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N-H···S Hydrogen Bonds in a Ferredoxin Model

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The Fe_4S_4 complex $\{(CH_3)_3NCH_2CONH_2\}_2[Fe_4S_4(^tBuS)_4]$ (**1**) was synthesized to replicate the ferredoxin active site with a subset of its N–H···S hydrogen bonds. The two cationic counterions mimic the polypeptide backbone of ferredoxin (Fd) as amide hydrogen-bond donors to sulfur atoms of the iron–sulfur cluster. X-ray crystallographic data show that the organic sulfur (S_γ) of one *tert*-butylthiolate ligand and one inorganic sulfur of the cluster core serve as N–H···S hydrogen-bond acceptors. The cluster core of complex **1** is tetragonally elongated in contrast to that of Fd, which is tetragonally compressed. This is the first observation of an elongated $[Fe_4S_4]^{2+}$ cluster core. Additionally, this is the first synthetic Fd model in which N–H···S hydrogen bonding to a cluster has been achieved.

Iron−sulfur (Fe−S) proteins are widely distributed in nature, where their predominant function is to transfer electrons.[1−6] The redox potentials of these proteins differ widely even in cases where the active site cluster structures are congruent. In the Fe_4S_4 ferredoxins, the focus of this paper, the median values of the redox potentials for the high-potential ferredoxin (HiPIP) and low-potential ferredoxin (Fd) proteins differ by about 700 mV, which is correlated with the hydrophobicity of the active site environment.[7−9] However, a relatively large range of redox potentials is found even for the Fd proteins and has been attributed to differences in the dipolar characteristics of the active site.[7−9] Significantly, the redox potentials of the proteins (approximately −0.40 V vs SHE) have not been replicated in cluster model compounds, whose relative redox potentials are quite low (approximately −1.3 V vs SCE).[10,11]

A few synthetic models have been reported in the study of hydrogen bonding and its effects on redox potentials in Fe_4S_4 ferredoxins. These models employed *o*-amidobenzenethiolate terminal ligands in which N−H···S hydrogen bonding was enforced by proximity and phenyl group rigidity.[12−16] In this communication, we describe a synthetic model compound, $\{(CH_3)_3NCH_2CONH_2\}_2[Fe_4S_4(^tBuS)_4]$ (**1**), in which N−H···S hydrogen bonds are donated by amide groups of the counterion $\{(CH_3)_3NCH_2CONH_2\}^+$, carbamoyltrimethylammonium acetamide (CTA^+). The hydrogen-bond acceptors consist of a bridging sulfide of the Fe_4S_4 cluster core and the sulfur of a *tert*-butylthiolate terminal ligand. Alkylthiolate terminal ligands are preferred as cysteine analogues in the study of hydrogen bonding.[17]

Complex **1** was synthesized in 35% yield by the modification of a method originally published by Christou and Garner in the synthesis of $(Et_4N)_2[Fe_4S_4(^tBuS)_4]$ (**2**).[18,19] X-ray diffraction quality crystals were isolated from a CH_3CN/ether

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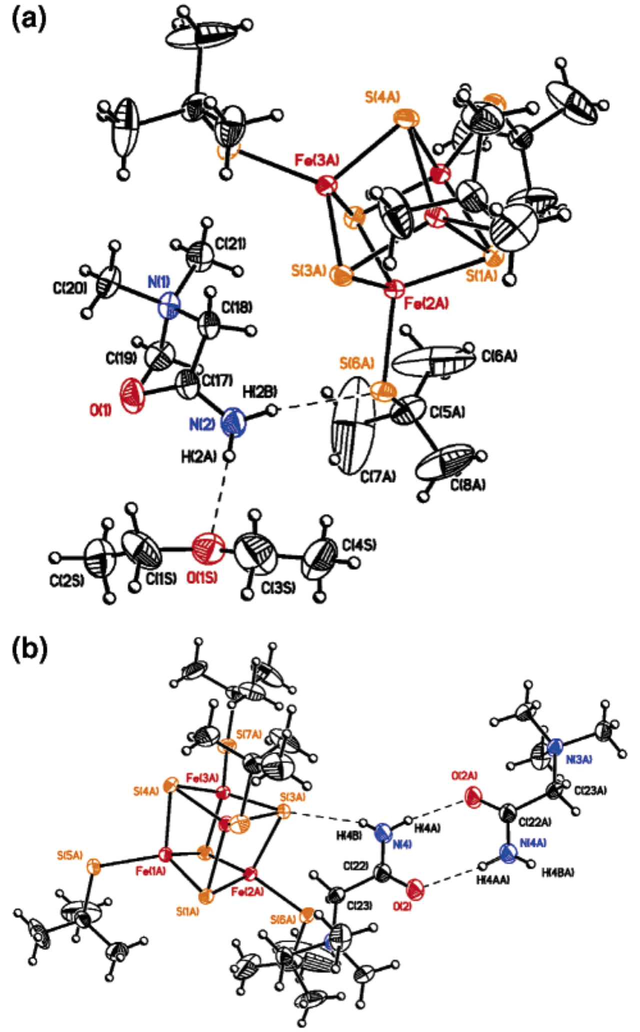

Figure 1. (a) ORTEP figure of complex **1** showing 30% probability ellipsoids. The N(2)−H(2B)···S(6A) hydrogen bond to S_γ and the N(2)−H(2A)···O(1S) hydrogen bond to ethyl ether are indicated by dashed lines. (b) ORTEP figure of complex **1** showing the N(4)−H(4B)···S(3A) hydrogen bond to the inorganic sulfur and the amide−amide hydrogen-bond dimers formed through N−H···O hydrogen bonds.

solution containing one extra equivalent of ^{t}BuSH. The crystals took the form of black tablets, with the formula $(CTA)_2[Fe_4S_4(^tBuS)_4]\cdot CH_3CH_2OCH_2CH_3$.[20] The sample gave satisfactory elemental analysis.

The UV−vis spectrum of **1** in acetonitrile is congruent with that of **2** in having peaks at 308 and 414 nm, characteristic of the *tert*-butylthiolate-ligated $[Fe_4S_4]^{2+}$ cluster.[10] In the proton NMR spectrum of **1**, recorded in CD_3CN, the *tert*-butyl thiolate resonance appears at its characteristic position of 2.7 ppm. A second smaller peak at 2.9 ppm likely belongs to the protons of a terminal ligand whose resonances are shifted by the hydrogen bonding of sulfur (S_γ) with a CTA counterion. The amide proton peaks of CTA appear at 6.3 and 6.9 ppm and are shifted from their diamagnetic solution positions of 8.3 and 7.7 ppm, respectively.[21]

The crystal structure of **1** is shown in Figure 1. On the basis of N−H group orientation and proximity to sulfur, two N−H···S hydrogen bonds are evident between the amide groups of the CTA cations and sulfur atoms of the anionic complex. The N(2)−H···S(6) hydrogen bond to thiolate sulfur (S_γ) has a length of 3.356(3) Å, which is typical of amide−alkylthiolate hydrogen bonds.[17,21,22] By contrast, the N(4)−H···S(3) hydrogen bond to inorganic sulfur is relatively long at 3.625(3) Å. Hydrogen-bond contacts are also observed between the counterions themselves, as is commonly found in CTA salts.[17,21]

In Fd, six of the eight sulfur atoms are N−H···S hydrogen-bond acceptors.[23,24] Hydrogen bonding is absent at two sulfur sites (sulfide and S_γ) that lie along one edge of the cluster in a plane that contains the S_4 axis of the tetragonally compressed cluster. Serendipitously, the hydrogen-bond pattern in complex **1** is the precise opposite in that hydrogen bonding occurs exclusively along one edge of the cluster in a plane that contains the S_4 axis.

A recent single-crystal X-ray crystallographic study of *Desulfovibrio africanus* ferredoxin I shows N−H···S contacts that conform to Donahue's criteria for hydrogen bonding in which significant N···S distances are confined to the range 3.25−3.55 Å, with hydrogen-bond angles that deviate by less than 25° from 180°.[25,26] Complex **1** displays a longer N−H···S bond to sulfide, but conforms to Donahue's angular criterion for hydrogen bonds. A more recent crystallographic analysis of *Bacillus thermoproteolyticus* ferredoxin reveals hydrogen-bond $N\cdots S_{inorg}$ distances up to 3.68 Å, with N−H···S angles that deviate by as much as 59° from linearity.[24] The weak hydrogen-bonding contact between the amide and cluster sulfide in complex **1** models the corresponding hydrogen bonds of Fd with reasonable accuracy.

Non-hydrogen-bonding ferredoxin model compounds have tetragonally compressed cores[27] (Table 1). These complexes exhibit two approximately parallel Fe_2S_2 planes that are perpendicular to a natural or imposed S_4 axis of the core and have relatively long bonds, designated by the symbol ⊥ in Table 1. The planes are separated by a set of four relatively short bonds parallel to the core axis that are designated by the symbol || in Table 1. In fact, tetragonally compressed core structures have been observed for all crystallographically characterized ferredoxin active sites and their model com-

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[20] Crystallographic data for $(CTA)_2[Fe_4S_4(^tBuS)_4]\cdot CH_3CH_2OCH_2CH_3$: $a = 11.8690(8)$ Å, $b = 24.1803(16)$ Å, $c = 17.5712(11)$ Å, $\alpha = 90°$, $\beta = 93.3790(10)°$, $\gamma = 90°$, $\mu = 1.492$ mm^{-1}, $V = 5034.1(6)$ Å^3, $Z = 4$, space group $P2(1)/n$, $T = 213(2)$ K, $\lambda = 0.71073$ Å, $D_{calcd} = 1.342$ g cm^{-3}. Final R indices [$I > 2\sigma(I)$]: R1 = 0.0483, wR2 = 0.1197. R indices (all data): R1 = 0.0608, wR2 = 0.1277.

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Table 1. Structural Comparisons of Selected $[Fe_4S^*_4(^tBuS)_4]^{2-}$ Clusters

	distance (Å)			volume ($Å^3$)[d]		
counterion	Fe−Fe	Fe−S*	Fe−SR	Fe_4	S_4	Fe_4S_4
$BzNMe_3^+$ [a]	2.734 ⊥[b] 2.767(10) ‖[c]	2.315(5) ⊥ 2.252(8) ‖	2.261(3)	2.45	5.55	9.68
Et_4N^+ [a]	2.749(2) ⊥ 2.764(3) ‖	2.294(2) ⊥ 2.274(3) ‖	2.254(3)	2.47	5.53	9.69
CTA^+ (**1**)	2.7309(6) ⊥ 2.7424(6) ‖	2.2722(9) ⊥ 2.3167(9) ‖	2.2541(9)	2.24	5.55	9.61

[a] Mascharak, P. K.; Hagen, K. S.; Spence, J. T.; Holm, R. H. *Inorg. Chim. Acta* **1983**, *80* (3), 157. [b] Bonds in planes perpendicular to the S_4 axis. [c] Bonds in planes parallel to the S_4 axis. [d] Edgell, J. J., Jr.; Brown, M. J. In *Electronic Proceedings of the 8th International Conference on Technology in Collegiate Mathematics*; Addison-Wesley: Boston, 1995; Paper 8-C92 (http://archives.math.utk.edu/ICTCM).

plexes, $[Fe_4S_4(SR)_4]^{n-}$, with *alkyl*thiolate terminal ligands in all three of their accessible oxidation states ($n = 1-3$).[11,28,29]

The formation of hydrogen bonds in complex **1** results in a departure from the previously observed structural motif of Fe_4S_4 clusters. The complex has D_{2d} symmetry like that noted earlier for the complex $[Fe_4S_4(^tBuS)_4]^{2-}$ in a non-hydrogen-bonding environment, for example, with Et_4N^+ counterions.[27] Viewed in greater detail, the symmetry of complex **1** is lowered somewhat by N−H···S hydrogen bonding to S(6). The Fe(2)−S(6) bond is slightly longer, at 2.2624(9) Å, than the other three iron thiolate bonds, which range from 2.2441(9) to 2.2563(9) Å (Table 1). No systematic effects on the other internuclear distances are observed except for a *tetragonal elongation* of the core. The four bonds parallel to the S_4 axis have an average length of 2.3167(9) Å, whereas the eight bonds that define the two Fe_2S_2 planes that are perpendicular to the axis have an average length of 2.2722(9) Å.

According to one view, the $[Fe_4S_4]^{2+}$ core can be represented as two reduced two-iron centers, $[Fe_2S_2]^{1+}$, that form parallel horizontal planes that are joined by antiferromagnetic coupling.[30,31] It is possible that hydrogen bonding to one inorganic sulfur atom could disrupt the symmetry and give rise to a net elongation of the $[Fe_4S_4]^{2+}$ core. An alternative view posits an intrinsic stereochemical softness of the reduced $[Fe_4S_4]^{1+}$ core to explain the occurrence of (unexpected) tetragonally compressed structures with alkylthiolate terminal ligands and elongated structures with benzenethiolate terminal ligands.[29] The reduced core structure could be subject to extrinsic environmental effects in the solid state. The more oxidized $[Fe_4S_4]^{2+}$ cores might share this property. Complex **1** provides a system in which such questions can be explored. The N−H···S(3) hydrogen bond is the first to be reported to inorganic sulfur in an Fe_4S_4 model complex. Through further spectroscopic analysis complex **1** might provide insight into the nature of amide−sulfide hydrogen bonds and their effects on the electronic structure and function of the Fd active site.

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Supporting Information Available: Listings of crystallographic data of $(CTA)_2[Fe_4S_4(^tBuS)_4]\cdot CH_3CH_2OCH_2CH_3$. (CIF), synthetic protocols, elemental analyses, UV−vis, and H NMR characterization of complex **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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