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Single-Step Insertion of Sulfides and Thiolate into Iron Carbide-Carbonyl Clusters: Unlocking the Synthetic Door to FeMoco Analogues

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Abstract: We report the one-step syntheses, X-ray structures, and spectroscopic characterization of synthetic iron clusters bearing inorganic sulfides or thiolate with interstitial carbide motifs. Treatment of historical iron-carbide-carbonyl clusters $[Fe_n(\mu_n-C)(CO)_m]^x$ (*n* = 5,6; m = 15,16; x = 0,-2) with electrophilic sulfur sources (S₂Cl₂, S₈) results in the formation of several μ_4 -S 'dimers of clusters' (1 and 2), and moreover the iron-sulfide-(sulfocarbide) clusters 3 and 4. The core 'carbide' motif in 3 and 4 is the sulfocarbide unit {C-S}4-, which serves as a structural model for a proposed intermediate in the radical-SAM biogenesis of the M-cluster. Furthermore, the 'electrophilic sulfur' strategy has been extended to provide the first ever thiolato-ironcarbide complex: An analogous reaction with toluylsulfenyl-chloride (tolS–Cl) affords the cluster $[Fe_5(\mu_5-C)(SC_7H_7)(CO)_{13}]^-$ (5). The 'electrophilic sulfur donor' strategy described herein provides a breakthrough towards developing logical syntheses of biomimetic iron-sulfur-carbide clusters like FeMoco.

The iron-sulfide-carbide cluster found in the active site of nitrogenase — particularly the Mo-dependent variant containing FeMoco — has served as inspiration for many avenues of research involving the structural, spectroscopic, biosynthetic and catalytic function of this unique cofactor. However, the chemical synthesis of the FeMoco cluster still stands as one remaining 'Holy Grail' in synthetic bioinorganic chemistry. The concomitant assembly of ferrous/ferric sites, sulfides, and an interstitial and purely inorganic carbide has to date remained elusive.

To this end, an array of synthetic models intended to emulate the ligation sphere of the cluster iron and molybdenum sites have been developed. Peters has reported an elegant series of iron complexes bearing ligands featuring chelating phosphines either anchored by an organic carbanion,¹ or bridged by an organic thiolate.² Additional complexes featuring various anchor atoms have provided valuable insight to the flexible mode of Fe-C bonding and have even demonstrated catalytic dinitrogen (N_2) reduction.¹⁻⁴ Relatedly, Holland has reported structures derived from sulfur-containing thiolate^{5,6} and sulfide ligands^{7,8} and has employed multimetallic metal sites that exhibit cooperative N₂ binding9 and high-nuclearity iron-sulfur clusters.10 Systematic work by Agapie has demonstrated electronic and catalytic modulation of iron cluster sites with interstitial light atoms.^{11,12} An incredibly thorough and long-standing research program by Tatsumi has yielded highly complex iron-sulfur structures of multiple nuclearities,13-15 which include structures bearing an interstitial sulfide as found in the nitrogenase P-cluster^{16,17} and a structure containing an interstitial oxide.¹⁸ In a similar vein, the Holm group reported an iron-sulfur cluster that incorporates a silyl-nitride into the cluster core.¹⁹ Two reports from our group demonstrated a series of interconversions between Fe₂S₂ and Fe₃S clusters in preliminary work for modeling carbon-atom insertion as seen in FeMoco biogenesis,^{20,21} although ultimately carbide insertion proved unsuccessful.



Figure 1. Structures of iron-molybdenum nitrogenase cofactor (FeMoco) and proposed NifB intermediate in FeMoco biogenesis (*left*); cluster 4 from this work (*right*).

Despite this remarkable progress in understanding the synthetic, structural and functional aspects of iron, sulfur and carbon motifs, the synthetic challenge of incorporating both the biomimetic interstitial carbide and inorganic sulfide has proven difficult. A recent report by Rauchfuss provided the first example of a synthetic cluster incorporating both these motifs in a multi-iron construct²² via an iron-carbide-carbonyl cluster precursor.²³ While past literature regarding these clusters has generally reported transformations upon the cluster core (e.g. oxidative removal of iron sites, substitution with heterometals);^{24–26} this family of iron clusters has proven difficult to control during ligand substitution. In fact, the sulfide exhibited in the Rauchfuss structure arises from a three-step removal of oxides from the SO₂-ligated structure first reported by Shriver,²⁷ and re-utilization of this strategy to coordinate a second sulfide proved unstable.²⁸ In this work, we for

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Scheme 1. Synthetic scheme depicting the electrophilic sulfurization of the Fe₆C dianion cluster by either S₂Cl₂ or elemental sulfur in the presence of a neutral Fe₅ cluster affords μ_4 -S cluster (1, 2), a {CS}⁴⁻ cluster (3, 4) and the non-carbide cluster [Fe₃S₂(CO)₉].

the first time achieve direct CO \rightarrow sulfide substitution upon the hexanuclear (NEt₄)₂[Fe₆(μ ₆-C)(CO)₁₆] first reported by Churchill.^{29,30} We find that treatment of this cluster (and its relatives) with electropositive or neutral sulfur reagents leads to cluster oxidation, CO loss, and binding of inorganic sulfide motifs (**Scheme 1**).

Reaction of $(NEt_4)_2[Fe_6(\mu_6-C)(CO)_{16}]$ with S_2Cl_2 resulted in a mixture of products. Crystallization of the charged species and subsequent X-ray diffraction revealed an asymmetric 'dimer of clusters' structure bridged by a 4-coordinate sulfide (**Figure 2**, *top*) of formula $(NEt_4)_2[[(CO)_{15}(\mu_6-C)Fe_6](\mu_4-S)][Fe_5(\mu_5-C)(CO)_{13}]$ (1). Alternatively, the introduction of elemental sulfur into a solution of $(Et_4N)_2[Fe_6(\mu_6-C)(CO)_{16}]$ plus the *five*-iron species $[Fe_5(\mu_5-C)(CO)_{15}]$ (Scheme 1, *bottom*) led to a *symmetric* dimer of Fe_5 clusters bridged by the same 4-coordinate sulfide motif (Figure 2, *bottom*), resulting in the simplified formula



Figure 2. Thermal ellipsoid plots (50% probability) of the anions of the μ_4 -S clusters 1 and 2.

$(NEt_4)_2\{[Fe_5(\mu_5-C)(CO)_{13}]_2(\mu_4-S)\}$ (2).

Moreover, our efforts to fully characterize the product profiles of the above reactions resulted in the notable isolation of three multisulfide-containing clusters. First, both reactions generate the wellknown, carbide-free cluster Fe₃S₂(CO)₉.^{31,32} More remarkably, crystallization of the Et₂O-soluble portion from the synthesis of 1 afforded red prisms of a CO-supported iron-sulfur cluster featuring a 'carbide-like' site, multiple sulfur atoms, and a 'dangler' iron (Figure 3, top) of formula [{Fe₄(κ_2 S- κ_4 C)(CO)₁₀}(μ_3 -S)(μ_3 - S_2)Fe(CO)₃ (3). The average Fe–C distance of 1.97 ± 0.04 Å is significantly longer than average for iron-carbonyl-carbide clusters (~1.90 Å) and is quite close to the average Fe–C distance found in FeMoco (2.00 ± 0.02 Å).33 While the presence of a C-S single bond [1.714(5) Å] precludes the central C atom from being an authentic C⁴⁻ carbide, this bonding motif is reminiscent of the proposed biogenesis mode of carbide insertion into the M-cluster as postulated by Wiig, Hu, Ribbe and Britt (Figure S15),³⁴⁻³⁶ in which a S-bound methyl group undergoes H• atom abstraction by radical S-adenosyl-L-methionine (SAM) before proceeding through dehydrogenation/deprotonation. Such intermediates would likely be difficult to isolate for crystallographic characterization. However, comparative spectroscopic studies of synthetic cluster compounds have previously demonstrated utility in determining structural aspects of nitrogenase, such as in the assignment of the central carbide (which itself utilized the [Fe₆C]²⁻ cluster as a reference compound). 37,38 The presence of the {C-S}⁴⁻ motif (i.e. tetra-deprotonated methylthiol) in 3 thus serves as the first rudimentary structural model for intermediates in Mcluster biosynthesis (see Supplementary Information, S23) or possibly alternative N₂ase-related C-S bond breaking enzymes.³⁹ Lastly, the Fe-S distances found in 3 are notable as their average distance of 2.27 ± 0.03 Å is considerably elongated compared to 1 and 2, placing it closer to that of FeMoco (2.25 ± 0.03 Å).

The analogous elucidation of the product profile in the synthesis of **2** identified yet another cluster: the phylochemically related, multi-sulfide cluster [{Fe₄(κ_2 S- κ_4 C)(CO)₁₀}(μ_3 -S)₂Fe(CO)₃] (**4**) (**Figure 3**, *bottom*). This cluster retains the core {C-S}⁴⁻ motif but dispenses with the *per*sulfide motif in favor of a *'bis*-sulfide' motif that again attaches a 'dangler' Fe5 site in a {FeS₂**Fe**(CO)₃} coordination motif. The average bond distances in

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4 are similar to those in 3 with the marked difference of average Fe–S distances of 2.25 \pm 0.03 Å, which is exactly on par with FeMoco (Table S4).



Figure 3. Thermal ellipsoid plots (50% probability) of the $\{\text{CS}\}^{4-}$ clusters 3 and 4.

The presence of a putatively ferrous 'dangler' Fe site in **3** (especially, with no Fe–Fe bond), and **4** with a more σ -donating coordination sphere ({FeS₃(CO)₃} in **3**; {FeS₂(CO)₃} in **4**) suggests that a progressive approach towards biologically relevant Fe^{II}/Fe^{III} sites is possible. DFT Mulliken charges analysis (B3PW91/6-31G) on the carbonyl C sites was evaluated as a proxy for π -backbonding. In cluster **3**, The C(O) sites on Fe5 exhibit the highest Mulliken charges (Figure 4, *right*), consistent with a decreased extent of π -backbonding due to the nominally higher oxidation state of Fe5. The Fe1 and Fe2 carbonyl C sites exhibited the greatest extent of CO π -backbonding, indicating that

the high Mulliken charge on these Fe sites cannot be entirely attributed to oxidation state. Similar analysis of **4** (**Figure S24**) reveals an Fe5 site that is of median oxidation state relative to the cluster.

We note that Mössbauer spectroscopy is notoriously difficult to interpret in iron carbonyl clusters due to the competing effects of formal oxidation state versus π -backbonding ligands, such that lower oxidation states in iron-carbonyls typically exhibit *higher isomer shifts* than higher oxidation states.⁴⁰ This counter-intuitive trend is somewhat realized in the analysis of Mulliken charges on the Fe sites in cluster **3**. The *six*-coordinate 'dangler' site Fe5 in {S₃Fe(CO)₃} ligation exhibits a higher Mulliken charge (+0.24) compared to the adjacent *seven*-coordinate Fe3 and Fe4 sites (+0.15) in {S₂(C)(Fe)₂Fe(CO)₂} ligation. Meanwhile, the distal *seven*-coordinate Fe1 and Fe2 sites in {S(C)(Fe)₂Fe(CO)₃} ligation both exhibit the highest extent of π -backbonding based on carbonyl metrics and DFT as well as the highest Mulliken charges (+0.25).

Thus, we deemed an electron spectroscopy method to be the preferred path of investigation. To spectroscopically probe for a ferrous site in 3, high-resolution XPS data in the Fe 2p region was collected (Figure 4, left). Component peak fitting reveals three distinct peaks at binding energies (BE) of 711.6, 709.4, and 707.5 eV in the $2p(3/_2)$ region and 724.6, 722.2, and 720.5 eV in the $2p(1/_2)$ region with approximately 1:2:2 peak area ratios. The lower BE $2p(3/_2)$ peaks at 709.4, and 707.5 eV are attributed to the four Fe sites that encircle the carbide. Furthermore, DFT reveals that the HOMO in 3 (Figure S22) is strongly localized in the Fe1-Fe2 bond, which further indicates that the lowest BE components (720.5 and 707.5 eV) are attributable to Fe1 and Fe2. These values are slightly higher binding energies relative to 1, [Fe₆]²⁻, and [Fe₅]⁰ (Figure S16), consistent with overall increased 'average' Fe oxidation state in 3. Finally, the highest binding energy feature at 711.6 eV is attributed to the dangler Fe5 site by both integration and BE, which falls within expected range for a ferrous and CO-supported iron site.41,42 Consistent with all the above data and interpretation, the overall increase in average and localized oxidation states in 3 is spectroscopically obvious in the higher CO stretching frequencies observed in the IR spectrum



Figure 4. Observed high-resolution X-ray photoelectron spectrum (XPS) and component fitting of the iron 2p region of cluster 3 (*left*) and calculated Mulliken charges (*right*) on Fe sites (*top*) and carbonyl C sites (*bottom*) of clusters 3.

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(Figure S9) where all v_{CO} values range upwards from 2002 cm⁻¹ (additionally consistent with the presence of a ferrous site).

Lastly - and critically - we deemed it essential to demonstrate the broad applicability of this 'electrophilic sulfur' approach towards sulfur-functionalized iron-carbide clusters relevant to FeMoco. Therefore, we sought to demonstrate thiolate incorporation by the analogous approach. As such, p-toluenethiol was chlorinated with NCS in situ43 and added into a DCE solution of the aforementioned [Fe₆]²⁻ (Figure 5). Crystals from fluorobenzene were obtained of the thiolate-appended [Fe₅]⁰ cluster (NEt₄)[Fe₅(μ ₅-C)(SC₇H₇)(CO)₁₃] (5), which represents the first ever iron-carbide-thiolate structure. The structure of 5 reveals the elimination of an {Fe(CO)₃Cl} from the $[Fe_6]^{2-}$ cluster, presumably by 'nucleophilic' attack by the dianionic cluster on the electrophilic toIS-CI reagent. The extension of the inorganic electrophilic sulfur strategy (S₂Cl₂, S₈) to organic sulfenyl-halides (RS-X) establishes a logical and viable synthetic pathway towards the assembly of FeMoco-related clusters derived from historical organometallic iron-carbide-carbonyl clusters.



Figure 5. Synthesis (*top*) and thermal ellipsoid plots (50% probability) (*bottom*) of the thiolato-iron-carbide cluster (NEt₄)[Fe₅(μ ₅-C)(SC₇H₇)(CO)₁₃] (5).

In summary, using two straight-forward and one-step reactions, we have synthesized and structurally characterized a pair of iron-'carbide' metalloclusters (**3** and **4**) that contain a biogenesisrelevant $\{C-S\}^{4-}$ core flanked by one or two true sulfides, as well as a 'dangler' ferrous site (in **3**). This demonstrates the first synthetic example of an iron cluster containing multiple sulfur sites and a 'carbide-like' site where both Fe···C and Fe···S distances are highly comparable to those in FeMoco (**Table S4**). The presence of the inorganic C–S unit is markedly reminiscent of a proposed biosynthetic pathway towards carbide insertion into FeMoco, which may provide valuable characterization information in proposing intermediates that occur throughout biogenesis. Critically, we have extended the 'electrophilic sulfur' approach for the incorporation of thiolates, where the first ever thiolato-ironcarbide species **5** was derived from an organic sulfenylchloride (toIS–CI). The incorporation of multiple sulfur sites and higher valent iron in $\mathbf{3}$ — coupled with the now-possible synthetic versatility of thiolate incorporation — now opens the full toolbox of bio-inorganic chelation chemistry and ligand design to be applied to the preparation of elusive synthetic models of FeMoco. We hereby assert that this method will finally 'unlock the synthetic door' to biomimetic models of the nitrogenase active site cluster.

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- [1] S. E. Creutz, J. C. Peters. J. Am. Chem. Soc. 2014, 136, 1105.
- [2] S. E. Creutz, J. C. Peters. J. Am. Chem. Soc., 2015, 137, 7310.
- [3] J. S. Anderson, J. Rittle, J. C. Peters. Nature 2013, 501, 84.
- [4] Y. Lee, N. P. Mankad, J. C. Peters. Nat. Chem. 2010, 2, 558.
- [5] I. Čorić, B. Q. Mercado, E. Bill, D. J. Vinyard, P. L. Holland. Nature 2015, 526, 96.
- [6] A. L. Speelman, I. Čorić, C. Van Stappen, S. DeBeer, B. Q. Mercado, P. L. Holland. J. Am. Chem. Soc. 2019, 141, 13148.
- [7] J. Vela, S. Stoian, C. J. Flaschenriem, E. Münck, P. L. Holland. J. Am. Chem. Soc. 2004, 126, 4522.
- [8] N. A. Arnet, T. R. Dugan, F. S. Menges, B. Q. Mercado, W. W. Brennessel, E. Bill, M. A. Johnson, P. L. Holland. J. Am. Chem. Soc. 2015, 137, 13220.
- [9] K. P. Chiang, S. M. Bellows, W. W. Brennessel, P. L. Holland. Chem. Sci. 2014, 5, 267.
- [10] D. E. DeRosha, N. A. Arnet, B. Q. Mercado, P. L. Holland. *Inorg. Chem.* 2019, 58, 8829.
- [11] C. J. Reed, T. Agapie. Inorg. Chem. 2017, 56, 13360.
- C. H. Arnett, J. T. Kaiser, T. Agapie. *Inorg. Chem.* **2019**, *58*, 15971.
 G. Moula, T. Matsumoto, M. E. Miehlich, K. Meyer, K. Tatsumi. Angew.
- Chemie Int. Ed. 2018, 57, 11594.
- [14] K. Tanifuji, S. Tajima, Y. Ohki, K. Tatsumi. Inorg. Chem. 2016, 55, 4512.
- [15] N. Taniyama, Y. Ohki, K. Tatsumi. Inorg. Chem. 2014, 53, 5438.
- [16] K. Tanifuji, C. C. Lee, Y. Ohki, K. Tatsumi, Y. Hu, M. W. Ribbe. Angew. Chemie Int. Ed. 2015, 54, 14022.
- [17] N. S. Sickerman, K. Tanifuji, C. C. Lee, Y. Ohki, K. Tatsumi, M. W. Ribbe, Y. Hu. J. Am. Chem. Soc. 2017, 139, 603.
- [18] S. Ohta, Y. Ohki, T. Hashimoto, R. E. Cramer, K. Tatsumi. *Inorg. Chem.* 2012, *51*, 11217.
- [19] G. Xu, Z. Wang, R. Ling, J. Zhou, X.-D. Chen, R. H. Holm. Proc. Natl. Acad. Sci. 2018, 115, 5089.
- [20] J. P. Shupp, A. R. Rose, M. J. Rose. Dalt. Trans. 2017, 46, 9163.
- [21] J. P. Shupp, A. R. Rose, M. J. Rose. Dalt. Trans. 2019, 49, 23.
- [22] L. Liu, T. B. Rauchfuss, T. J. Woods. Inorg. Chem. 2019, 58, 8271.
- [23] E. H. Braye, L. F. Dahl, W. Hubel, D. L. Wampler. J. Am. Chem. Soc. 1962, 84, 4633.
- [24] M. Tachikawa, A. C. Sievert, E. L. Muetterties, M. R. Thompson, C. S. Day, V. W. Day. J. Am. Chem. Soc. 1980, 102, 1725.
- [25] S. Kuppuswamy, J. D. Wofford, C. Joseph, Z. Xie, A. K. Ali, V. M. Lynch, P. A. Lindahl, M. J. Rose. *Inorg. Chem.* **2017**, *56*, 5998.
- [26] C. Joseph, S. Kuppuswamy, V. M. Lynch, M. J. Rose. Inorg. Chem. 2018, 57, 20.
- [27] P. L. Bogdan, M. Sabat, S. A. Sunshine, C. Woodcock, D. F. Shriver. *Inorg. Chem.* **1988**, *27*, 1904.
- [28] L. Liu, T. J. Woods, T. B. Rauchfuss. Eur. J. Inorg. Chem. 2020, 3460.

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- [29] M. R. Churchill, J. Wormald, J. Knight, M. J. Mays. J. Am. Chem. Soc. 1971, 93, 3073.
- [30] M. R. Churchill, J. Wormald. J. Chem. Soc., Dalt. Trans. 1974, 2410.
- [31] C. H. Wei, L. F. Dahl. Inorg. Chem. 1965, 4, 493.
- [32] A. J. Bard, A. H. Cowley, J. K. Leland, G. H. N. Thomas, N. C. Norman, P.
- Jutzi, C. P. Morley, E. Schlüter. J. Chem. Soc., Dalt. Trans. 1985, 1303.
 [33] L.-M. Zhang, C. N. Morrison, J. T. Kaiser, D. C. Rees. Acta Crystallogr. Sect. D Struct. Biol. 2015, 71, 274.
- [34] J. A. Wiig, Y. Hu, C. C. Lee, M. W. Ribbe. Science 2012, 337, 1672.
- [35] J. A. Wiig, Y. Hu, M. W. Ribbe. Nat. Commun. 2015, 6, 8034.
- [36] L. A. Rettberg, J. Wilcoxen, C. C. Lee, M. T. Stiebritz, K. Tanifuji, R. D. Britt, Y. Hu. Nat. Commun. 2018, 9, 2824.
- [37] M. U. Delgado-Jaime, B. R. Dible, K. P. Chiang, W. W. Brennessel, U. Bergmann, P. L. Holland, S. DeBeer. Inorg. Chem. 2011, 50, 10709.
- [38] K. M. Lancaster, M. Roemelt, P. Ettenhuber, Y. Hu, M. W. Ribbe, F. Neese, U. Bergmann, S. DeBeer. *Science* 2011, 334, 974.
- [39] J. A. North, F. R. Tabita et al. Science 2020, 369, 1094.
- [40] J. McGale, G. E. Cutsail III, C. Joseph, M. J. Rose, S. DeBeer. Inorg. Chem. 2019, 58, 12918.
- [41] A. P. Grosvenor, B. A. Kobe, M. C. Biesinger, N. S. McIntyre. Surf. Interface Anal. 2004, 36, 1564.
- [42] M. Barber, J. A. Connor, M. F. Guest, M. B. Hall, I. H. Hillier, W. N. E. Meredith. Faraday Discuss. Chem. Soc. 1972, 54, 219.
- [43] A. Ghosh, M. Lecomte, S.-H. Kim-Lee, A. T. Radosevich. Angew. Chem. Int. Ed. 2019, 58, 2864.

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Entry for the Table of Contents



Approaching High-Fidelity FeMoco Models: At first glance, CO-supported iron-carbide clusters are an appealing synthetic starting point for modeling the carbide-containing FeMoco cluster. However, these compounds have historically been uncontrollable towards traditional $CO \rightarrow S$ substitution methods. We demonstrate an approach utilizing unconventional, electrophilic sulfur reagents to achieve carbide-containing multi-sulfide multi-iron clusters.

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