}} = \frac{kN}{8\pi\epsilon_0 D}\sum_{i\neq j}{}_{\mathrm{red}}\frac{q_iq_j}{d_{ij}} - \sum_{i\neq j}{}_{\mathrm{ox}}\frac{q_iq_j}{d_{ij}} \tag{14}$$

A microscopic dielectric constant (D_i) of 1 corresponding to free space has been implicit in calculations of the lattice energies of salts such as NaCl. However, the effective microscopic dielectric constant (D_E) for a cluster in solution should be dependent on the macroscopic dielectric constant of the solvent. Kirkwood and Westheimer[26] and more recently Ramachandran and Srinivasan[27] have derived an equation for D_E to calculate the electrostatic interaction of charged atoms or groups of atoms. Accordingly, the effective dielectric constant is dependent on the internal dielectric constant D_i, the dielectric constant of the surrounding medium, and a parameter x which is dependent on the ratio of the distance separating the charges and the size of the spherical cavity surrounding the charges. The molar electrostatic potential energy change associated with a change in oxidation state of a cluster in polar and nonpolar dielectrics may then be estimated by (eq. 15 and 16)

$$\Delta U_{\mathrm{redox}} = \frac{kN}{8\pi\epsilon_0}\left(\sum_{i\neq j}{}_{\mathrm{red}}\frac{q_iq_j}{d_{ij}} - \sum_{i\neq j}{}_{\mathrm{ox}}\frac{q_iq_j}{d_{ij}}\right)\frac{1}{D_E{}^P} \tag{15}$$

$$\Delta U_{\mathrm{redox}} = \frac{kN}{8\pi\epsilon_0}\left(\sum_{i\neq j}{}_{\mathrm{red}}\frac{q_iq_j}{d_{ij}} - \sum_{i\neq j}{}_{\mathrm{ox}}\frac{q_iq_j}{d_{ij}}\right)\frac{1}{D_E{}^N} \tag{16}$$

Differences between the redox potentials of natural and synthetic clusters in aqueous and nonaqueous media may then in part be related to differences in electrostatic potential energy changes for the redox processes as given by eq 17

$$\Delta(\Delta U_{\mathrm{redox}})_{\mathrm{N\text{-}P}} = \frac{kN}{8\pi\epsilon_0}\left(\sum_{i\neq j}{}_{\mathrm{red}}\frac{q_iq_j}{d_{ij}} - \sum_{i\neq j}{}_{\mathrm{ox}}\frac{q_iq_j}{d_{ij}}\right)\left(\frac{1}{D_E{}^N} - \frac{1}{D_E{}^P}\right) \tag{17}$$

Table II indicates the magnitude of the electrostatic potential energy changes corresponding to the iron-sulfur cluster redox reactions (eq 1-3) in dimethylformamide and water. The combined effects of solvent dielectric on differences in the free energy change accompanying a change in oxidation state of an iron-sulfur cluster may be represented by

$$\Delta(\Delta G_{\mathrm{redox}})_{\mathrm{N\text{-}P}} = \frac{Ne^2}{2r}\left(z^2{}_{\mathrm{red}} - z^2{}_{\mathrm{ox}}\right)\left(\frac{1}{\epsilon_N} - \frac{1}{\epsilon_P}\right) + \frac{kN}{8\pi\epsilon_0}\left(\sum_{i\neq j}{}_{\mathrm{red}}\frac{q_iq_j}{d_{ij}} - \sum_{i\neq j}{}_{\mathrm{ox}}\frac{q_iq_j}{d_{ij}}\right)\left(\frac{1}{D_E{}^N} - \frac{1}{D_E{}^P}\right) \tag{18}$$

Table III. Calculated and Observed Differences in Redox Potentials of Synthetic Analogues and Proteins

Iron cluster	Calcd (V)	Obsd (V)
$[Fe(SR)_4]$	$\Delta E_0{}^{-/2-}{}_{(\mathrm{DMF\text{-}H_2O})} = -0.399$	$\Delta E_0{}^{-/2-}{}_{(\mathrm{Analog\text{-}Rd})} = -0.73$[a]
$[Fe_2S_2(SR)_4]$	$\Delta E_0{}^{2-/3-}{}_{(\mathrm{DMF\text{-}H_2O})} = -0.453$	$\Delta E_0{}^{2-/3-}{}_{(\mathrm{Analog\text{-}Fd})} = -0.85$[b]
$[Fe_2S_2(SR)_4]$	$\Delta E_0{}^{3-/4- \,-\, 2-/3-}{}_{\mathrm{DMF}} = -1.29$	$\Delta E_0{}^{3-/4- \,-\, 2-/3-}{}_{\mathrm{Analog}} = -0.3$[c]
$[Fe_4S_4(SR)_4]$	$\Delta E_0{}^{2-/3-}{}_{(\mathrm{DMF\text{-}H_2O})} = -0.373$	$\Delta E_0{}^{2-/3-}{}_{(\mathrm{Analog\text{-}Fd})} = -0.62$[d]
$[Fe_4S_4(SR)_4]$	$\Delta E_0{}^{2-/3- \,-\, -/2-}{}_{\mathrm{DMF}} = -1.245$	$\Delta E_0{}^{2-/3- \,-\, -/2-}{}_{\mathrm{Analog}} = -1.300$[e]

Observed differences correspond to: [a] analog, $(SR)_4 \equiv [(SCH_2)_2C_6H_4]_2$,[16] and Rd = *Clostridium pasteurianum* rubredoxin;[17] [b] analog, $(SR)_4 \equiv [(SCH_2)_2C_6H_4]_2$, and Fd = spinach ferredoxin;[18,19] [c] difference between indicated redox potentials of analog with $(SR)_4 \equiv [(SCH_2)_2C_6H_4]_2$;[14] [d] analog, R = $CH_2C_6H_5$[12] and Fd = *Cl. pasteurianum* ferredoxin;[28] [e] difference between indicated redox potentials with (SR) ≡ $[SC(CH_3)_3]$.

Finally the differences between the free energy changes for a redox process in different solvents can be related to the difference between the redox potentials of the two systems

$$\Delta E_{0(\mathrm{N\text{-}P})} = -\frac{\Delta(\Delta G_{\mathrm{redox}})_{\mathrm{N\text{-}P}}}{nF} = -\left\{\frac{Ne^2}{2rF}\left(z^2{}_{\mathrm{red}} - z^2{}_{\mathrm{ox}}\right)\left(\frac{1}{\epsilon_N} - \frac{1}{\epsilon_P}\right) + \frac{kN}{8\pi\epsilon_0 F}\left(\sum_{i\neq j}{}_{\mathrm{red}}\frac{q_iq_j}{d_{ij}} - \sum_{i\neq j}{}_{\mathrm{ox}}\frac{q_iq_j}{d_{ij}}\right)\left(\frac{1}{D_E{}^N} - \frac{1}{D_E{}^P}\right)\right\} \tag{19}$$

The equation may be evaluated for values of ϵ_P and ϵ_N corresponding to water and those nonaqueous solvents used to characterize the redox properties of the synthetic cluster analogues, respectively. Values of r and d_{ij} may be derived from crystal structure data on the synthetic analogues.[12-16] Calculated values of ΔE_0 for reversible redox reactions of synthetic clusters in nonaqueous solvents are indicated in Table III together with some experimentally observed differences. Also included are calculated values for the contribution of solvent dielectric to the differences between the redox potentials of additional redox reactions of the clusters.

It has been observed that the iron-sulfur clusters in proteins are surrounded to various extents by the polypeptide. Thus, while the iron-sulfur center in rubredoxin appears to be at the surface of the molecule,[6,7] crystal structures of a bacterial ferredoxin[10] and a HP iron protein[8,9,11] suggest that the Fe-S clusters are significantly shielded from the solvent. The local dielectric constant of the environment of a cluster may then be significantly different from that of water. The following equation has previously been derived[29] to estimate the effect of a spherical shell of lower dielectric constant than water on charging energies associated with a redox center in a protein

$$\Delta G^\circ{}_{\mathrm{el}} = \frac{Nz^2e^2}{2}\left(\frac{1}{r_1} - \frac{1}{r_2}\right)\left(\frac{1}{\epsilon_N} - \frac{1}{\epsilon_P}\right) \tag{20}$$

where r_1 is the radius of the redox center and r_2 is the radius of the surrounding shell. Applying this equation to the present system, the difference in charging energies for the redox process is according to eq 9

$$\Delta(\Delta G_{\mathrm{redox}})_{\mathrm{N\text{-}P}} = \frac{Ne^2}{2}\left(z^2{}_{\mathrm{red}} - z^2{}_{\mathrm{ox}}\right)\left(\frac{1}{r_1} - \frac{1}{r_2}\right)\left(\frac{1}{\epsilon_N} - \frac{1}{\epsilon_P}\right) \tag{21}$$

Table IV. Calculated ΔE_0 Values in Volts[a]

	$r_2 - r_1$, Å						
ϵ	1.5	2.5	3.5	4.5	5.5	6.5	7.5
10	0.591	0.838	1.020	1.161	1.272	1.365	1.436
20	0.253	0.358	0.435	0.496	0.543	0.581	0.613
30	0.139	0.198	0.240	0.273	0.300	0.321	0.340
40	0.087	0.123	0.149	0.170	0.186	0.201	0.210
50	0.049	0.070	0.085	0.096	0.105	0.113	0.120
60	0.027	0.038	0.045	0.052	0.056	0.061	0.064
70	0.013	0.015	0.018	0.021	0.022	0.024	0.025

[a] ΔE_0 corresponds to the potential difference between a cluster surrounded by a dielectric shell in water and a cluster in water.

The D_E will in addition be dependent on the nature of the surrounding shell such that the electrostatic potential energies will also be affected. The right expression in eq 20 may be equated to the difference in charging energies of an ion in a polar medium and an ion in a medium of average dielectric constant (ϵ_{ave}) which is equivalent to the surrounding shell in the polar medium as given by

$$\frac{Nz^2e^2}{2}\left(\frac{1}{r_1}\right)\frac{1}{\epsilon_{ave}} - \frac{Nz^2e^2}{2}\left(\frac{1}{r_1}\right)\frac{1}{\epsilon_P} = \frac{Nz^2e^2}{2}\left(\frac{1}{r_1} - \frac{1}{r_2}\right)\left(\frac{1}{\epsilon_N} - \frac{1}{\epsilon_P}\right) \quad (22)$$

From the above equation we obtain for ϵ_{ave}

$$\frac{1}{\epsilon_{ave}} = \left(\frac{r_2 - r_1}{r_2}\right)\left(\frac{1}{\epsilon_N} - \frac{1}{\epsilon_P}\right) + \frac{1}{\epsilon_P} \quad (23)$$

An ϵ_{ave} may be used to estimate the D_E according to the Kirkwood-Westheimer equation such that the effect of a surrounding shell on the electrostatic potential energy changes in the cluster may be determined. The combined effects of such a shell on the redox potential of a cluster may be evaluated for values of r_2 corresponding to different thicknesses ($r_2 - r_1$) of the spherical volume element and different values of ϵ_N. Values of ΔE_0 calculated for the four-iron cluster are recorded in Table IV.

Discussion

Calculated values for ΔG_{redox} in Table I indicate that the solvent dielectric may have a significant effect on the free energy change for a redox process accompanied by a change in charge. Noting the relationship between ΔG_{redox} and E_0 (eq 4) the results indicate that the redox potential of an iron-sulfur cluster should be more negative in solvents of lower dielectric constant than in solvents of higher dielectric constant. This result derives from the fact that reduction of the clusters leads to an increase in the absolute charge of the clusters which according to the Born equation results in a positive free energy change for reaction. It may be noted that four iron clusters[20,29] have been synthesized with different charge due to the presence of neighboring groups on the alkyl and aryl thiols. Thus one might consider the effects of charging on the aryl derivatives $[Fe_4S_4(SC_6H_5)_4]^{2-}$ and $[Fe_4S_4(SC_6H_4\text{-}p\text{-}NMe_3)_4]^{2+}$ and the alkyl derivatives $[Fe_4S_4(SC_3H_7)_4]^{2-}$ and $[Fe_4S_4(SCH_2CH_2CO_2)_4]^{6-}$. The redox potential for the *p*-trimethylammonium compound falls on the $E_{1/2}$ vs. σ_p straight line.[29] The potential for the 3-mercaptopropionate derivative in aqueous solution is very close to that of clostridial ferredoxin.[20] These observations might imply that no significant charging effects on the $E_{1/2}$ are evident. We suggest, however, that the charging effects for the different derivatives in equivalent environments should be approximately equal. This may be justified in terms of the large separation of charges associated with the primary coordination sphere of the cluster and the neighboring groups of the thiols. CPK models indicate a separation of approximately 6 Å between the thiolate sulfur and the neighboring charged group. Thus the iron-sulfur center may interact directly with the solvent. These systems may be compared to a complex whose primary coordination sphere in the oxidized state is more highly charged than the reduced state such as the model heme complex bispyridine mesohemedimethyl ester. In the latter case the use of the Born equation leads to the prediction that the redox potential should be more positive in solvents of lower dielectric constant than in higher dielectric constant.[30] These considerations may in part be related to the liquid junction potential, E_{lj}, associated with the determination of the redox potential of a couple in nonaqueous solvents utilizing an aqueous reference electrode. Holm and co-workers have considered the liquid junction potential[29,31] in attempting to account for part of the potential difference between the synthetic analogues measured in nonaqueous solvents and the proteins measured in water. They utilized the pilot ion method to estimate this potential. However, the pilot ions used to measure the E_{lj} correspond to redox couples which are more highly charged in the oxidized than in the reduced state. The E_{lj}, defined by $E_S - E_{H_2O}$, was observed to be positive which is also consistent with the prediction derived from the Born equation. The use of a positive E_{lj} led to the conclusion[29] that the redox potentials of the clusters without a liquid junction should be even more negative than the measured potentials in nonaqeous solvents. By contrast the present model suggests that the differences between the potentials of the natural and synthetic systems measured in aqueous and nonaqueous solutions could in part be accounted for by the electrostatic effect of the charged clusters with environments of different dielectric.

Calculated values of ΔU (Table II) further indicate that the solvent dielectric may strongly influence the magnitude of the electrostatic interactions within the cluster. The proposed model suggests that the solvent dielectric influences the effective microscopic dielectric and therefore effects the free energy change accompanying a redox reaction. The results also predict that the redox potentials of the clusters should be more negative in solvents of lower dielectric constant than in solvents of higher dielectric. It should be noted that the magnitude of the calculated potential differences due to this effect is dependent on the magnitude of the point charges in the complexes. While formal charges were used for Fe and S atoms, the effective charges on the iron and sulfur atoms may be significantly lower as a result of the effects of covalency. As a consequence, the calculated differences between the electrostatic potential energy changes for reduction of the complexes represent maximum values. Furthermore it may be noted that the tabulated values do not take into account the observed equivalence of the iron atoms in the four iron clusters.[32,33] However, no significant differences in calculated values result from the assignment of equal fractional charges to the iron atoms.

The magnitude of the calculated values for the combined effects of solvent dielectric on differences in redox potentials (Table III) suggests that they may represent a significant contribution to the observed differences between synthetic analogues and the proteins. The observed differences shown in Table III correspond to simple alkyl or arylthiolate complexes. It has been reported[26] that half-wave potentials of numerous alkylthiolate analogues of the four iron clusters are linearly related by Taft σ substituent parameters. Introduction of cysteinyl ligands yields complexes[29,31] which have half-wave potentials which are significantly less negative than many of the alkylthiolate analogues. The $[Fe_4S_4(S\text{-}Cys(Ac)NHMe)_4]^{2-/3-}$ complex exhibited a half-wave potential $E_{1/2}$ in DMF of -1.07 V[29] vs. the saturated calomel electrode (SCE). The *Cl. pasteurianum* Fd exhibited a $E_{1/2}$ of -0.57 V against the SCE.[28] Thus a potential difference of ~0.5 V may be observed between this analogue and the protein. This may be compared to a calculated value of 0.37 for the difference between the potential of the cluster in DMF and H_2O. The model also adequately accounts for the observed differences between the 2−/3− and −/2− redox potentials of a four-iron cluster analogue as reported in Table III. However, it is evident from a comparison of the calculated and observed differences for the two-iron cluster analogues, that additional factors contribute to the difference between successive redox potentials of a cluster. The model is further consistent with the observation that the $E_{1/2}$ potentials of $[Fe_4S_4(S\text{-}Cys(Ac)NHMe)_4]^{2-/3-}$ become progressively less negative as the solvent dielectric increases from DMF to Me_2SO to 80% Me_2SO-20% H_2O.[29,34] A calculated difference of 0.150 V between DMF and Me_2SO may be compared to differences of 0.060 and 0.157 V obtained from reported redox potentials.[29,31]

Data in Table IV indicate that the effect of a dielectric shell surrounding an iron–sulfur center in water is strongly dependent on the dielectric constant of the shell and its thickness. Thus a cluster surrounded by a shell of low dielectric would be expected to have a potential significantly lower than that of the cluster in water, approaching that of the cluster in the nonaqueous dielectric as the thickness of the shell increases. By contrast a shell of relatively high dielectric contrast will have only a minor effect on the redox potential. In attempting to account for the influence of a polypeptide environment on the redox potential of an iron–sulfur center it may be difficult to assign an appropriate value of ϵ to the environment. Unlike a homogeneous dielectric, the environment of an iron–sulfur center in a protein will likely be composed of a number of different groups. Thus while it may be expected that the hydrocarbon side-chains of amino acids would contribute to a dielectric less than ten, the large dipole moment associated with the amide group of the peptide backbone may contribute to a local dielectric equal to or greater than water as suggested by the very high dielectric constant of *N*-methylacetamide. The data do suggest a manner by which a polypeptide may alter the redox potential of a cluster through nonbonded interactions. Thus an environment composed of nonpolar amino acid side-chains would contribute to a redox potential which is more negative than that of a cluster surrounded by more polar amino acid side-chains. The present model may thus provide an additional basis for understanding the differences between the redox properties of the four-iron sulfur centers in proteins. The iron–sulfur center in the HP proteins may be more deeply embedded in the polypeptide than in the ferredoxins and/or surrounded by groups which provide a less polar environment. This is consistent with the observation[35] that the HP protein from *Chromatium* exhibits redox properties in 80% Me_2SO which are more nearly similar to the redox properties of the synthetic analogues and the bacterial ferredoxins. Most recently a protein has been reported to have two four-iron clusters which function between the same pair of oxidation states as the Fe-S cluster in the HP proteins, although the midpoint reduction potentials of the two clusters are ~760 mV different.[36] Although the data in Table IV apply to the redox reaction described by eq 3, large potential differences for the −/2− redox reaction may also be expected between centers whose local polypeptide environments have sufficiently different polarities and dimensions. The present model does not exclude the influence of protein structural effects on the redox potential of a cluster. The proposed model does suggest that environmental effects of solvent and protein may provide a significant contribution to the redox properties of analogues and proteins.

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