A Capable Bridging Ligand for Fe-Only Hydrogenase: Density Functional Calculations of a Low-Energy Route for Heterolytic Cleavage and Formation of Dihydrogen

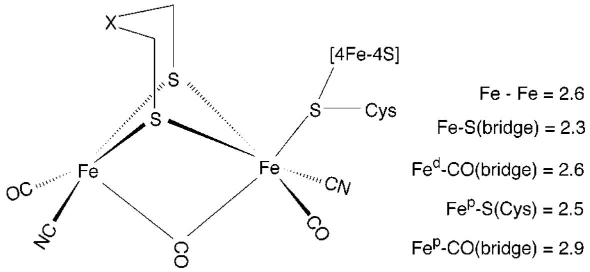
Hua-Jun Fan and Michael B. Hall*

Department of Chemistry, Texas A&M University
TAMU 3255, College Station, Texas 77843-3255

Received November 30, 2000

When di(thiomethyl)amine (DTMA) is used as the bridging ligand in a diiron model for the active site of the Fe-only hydrogenase, density functional calculations show that the bridgehead N atom is a suitable base and provides a kinetically and thermodynamically favorable route for the heterolytic cleavage or formation of dihydrogen. The reaction with this N base is much more favorable than that with other bases such as terminal CN or bridging S. A strong Fe−H$^{\delta-}$•••H$^{\delta+}$−N “dihydrogen bond” is found in the H_2 heterolytic cleavage product.

As key members of the metalloproteins that catalyze the reversible reaction of dihydrogen to protons and electrons, Fe-only hydrogenases have recently piqued the interest of both experimentalists[1−4] and theoretists.[5] These studies established that the active site of the enzyme consists of a diiron complex linked to a [4Fe-4S] cluster. Infrared spectroscopic studies on Fe-only hydrogenases from *Desulfovibrio vulgaris* (DvHase)[3a−c] and *Desulfovibrio desulfuricans* (DdHase)[3d] and X-ray crystal structures of those from *Clostridium pasteurianum* (CpHase)[2b] and DdHase[2c] suggest that this diiron complex has the general structure shown below. EPR[1c−e,3c] and Mössbauer[1f−g] studies suggest that an oxidized inactive H-cluster (EPR silent) can be partially reduced to a catalytically active paramagnetic form, then further reduced by H_2 to an EPR silent form. Both inorganic model studies[4] and theoretical calculations[5] suggest that a catalytic cycle involving Fe(II)-Fe(II) ↔ Fe(I)-Fe(II) ↔ Fe(I)-Fe(I) species is more likely than one involving Fe(III)-Fe(III) ↔ Fe(III)-Fe(II) ↔ Fe(II)-Fe(II) species, as suggested in earlier studies.



The heterolytic cleavage of dihydrogen is a critical step in the catalytic cycle.[6] Using density functional methods (DFT) and 1,3-propanedithiolate (PDT) as the bridging ligand, Cao and Hall[5] showed that cleaving the dihydrogen by transferring the proton to the bridging-S has a barrier of 17.4 kcal/mol and a product that is 15.3 kcal/mol less stable than the dihydrogen complex. On the other hand, transferring the proton to the CN ligand has a much higher barrier (37.8 kcal/mol), even though the product is −0.3 kcal/mol more stable than the dihydrogen complex. Thus, these two proposed pathways are either kinetically unfavorable (CN) or thermodynamically unfavorable (S).

This dilemma prompted us to seek an alternative pathway, specifically one involving another base near the active site to accept the proton. From the X-ray crystal structure of CpHase[2b] and DdHase,[2c] it is not clear whether the covalently bound atoms in the bridging ligand are C, N, or O since they would be indistinguishable.[2a] Two observations, the close contact between the bridgehead atom X and the sulfur of C178 in DdHase[2a] and the close contact between X and O(CO) after inhibition by CO addition,[3d] suggest a hydrogen-bond linkage and therefore a more electronegative element than C at this position. In addition, a new candidate for the bridging ligand such as DTMA instead of PDT has the immediate advantage of an alternative base to accept the proton in the heterolytic cleavage.[2d] In this paper we will use $[(H_2)(CO)(CN)Fe^{d}(\mu\text{-DTMA})(\mu\text{-CO})Fe^{p}(CO)(CN)(SMe)]^-$ (DTMA = SCH_2NHCH_2S, Me = CH_3, Fe^{d} = distal iron, Fe^{p} = proximal iron) as a model complex to study the dihydrogen heterolytic cleavage and formation pathways.

The geometries of the species in this study have been optimized by DFT methods in Gaussian 98,[7] with the Becke hybrid exchange functional[8] and the Lee−Yang−Parr correlation function[9] (B3LYP). The basis set is the same as that used in the previous study;[5] with effective core potentials (ECP),[10] an improved 4p function[11] and an f polarization function[12] on the Fe atoms; polarized ECP[10,13]

---

(1) (a) Adams, M. W. W. *Biochim. Biophys. Acta* **1990**, *1020*, 115. (b) Adams, M. W. W.; Stiefel, E. I. *Science* **1998**, *282*, 1842. (c) Adams, M. W. W.; Mortenson, L. E. *J. Biol. Chem*. **1984**, *259*, 7045. (d) Adams, M. W. W. *J. Biol. Chem*. **1987**, *262*, 15054. (e) Zambrano, I. C.; Kowal, A. T.; Mortenson, L. E.; Adams, M. W. W.; Johnson, M. K. *J. Biol. Chem*. **1989**, *264*, 20974. (f) Rusnak, F. M.; Adams, M. W. W.; Mortenson, L. E.; Munck, E. *J. Biol. Chem*. **1987**, *262*, 38. (g) Popescu, C. V.; Munck, E. *J. Am. Chem. Soc*. **1999**, *121*, 7877. (h) Morelli, X.; Czjzek, M.; Hatchikian, C. E.; Bornet, O.; Fontecilla-Camps, J. C.; Palma, N. P.; Moura, J. J. G.; Cuerlesquin, F. *J. Biol. Chem*. **2000**, *275*, 23204.

(2) (a) Nicolet, Y.; Lemon, B. J.; Fontecilla-Camps, J. C.; Peters, J. W. *Trends Biochem. Sci*. **2000**, *25*, 138. (b) Peters, J. W.; Lanzilotta, W. N.; Lemon, B. J.; Seefedt, L. C. *Science* **1998**, *282*, 1853 (Errata: *283*, 35; *283*, 2102). (c) Nicolet, Y.; Piras, C.; Legrand, P.; Hatchikian, C. E.; Fontecilla-Camps, J. C. *Structure* **1999**, *7*, 13. (d) Nicolet, Y.; De Lacey, A. L.; Vernède, X.; Fernandez, V. M.; Hatchikian, E. C.; Fontecilla-Camps, J. C. *J. Am. Chem. Soc*. **2001**, *123*, 1596.

(3) (a) Pierik, A. J.; Hulstein, M.; Hagen, W. R.; Albracht, S. P. J. *Eur. J. Biochem*. **1998**, *258*, 572. (b) Van der Spek, T. M.; Arendsen, A. F.; Happe, R. P.; Yun, S.; Bagley, K. A.; Hagen, W. R.; Albracht, S. P. J. *Eur. J. Biochem*. **1997**, 237, 629. (c) Pierik, A. J.; Hagen, W. R.; Redeker, J. S.; Wolbert, R. B. G.; Boersma, M.; Verhagen, M. F. J. M.; Grande, H. J.; Veeger, C.; Mustsaers, P. H. A.; Sand, R. H.; Dunham, W. R. *Eur. J. Biochem*. **1992**, *209*, 63. (d) De Lacey, A. L.; Stadler, C.; Cavazza, C.; Hatchikian, E. C.; Fernandez, V. M. *J. Am. Chem. Soc*. **2000**, *122*, 11232.

(4) (a) Lyon, E. J.; Georgakaki, I. P.; Reibenspies, J. H.; Darensbourg, M. Y. *Angew. Chem., Int. Ed*. **1999**, *38*, 3178. (b) Rauchfuss, T. B.; Contakes, S. M.; Schmidt, M. *J. Am. Chem. Soc*. **1999**, *121*, 9736. (c) Cloirec, A. L.; Best, S. P.; Borg, S.; Davies, S. C.; Evans, D. J.; Hughes, D. L.; Pickett, C. *J. Chem. Commun*. **1999**, 2285. (d) Lai, C. H.; Lee, W. Z.; Miller, M. L.; Reibenspies, J. H.; Darensbourg, D. J.; Darensbourg, M. Y. *J. Am. Chem. Soc*. **1998**, *120*, 10103.

(5) Cao, Z.; Hall, M. B. *J. Am. Chem. Soc*. **2000** (in press).

(6) (a) Huhmann-Vincent, J.; Scott, B. L.; Kubas, G. J. *Inorg. Chim. Acta* **1999**, *294*, 240. (b) Abdur-Rashid, K.; Fong, T. P.; Greaves, B.; Gusev, D. G.; Hinman, J. G.; Landau, S. E.; Lough, A. J.; Morris, R. H. *J. Am. Chem. Soc*. **2000**, *122*, 9155.

(7) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *GAUSSIAN 98*, Revision A7; Gaussian, Inc.: Pittsburgh, PA, 1998.

(8) Becke, A. D. *J. Chem. Phys*. **1993**, *98*, 5648.

(9) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev*. **1988**, *37*, 785.

(10) Hay, P. J.; Wadt, W. R. *J. Chem. Phys*. **1985**, *82*, 299.

(11) Couty, M.; Hall, M. B. *J. Comput. Chem*. **1996**, *17*, 1359.

(12) Ehlers, A. W.; Bohme, M.; Dapprich, S.; Gobbi, A.; Hollwarth, A.; Jonas, V.; Kohler, K. F.; Stegmann, R.; Veldkamp, A.; Frenking, G. *Chem. Phys. Lett*. **1993**, *208*, 111.

(13) Hollwarth, A.; Bohme, M.; Dapprich, S.; Ehlers, A. W.; Gobbi, A.; Jonas, V.; Kohler, K. F.; Stegmann, R.; Veldkamp, A.; Frenking, G. *Chem. Phys. Lett*. **1993**, *208*, 237.

10.1021/ja004120i CCC: $20.00

Table 1. DFT Energies (kcal/mol) for the Dihydrogen Cleavage Reaction in Fe-Only Hydrogenase Models

ligand (base)	state	ΔE	ΔE_{ZPE}	ΔG
DTMA	TS	6.53	5.07	4.91
(N)	product	2.62	4.13	3.46
DTMA	TS	32.3	29.83	29.83
(CN)	product	−6.10	−5.40	−5.66
PDT[a]	TS	37.8		
(CN)	product	−0.3		
PDT[a]	TS	17.4		
(S)	product	15.3		

[a] Reference 5.

on S; 6-311G(dp)[14a] on active H's; and D95V*[14b] on CO, CN, and the N in DTMA.

A new pathway is possible by using DTMA's bridgehead N as the base. The calculated energies for the dihydrogen heterolytic cleavage reaction with this N atom as the base are summarized in Table 1: relative energies without and with zero-point-energy ($\Delta E^{\ddagger}$, ΔE°, and $\Delta E^{\ddagger}_{\mathrm{ZPE}}$, $\Delta E^{\circ}_{\mathrm{ZPE}}$), and free energies corrected to room temperature ($\Delta G^{\ddagger}$, ΔG°). For comparison purposes, the pathway involving terminal CN as a base with DTMA as the bridging ligand and pathways involving terminal CN and bridging S atoms as bases with PDT as the bridging ligand[5] are also listed in Table 1. These results show that the energy barrier for the dihydrogen heterolytic cleavage reaction has a much lower barrier when using N(DTMA) as a base than when using any of the other bases. Furthermore, the product with N(DTMA) as the base is suitably stable, as it is only 2.6 kcal/mol above the reactant energy. Although this product is 8.7 kcal/mol less stable than the product with terminal CN as a base (DTMA), our results for proton transfer to CN with DTMA as the bridging ligand, which are similar to those with PDT as the bridging ligand,[5] show a very large barrier. Because of this 32 to 38 kcal/mol barrier, using the terminal CN as a base is not feasible with either PDT or DTMA. Although we have not repeated the calculations for transfer of the proton to the bridging S, previous results with PDT as a bridging ligand suggested that this reaction would be thermodynamically much less favorable than transfer of the proton to the N of DTMA. These differences in the energy barriers and the relative stabilities of the products are preserved on the free energy surface. When using the N atom as the base, the cleavage reaction has $\Delta G^{\ddagger} = 4.9$ kcal/mol and $\Delta G^{\circ} = 3.5$ kcal/mol, and the H_2 formation reaction has $\Delta G^{\ddagger} = 1.6$ kcal/mol and $\Delta G^{\circ} = -3.5$ kcal/mol.

The optimized geometries for this new reaction pathway involving Fe(II)-Fe(II) species are shown in Figure 1. Form **1** is a dihydrogen complex with H_2 bound to the Fe^d site. This geometry is similar to the corresponding species with PDT as the bridging ligand.[5] In the transition state, **2**, the H−H bond has lengthened from 0.82 in **1** to 1.03 Å, and the "proton" has moved to within 1.35 Å of the bridgehead N, and the "hydride" has moved to 1.58 Å from the Fe^d. In following this motion the bridging CO moves close to the Fe^d and away from Fe^p. The H···H distance of the cleavage product **3** is 1.47 Å. This distance is relatively short for a nonbonded contact, even shorter than typical $M{-}H^{\delta-}\cdots H^{\delta+}{-}N$ "dihydrogen bonds" which are 1.7−1.9 Å,[16] and suggests an especially strong $M{-}H^{\delta-}\cdots H^{\delta+}{-}N$ "dihydrogen bond". Peris et al.[16b] suggest three factors that contribute to the strength of the H···H bond in the Ir−H···H−N example, two of which may be applicable here: one, the geometry of the complex allows or supports a close contact between the proton and hydride, and two, the increasing trans influence of the bridging CO weakens the Fe−hydride bond. Both of these factors may favor a strong H···H interaction in our model complex. As a result, the corresponding N−H bond length is 0.04 Å longer than the other N−H bond on this N atom, and the Fe^d−H bond length is 0.05 Å longer than the Fe^d−H bond in the closely related species with the PDT ligand.

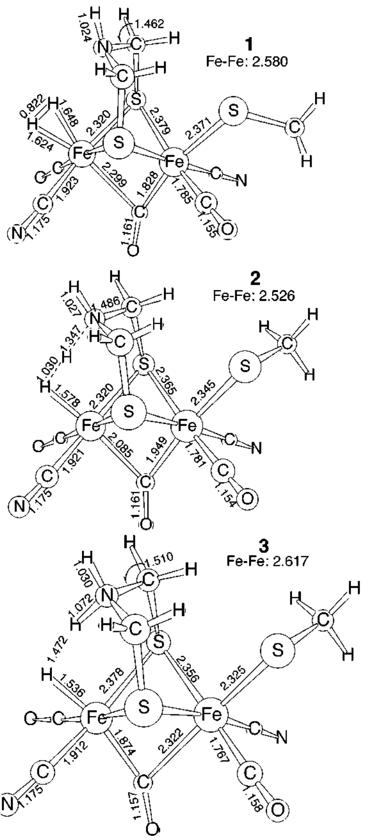


Figure 1. The DFT optimized geometries (Å, deg) of the model complexes involving the H_2 heterolytic cleavage reaction. The dihydrogen complex **1** is a stable minimum on the energy surface, the transition state **2** has one imaginary frequency, and the cleavage product **3** is again a stable minimum on the energy surface.

In conclusion, the presence of a bridgehead N in the DTMA ligand not only explains the close contact with C178 as observed in the X-ray structure of DdHase,[2a] but also provides a low-energy barrier and a suitably stable product for the dihydrogen heterolytic cleavage, or formation, reaction.

Acknowledgment. We gratefully acknowledge the National Science Foundation (Grant No. CHE 9800184) and The Welch Foundation (Grant No. A-648) for financial support of this work. We also thank A. L. De Lacey, V. M. Fernandez, J. C. Fontecilla-Camps, J. W. Peters, and M. Y. Darensbourg for helpful discussions.

Supporting Information Available: The optimized geometries of these complexes (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA004120I

---

[14] (a) Krishnan, R.; Binkley, J. S.; Seeger, R.; Pople, J. A. *J. Chem. Phys.* **1980**, *72*, 650. (b) Dunning, T. H., Jr.; Hay, P. J. *Modern Theoretical Chemistry*; Schaefer, F. F., III, Ed.; Plenum: New York, 1976; Vol. 3, p 1.

[15] Niu S.; Thomson, L. M.; Hall, M. B. *J. Am. Chem. Soc.* **1999**, *121*, 4000.

[16] (a) Crabtree, R. H.; Siegbahn, P. E. M.; Eisenstein, O.; Rheingold, A. L.; Koetzle, T. F. *Acc. Chem. Res.* **1996**, *29*, 348. (b) Peris, E.; Lee, J. C.; Rambo, J. R.; Eisenstein, O.; Crabtree, R. H. *J. Am. Chem. Soc.* **1995**, *117*, 3485. (c) Stevens, R. C.; Bau, R.; Milstein, D.; Blum, O.; Koetzle, T. F. *J. Chem. Soc. Dalton Trans.* **1990**, 1429. (d) Lee, J. C.; Rheingold, A. L.; Muller, B.; Pregosin, P. S.; Crabtree, R. H. *J. Chem. Soc. Chem. Commun.* **1994**, 1021. (e) Lough, A. J.; Park, S.; Ramachandran, R.; Morris, R. H. *J. Am. Chem. Soc.* **1994**, *116*, 8356.