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Synthesis, structure and electrochemical property of diphenylacetypene-substituted diiron azadithiolates as active site of Fe-only hydrogenases

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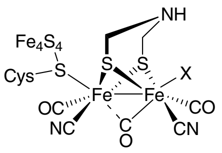
Abstract—The model complexes **1**–**3** of functionalized azadithiolate (ADT)-bridged Fe-only hydrogenases, $[Fe_2(Co)_6(\mu\text{-ADT})\text{-}C_6H_4C{\equiv}CR]$ [R = $C_6H_4NO_2$-4 (**1**), C_6H_5 (**2**), $C_6H_4OCH_3$-4 (**3**)] have been synthesized in high yields under mild conditions by using Sonogashira reaction. Spectroscopic study and X-ray crystal structural analysis of **1** demonstrate that the model complexes retain the butterfly structure of 2Fe2S model analogues. The intermolecular C–H···O, C–H···π hydrogen bonding and π–π interactions play important roles in molecular packing of **1**. In the presence of HOAc, complex **1** features the catalytic electrochemical proton reduction.

The crystal structures of Fe-only hydrogenases isolated from *C. pasteurianum*[1] and *D. desulfuricans*[2] have indicated that the active site of the enzyme comprises a butterfly 2Fe2S cluster with one of Fe atoms linked to a cuboidal 4Fe4S cluster through the S atom of cysteinyl ligand, in which the 4Fe4S cluster probably mediates the electron transfer, while the 2Fe2S subunit is responsible for the evolution of hydrogen. After elucidation of the structures, the Fe-only hydrogenases have received intense scrutiny with a focus on both functional and structural modeling.[3–6] A large number of 2Fe2S complexes that exhibit electrochemically catalytic features appear subsequently,[3–11] aimed at achieving high efficiency in hydrogen production on the basis of the simple reversible reaction: $2H^+ + 2e \leftrightarrow H_2$.

Recently, spectroscopic, crystallographic and theoretical studies suggested the dithiolate ligand bridged between the two iron atoms of 2Fe2S cluster is an azadithiolate SCH_2NHCH_2S (ADT) group, as shown in Scheme 1.[12–14] Inspired by the coordinated sphere structure of Fe-only hydrogenases, the electron-donating cyanide and phosphine ligands have been introduced by ligand-exchange reaction with carbonyl diiron dithiolates to increase the electron density of the Fe^I–Fe^I bond, and thereby facilitate protonation at this position under electrochemical condition.[7–11,15–19] At the same time, the functionalization of the bridge of azadithiolate ADT[20–25] has not yet enjoyed the same level of success because 2Fe2S cluster is always sensitive toward air and moisture, and apt to decomposition under any improper reaction conditions. Seeking desired synthetic protocols that are capable of affording high yield of 2Fe2S model analogues and achieving catalytic activities comparable to that found in the natural system represents a major target from the synthetic and biomimetic point of view.



Scheme 1.

The Sonogashira reaction,[26] a palladium-catalyzed cross-coupling reaction of terminal alkynes with arylhalides, provides an efficient and versatile method of

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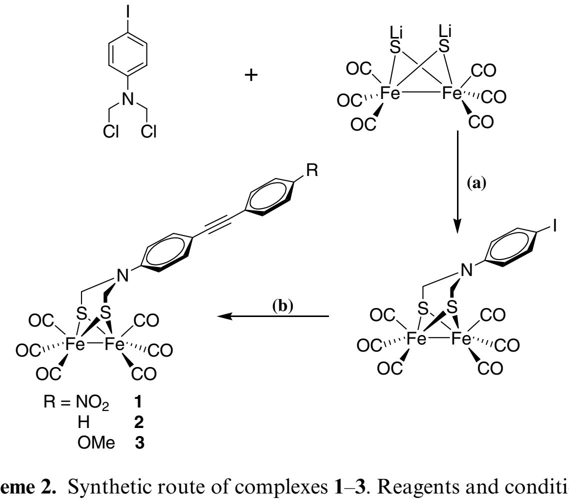
forming the C–C bond in organic synthesis, affording simplified molecular structures of aromatic alkynes. It is expected that this reaction may be employed in the functionalization of ADT-bridged 2Fe2S model analogues. In the present work, we report that using Sonogashira reaction the synthesis of diphenylacetypene-functionalized model complexes **1**–**3** can be achieved in high yields. Spectroscopic study and X-ray crystal structural analysis of **1** demonstrate that the model complexes retain the butterfly structure of 2Fe2S model analogues. The intermolecular weak interactions including C–H···O and C–H···π hydrogen bonding and π–π interactions exist in the molecular packing of **1**. Protonation of complex **1** results in no obvious changes in UV–vis, ^{1}H NMR and IR spectroscopy. Thus, the cyclic voltammetric behavior of an electrocatalytic proton reduction process in the presence of HOAc is attributed to the active sites of Fe-only hydrogenases in model complex **1**.

The synthetic strategy for making the ADT-bridged 2Fe2S complexes **1**–**3** is based on a CuI-catalyzed iodide-to-acetylide metathesis. According to the procedure described by Rauchfuss,[27,28] [(4-iodophenyl)(μ-ADT)$Fe_2(CO)_6$][20] was synthesized using lithium salt [(μ-LiS)$_2Fe_2(CO)_6$] (generated in situ from [(μ-S)$_2$-$Fe_2(CO)_6$] and Et_3BHLi in THF at −78 °C) and *N*,*N*-bis(chloromethyl)-4-iodoaniline as the reagents. As shown in Scheme 2, complex **1** was prepared by the straightforward reaction of [(4-iodophenyl)(μ-ADT)-$Fe_2(CO)_6$] with 1.5 equiv of 4-nitrophenylacetylene in THF in the presence of CuI and triethylamine. After separation by chromatography on silica gel eluted with petroleum ether and CH_2Cl_2, complex **1** was obtained as red crystals in good yield.[29] Temperature was found to influence the isolated yield of complex **1**. When the reaction was carried out at room temperature, complex **1** was obtained in 78% yield. Upon increasing the temperature to 40–50 °C, a much higher yield of 90% could be achieved.



Scheme 2. Synthetic route of complexes **1**–**3**. Reagents and conditions: (a) THF, −78 °C, 15 min; (b) $RC_6H_4C{\equiv}CH$, THF/NEt_3, $Pd(PPh_3)_2Cl_2$/CuI, 40–50 °C, 3 h.

To establish the generality of the reaction, phenylacetylene and 4-methoxyphenylacetylene which are electronically different from 4-nitrophenylacetylene were selected to react with [(4-iodophenyl)(μ-ADT)$Fe_2(CO)_6$]. As expected, complexes **2**[30] and **3**[31] could also be prepared in red crystals in 78% and 85% yields, respectively (Scheme 2). These results indicate that Sonogashira cross-coupling reaction is reliable, high efficient, and tolerates both electron-donating and electron-accepting functional groups under mild condition.

IR, ^{1}H, ^{13}C NMR, MS spectral data and satisfactory elemental analyses confirmed the identity of complexes **1**–**3**.[29–31] Unlike the triple bond exhibiting the weak absorption at around 2210 cm^{-1}, several strong absorption bands ranging from 2085 to 1960 cm^{-1} (the stretching of their terminal carbonyls) dominate the IR spectra of **1**–**3**, implying that the Sonogashira reaction would not interfere with the electron distribution of the coordination sphere. The chemical shifts of complexes **1**–**3** for their CH_2 groups on ADT bridge shifts to a relatively lower field at 4.35–4.33 ppm as compared with that for [(4-iodophenyl)(μ-ADT)$Fe_2(CO)_6$] ($\delta = 4.28$ ppm). The downfield shift may be attributed to the delocalization of electrons on nitrogen of ADT to the 4-substituted diphenylacetypene. However, the coordinated CO ligands in complexes **1**–**3** are located at ca. ~207 ppm in ^{13}C NMR spectroscopy, similar to the reported 2Fe2S model complexes.[20–23]

The X-ray crystal structural analysis of **1** further confirmed the butterfly structure of the model complexes.[29] Single crystal of **1** was obtained by immersion of hexane into dichloromethane solution. A dark red single crystal with dimensions 0.22 × 0.20 × 0.12 mm was used for data collection at 294 K on a Bruker Smart 1000 X-ray diffractometer. The crystal belongs to the triclinic crystal system of *P*-1 space group with unit cell parameters of $a = 7.6369(18)$ Å, $b = 9.177(2)$ Å, $c = 19.010(4)$ Å; $\alpha = 84.110(4)°$, $\beta = 87.509(4)°$, $\gamma = 65.421(3)°$. The two Fe atoms and the two S atoms form a butterfly conformation with the torsion angle of S(2A)–Fe(1A)–Fe(2A)–S(1A) being equal to 108.44°, in which the two metal atoms are connected through a Fe–Fe single bond. The Fe–Fe distance of 2.5025(7) Å is shorter than that in the structure of *C. pasteurianum* and *D. desulfuricans* (ca. 2.6 Å),[1,2] but comparable to those reported 2Fe2S analogues (2.49–2.51 Å).[20–25] The C≡C bond length is within the expected range (C(15A)–C(16A) = 1.191(5) Å), and its angle is nearly 180° (C(12A)–C(15A)–C(16A) = 176.8(4)°). The dihedral angle of the two triple bond-linked phenyl rings is 57.3°. The sum of the C–N–C angles of C(9A)–N(1A)–C(7A), C(9A)–N(1A)–C(8A), C(7A)–N(1A)–C(8A) around the nitrogen atom equals to 357.5°, suggesting that the N(1A) atom is sp^{2}-hybridized, and thereby the p–π electron communication exists between the substituted phenyl ring and the p-orbital of the nitrogen atom. The aryl group on the bridged N(1A) atom slants to the Fe(1A) site as a result of the two fused six-membered rings: N(1A)C(7A)S(1A)Fe(2A)S(2A)C(8A) and N(1A)C(7A)S(1A)Fe(1A)S(2A)C(8A). The former ring is in a chair conformation, while the latter one is in a boat conformation. Apparently, the angle of C(1A)–Fe(1A)–Fe(2A) is 6° larger than that of C(6A)–Fe(2A)–Fe(1A).

The strong intermolecular C–H···O and C–H···π hydrogen bonding interactions were found to direct the molecular packing of **1**. Each molecule uses its two specific hydrogen atoms of phenyl ring to bind the oxygen atom of nitro group and benzene in adjacent two molecules, respectively. The H···O distance of 2.473 Å in C(18B)–H(18B)···O(7A) and C(18C)–H(18C)···O(7B) hydrogen bonding with C–H···O angle of 162.7° observed is appreciably shorter than the sum of the van der Waals radii for H (1.20 Å) and O (1.52 Å), respectively. The H···π distance of ca. 2.979 Å (the lengths of hydrogen atom of phenyl ring to the each carbon atoms of the acceptor equal to 3.189, 3.399, 3.703, 3.790, 2.853, and 2.743 Å, respectively) also suggests that the C–H···π intermolecular interaction play an important role in the molecular assembly. As sketched in Figure 1, the intermolecular contacts of C–H···O and C–H···π interactions lead to the formation of one-dimensional assemblies along *a*-direction, in which the molecules of **1** interact with each other in a 'head-to-head' manner. In addition, the π–π interaction with distance of 3.566 Å can be clearly observed when viewed along the *a*-axis in the crystal lattice. The intermolecular interactions including C–H···O and C–H···π hydrogen bonding and π–π interactions cooperate with each other to afford such a synergistic molecular packing, which are comparable to those of the enzymes existed in nature.[1,2,11]

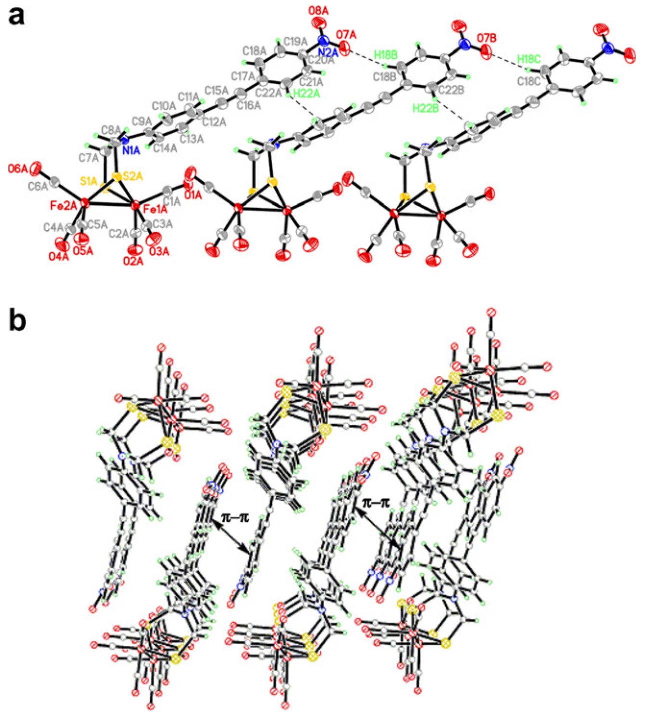


Figure 1. (a) The ORTEP (ellipsoids at 30% probability level) view of complex **1** and the one-dimensional assembly along *a*-direction. (b) Crystal packing observed when viewed along the *a*-axis.

It has been established that iron core serves as a catalytic center in the formation of Fe–H hydride and the process of H_2 evolution by Fe-only hydrogenases.[3–6] To evaluate the redox properties of the model complexes, cyclic voltammetric study of **1** was performed in acetonitrile solution with 0.1 M $n\text{-Bu}_4\text{NPF}_6$ as supporting electrolyte. An irreversible oxidation and a quasi-reversible reduction peaks for **1** were observed at 0.64 and −1.48 V versus Ag/Ag$^+$, respectively, which are subsequently assigned to $[\text{Fe}^{\text{I}}\text{Fe}^{\text{I}}] \rightarrow [\text{Fe}^{\text{II}}\text{Fe}^{\text{I}}] + e^-$ and $[\text{Fe}^{\text{I}}\text{-Fe}^{\text{I}}] + e^- \rightarrow [\text{Fe}^0\text{Fe}^{\text{I}}]$ one-electron processes (Fig. 2). Evidently, N-bridged ADT model complex **1** is more easily oxidized or reduced as compared with C-bridged all-carbonyl diiron complex ($E_{\text{ox}} = 0.84$ V and $E_{\text{red}} = -1.57$ V vs Ag/Ag$^+$).[9]

The proton reduction behavior of complex **1** was verified by cyclic voltammograms in the presence of HOAc. As shown in Figure 2, the current intensity of the initial reduction peak at −1.48 V increased with the addition of HOAc. The first irreversible peak was gradually anodic shifted to −1.25 V upon addition of 28 equiv of HOAc. Simultaneously, the second quasi-reversible reduction peak gradually appeared at −1.52 V with the increased current intensity, but the height is lower relative to the first reduction peak. Such a cyclic voltammetric behavior characterizes an electrocatalytic proton reduction process.

As elucidated in *p*-benzyl-substituted ADT-bridged 2Fe2S complex,[21] the importance of the nitrogen heteroatom of ADT-bridge was proposed to its potential for protonation in its position close to the active site, which offered a thermodynamically and kinetically favorable pathway for hydrogen evolution in the natural system. However, not any subtle change in the IR, ^{1}H NMR or UV–vis spectroscopy of either complex **1** or the model compound of 4′-*N*,*N*-dimethyl-4-nitrodiphenylacetypene was observed in the presence of HOAc, even at high concentration (Fig. S1–S3). In this situation, the active sites of Fe-only hydrogenases in complex **1** are in fact responsible for the electrochemical H_2 evolution

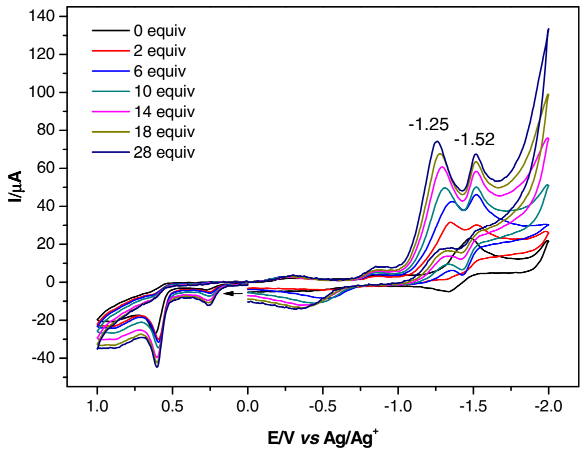


Figure 2. Cyclic voltammogram of complex **1** (0.5 mM) with HOAc (0–14 mM) in 0.1 M of $n\text{-Bu}_4\text{NPF}_6$ in CH_3CN at a scan rate of 100 mV S^{-1}.

in the presence of HOAc. At the present stage, the decomposition of complex **1** toward strong acid of $HClO_4$ limited further mechanism investigation.

In summary, we have demonstrated that Sonogashira reaction can be used as an efficient protocol for the preparation of functionalized 2Fe2S analogues. Three functionalized complexes **1**–**3** have been synthesized in high yields under mild conditions. Spectroscopic study and X-ray crystal structural analysis of **1** demonstrate that the model complexes retain the butterfly structure of 2Fe2S model analogues. The intermolecular C–H···O, C–H···π hydrogen bonding and π–π interactions play important roles in molecular packing of **1**. It is of significance that complex **1** features the catalytic electrochemical proton reduction in the presence of HOAc. Further understanding the working mechanism of the synthesized 2Fe2S analogues is ongoing in our laboratory.

Acknowledgments

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Supplementary data

Instrumentation, materials and synthetic details of **1**–**3**, the absorption spectra and ^1H NMR spectra of **1** in the absence and presence of HOAc, X-ray crystallographic data of **1**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.04.129.

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29. Note for complex **1**: ^1H NMR ($CDCl_3$, 400 MHz δ ppm): δ 8.21 (d, $J = 8.6$ Hz, 2H), 7.64 (d, $J = 8.5$ Hz, 2H), 7.52 (d, $J = 8.6$ Hz, 2H), 6.74 (d, $J = 8.5$ Hz, 2H), 4.35 (s, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz δ ppm): 206.9, 146.9, 145.2, 133.9, 132.1, 130.8, 123.8, 115.5, 113.4, 95.3, 87.4, 49.6; HR-ESI-MS (m/z): calcd for $[C_{22}H_{12}Fe_2N_2O_8S_2{+}H^+]$: 608.8812 $(M{+}H)^+$, found: 608.8787; Elemental analysis (%) calcd for $C_{22}H_{12}Fe_2N_2O_8S_2$: C 43.45, H 1.99, N 4.61; found: C 43.31, H 2.06, N 4.66; IR (CH_2Cl_2, ν cm^{-1}): ν (CO): 2073.5, 2033.8, 1993.4; ν (C≡C): 2210.8; ν (NO_2): 1513.9, 1341.0. Crystallographic data for complex **1** can be obtained free of charge from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB2 1EZ, UK; e-mail: deposit@ccdc.cam.ac.uk. (CCDC No. 643212).
30. Note for complex **2**: ^1H NMR ($CDCl_3$, 400 MHz, δ ppm): 7.51–7.48 (m, 4H), 7.33 (m, 3H), 6.72 (d, $J =$ 8.1 Hz, 2H), 4.34 (s, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): 207.0, 144.4, 133.5, 131.6, 128.5, 128.1, 123.7, 115.5, 114.9, 89.5, 88.8, 49.6; HR-ESI-MS (m/z): calcd for $[C_{22}H_{13}Fe_2$-

NO_6S_2+H^+]: 563.8961 $(M+H)^+$, found: 563.8974; Elemental analysis (%) calcd for $C_{22}H_{13}Fe_2NO_6S_2$: C 46.92, H 2.33, N 2.49; found: C 47.04, H 2.47, N 2.78; IR (CH_2Cl_2, *v* cm^{-1}): *v* (CO): 2071.6, 2034.9, 2007.4, 1985.6; *v* (C≡C): 2209.3.

31. Note for complex **3**: ^1H NMR ($CDCl_3$, 400 MHz, δ ppm): 7.48–7.45 (m, 4H), 6.88 (d, *J* = 8.6 Hz, 2H), 6.71 (d, *J* = 8.6 Hz, 2H), 4.34 (s, 4H), 3.83 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): 207.0, 159.6, 144.1, 133.3, 133.0, 115.8, 115.5, 115.2, 114.1, 88.7, 88.1, 55.4, 49.7, 14.47; HR-ESI-MS (*m*/*z*): calcd for [$C_{23}H_{15}Fe_2NO_7S_2$+H^+]: 593.9067 $(M+H)^+$, found: 593.9050; Elemental analysis (%) calcd for $C_{23}H_{15}Fe_2NO_7S_2$: C 46.57, H 2.55, N 2.36; found: C 46.69, H 2.65, N 2.53; IR (CH_2Cl_2, *v* cm^{-1}): *v* (CO): 2083.1, 2031.3, 1998.4, 1963.4; *v* (C≡C): 2208.0.