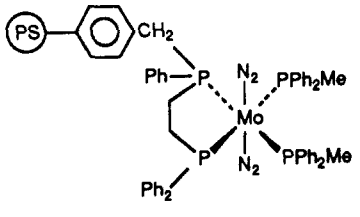
$$\{Mo(NNH_2)\} \rightarrow \{Mo(III)\} + N_2 + 2H^+ + 3e \quad (2)$$

$$3e + \{Mo(NNH_2)\} \xrightarrow{H^+} \{Mo(III)\} + 2[NH_4]^+ \quad (3)$$

molybdenum-containing product isolated in these reactions is $[MoX_3L_3]$. In order to study the electron transfer properties of unsubstituted hydrazido(2-) complexes, it is necessary to prevent or control disproportionation. To prevent interaction between hydrazido(2-) complexes, efforts have been made to site-isolate complexes by anchoring them to a microreticular resin. It is the successful results of this work that we report here.

The $\{Mo(N_2)_2\}$ moiety was attached to a phosphinated polystyrene-divinylbenzene (2%) resin[11] by a phosphine-exchange method similar to that employed by Dubois[12] to attach $\{Mo(N_2)_2\}$ to phosphinated polyacrylamide resins. Since loss of a phosphine ligand is the first step in the conversion of the hydrazido(2-) complex to ammonia, attachment of $\{Mo(N_2)_2\}$ to the resin must be through a chelating ligand. The $P(Ph)CH_2CH_2PPh_2$, diphos, moiety was bonded to polystyrene, PS, by the reaction of $LiP(Ph)CH_2CH_2PPh_2$ with chloromethylated polystyrene, following a procedure reported by Pittman and Hirao.[13] A ^{31}P NMR[15] spectrum of the solvent-swollen resin clearly showed a distinct resonance for each of the two different phosphorus atoms. Elemental analysis of the polymer indicated that the phosphine loading was >85%.[16]

A sample of *trans*-$[Mo(N_2)_2(PMePh_2)_4]$ (**1**)[17] in THF was added to the phosphinated resin, PS-diphos, swollen in THF. After 48 h of stirring, the bright orange resin was isolated.[18] Absorptions due to the symmetric and antisymmetric $\nu(N_2)$ were clearly visible in the difference FTIR spectrum. The ^{31}P NMR



spectrum of the solvent-swollen complex clearly showed two broad resonances: one for coordinated PPh_2Me and the other for the unresolved pair of phosphorus atoms of $-P(Ph)CH_2CH_2PPh_2$. The chemical shifts were very similar to those of the phosphorus atoms in *trans*-$[Mo(N_2)_2(dppe)(PPh_2Me)_2]$, where dppe = $Ph_2PCH_2CH_2PPh_2$.[19]

Reaction of *trans*-$[Mo(N_2)_2(PS\text{-}diphos)(PPh_2Me)_2]$ (**2**) with excess fluoroboric acid in THF afforded the hydrazido(2-) complex $[MoF(NNH_2)(PS\text{-}diphos)(PPh_2Me)_2]BF_4$.[20] This is the first report of the successful reaction of N_2 in a resin-supported transition-metal complex. In the FTIR spectrum, $\nu(NH)$ absorptions were identical (±4 cm^{-1}) with those in $[MoF(NNH_2)(dppe)(PPh_2Me)_2]BF_4$.[21]

Reaction of *trans*-$[Mo(N_2)_2(dppe)(PPh_2Me)_2]$ with HBr in THF produced 0.68 mol of ammonia per mol of Mo.[5] The reaction of **2** with HBr (20 mol) in THF for 48-72 h yielded *no ammonia*. This result is precisely what is expected if the disproportionation hypothesis outlined above is correct.

Reaction of **2** with HBr in CH_2Cl_2 for 48 h produced no ammonia and 0.24 mol of hydrazine per mol of Mo. The same reaction carried out with *trans*-$[Mo(N_2)_2(dppe)(PPh_2Me)_2]$ produced 0.42 mol of hydrazine and 0.41 mol of ammonia per mol of Mo. Thus, the formation of hydrazine showed that (i) the N_2 ligand of a complex anchored to a resin will undergo chemistry beyond the hydrazido(2-) stage and (ii) hydrazine formation occurs at a single metal site.

In order to further test the hypothesis, a 1:1 mixture of **1** and **2** was treated with HBr in THF. The yield of ammonia from the mixture was 1.01 mol per mol of **1** compared with 0.77 mol per mol of **1** for **1** with acid,[22] a 30% increase in ammonia yield. Furthermore, oxidation by sodium hypochlorite solution of the ammonia produced in the acid reaction of a mixture of **1** and the anchored complex that was labeled with $^{15}N_2$ (>90%) resulted in the recovery of dinitrogen-28, dinitrogen-29 significantly above background measurements, and a trace of dinitrogen-30. Identical results were obtained when the corresponding hydrazido(2-) complexes that had been prepared separately were mixed and reacted with HBr. Thus, the presence of the homogeneous molybdenum N_2 complex led to reduction of the anchored complex with resulting formation of $^{15}NH_3$.

Work is underway to discovery other reagents that will convert N_2 and NNH_2 that are coordinated to anchored metal complexes into ammonia and hydrazine.

Acknowledgment. We are grateful to the National Institutes of Health (Grant GM-38613) for support of this research. Additional funding was provided by the University of Nebraska Research Council and NIH Biomedical Research Support Grant RR-07055.

(11) Chloromethylated polystyrene (2% divinylbenzene), 1.06 ± 0.05 mmol of Cl/g of resin, 16% chloromethylated, was purchased from Eastman Kodak Co.

(12) Dubois, D. L. *Inorg. Chem.* **1984**, *23*, 2047-2052.

(13) Pittman, C. U., Jr.; Hirao, A. *J. Org. Chem.* **1978**, *43*, 640-626. For example, the reaction of brominated polystyrene with $LiP(Ph)CH_2CH_2PPh_2$.

(14) This footnote was deleted on revision.

(15) The $^{31}P\{^1H\}$ NMR spectra (C_6D_6, 23 °C) were obtained with a Varian VXR-200 spectrometer operating at 80.894 MHz. Chemical shifts are referenced to PPh_3 (-5.8 ppm; 85% H_3PO_4 = 0.0 ppm). The phosphorus atom assignments are as follows: $-CH_2P_a(Ph)CH_2CH_2P_bPh_2$, P_xPh_2Me.

(16) Anal. Found: C, 86.57; H, 7.29; P, 5.33; Cl, 0.81 (by difference) corresponds to 0.86 mmol of ligand/g of resin. ^{31}P NMR: δ -13.36 (brd, 1, J_{PP} = 23.5 Hz, P_a), -16.19 (brs, 1, P_b). The narrower resonance (doublet) was assigned to the phosphorus atom with lesser restriction to rotation in the solvent-swollen polymer.

(17) George, T. A.; Noble, M. E. *Inorg. Chem.* **1978**, *17*, 1678-1679.

(18) *trans*-$[Mo(N_2)_2(PS\text{-}diphos)(PPh_2Me)_2]$. ^{31}P NMR: δ 63 (b, $P_{a,b}$), 21 (b, P_x). IR: $\nu(NN)$ 2022 (w), 1946 (vs) [$^{15}N_2$ 1950 (w), 1880 (vs)] cm^{-1}. Anal. Found: Mo, 4.48; P, 6.25. Mo/P ratio = 1.0/4.2. Calcd: N, 3.04. Found: N, 2.90 (N_2 gas measurement following oxidation by Br_2 in CH_2Cl_2).

(19) George, T. A.; Kovar, R. A. *Inorg. Chem.* **1981**, *20*, 285-287.

(20) $[MoF(NNH_2)(PS\text{-}diphos)(PPh_2Me)_2]BF_4$. IR: $\nu(NH)$ 3333 (m), 3253 (s), 3163 (m) cm^{-1}. ^{31}P NMR: δ 43 (b, $P_{a,b}$), 8 (b, P_x).

(21) George, T. A.; Kaul, B. B., unpublished results.

(22) Yields of ammonia are ±3%. Total nitrogen balances for the two reactions are 75 and 77%, respectively.

Total Synthesis of *dl*-Indolizomycin

Guncheol Kim, Margaret Y. Chu-Moyer, and Samuel J. Danishefsky*

Department of Chemistry, Yale University
New Haven, Connecticut 06511

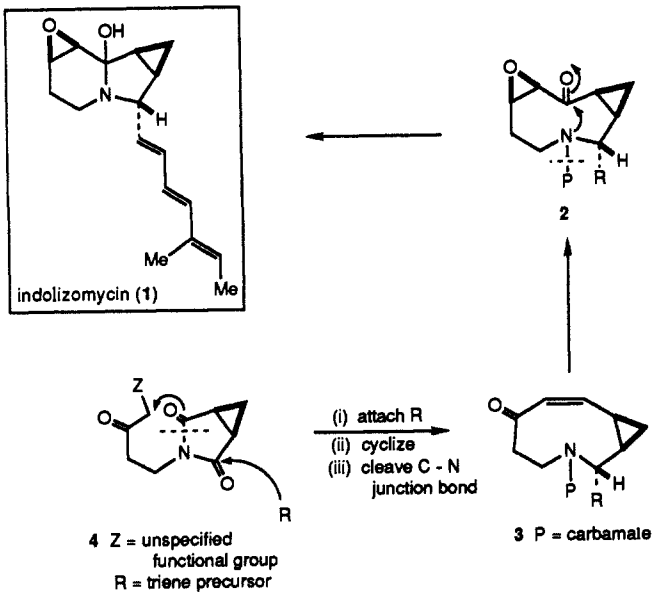
Received October 10, 1989
Revised Manuscript Received December 19, 1989

The possibility of using mutant microorganisms to produce novel structures is well recognized. An interesting extension of this theme was recently described by Umezawa and colleagues.[1] The Japanese workers achieved a protoplast fusion of two non-antibiotic-producing strains (*Streptomyces teryimanensis* HM16 and *Streptomyces grisline* NPI-1). There were elaborated new clones from which a particular strain (SK2-52) was especially effective in producing antibiotics. It was in this way that the bioengineered antibiotic called indolizomycin (**1**) was isolated. Indolizomycin production in SK2-52 may be the result of enzymic machinery derived from recombinant genes. Alternatively it might reflect newly fashioned mechanisms for expressing "silent" genes already present in one of the parents.

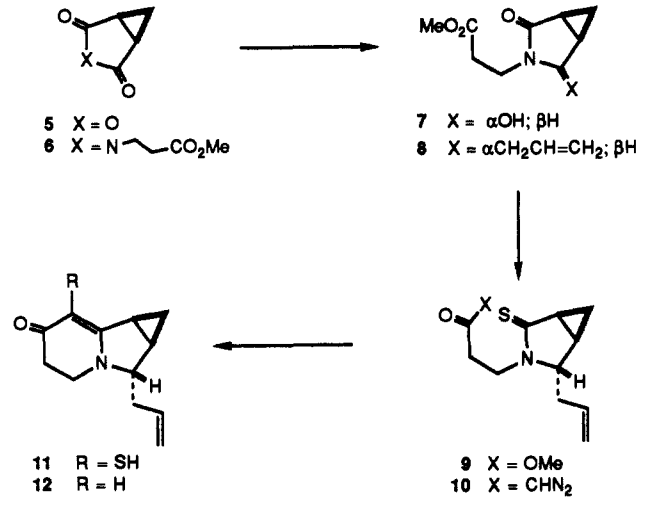
(1) (a) Gomi, S.; Ikeda, D.; Nakamura, H.; Naganawa, H.; Yamashita, F.; Hotta, K.; Kondo, S.; Obami, Y.; Umezawa, H.; and Itaka, Y. *J. Antibiot.* **1984**, *37*, 1491. (b) Yamashita, F.; Hotta, K.; Kurasawa, S.; Okami, Y.; Umezawa, H. *J. Antibiot.* **1985**, *38*, 58.

0002-7863/90/1512-2003$02.50/0 © 1990 American Chemical Society

Scheme I



Scheme II

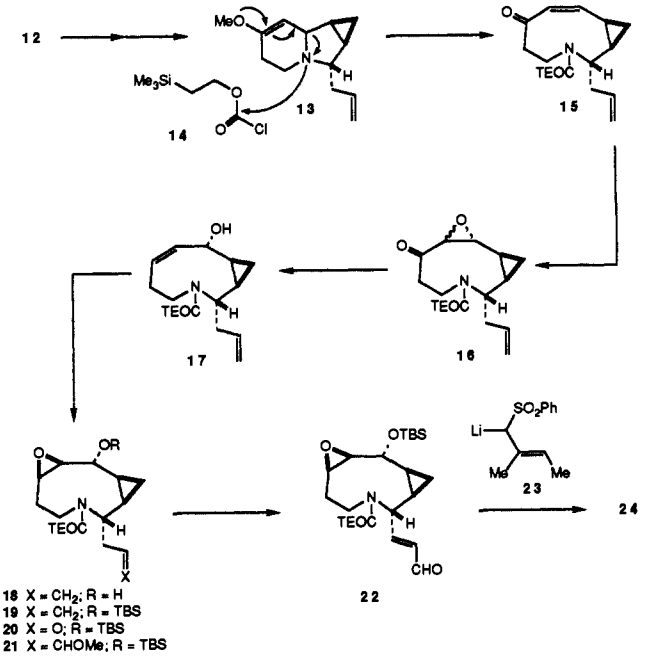


Perhaps not surprising in light of its unconventional lineage, the structure of indolizomycin is unique. Also adding to the challenge (and incentive!) of a total synthesis exercise is the serious instability of indolizomycin (substantial decomposition in several hours under neutral conditions at room temperature). Therefore receipt of a comparison sample from Japan for validating a claim of total synthesis would not be possible. Thus it would be necessary to be particularly rigorous in defining the structures of synthetic intermediates.

The precise source of lability of indolizomycin, while not known, must surely be related to the confluence of the conjugated triene, cyclopropane, epoxy, and carbinolamine functionalities. Our strategy for reducing the problem to manageable proportions envisioned a late introduction of the triene. The carbinolamine linkage would emerge upon unveiling of an amino group from a keto urethane precursor **2**.[2] The latter would arise from an intermediate nine-membered enone of the type **3**. Such a system would have been elaborated from **4** after appropriate attachment of a triene handle (see substituent R), lactam annulation, and cleavage of a carbon–nitrogen junction bond (see dotted lines in **4**). We report herein a total synthesis of *dl*-indolizomycin and

(2) In this approach we were borrowing an element from the tactics employed by Kishi and co-workers in the synthesis of mitomycins. However, the instability of **1** is much more serious than that of the mitomycins. For an analysis of the mitomycin plan, see: Kishi, Y. *J. Nat. Prod.* **1979**, *42*, 549.

Scheme III



the development of new chemistry to service the connection and fragmentation constructs contemplated in Scheme I.

Near quantitative conversion of **5**[3a] to **6**[3b,4a,b] (Scheme II) resulted from reaction of the former with *N*-(triphenylphosphoranylidene)-β-alanine methyl ester. Reduction of **6** with sodium borohydride in methanol afforded a 90% yield of carbinol amide **7**.[4a] Treatment of the corresponding methoxy lactam with $TiCl_4$–allyltrimethylsilane[5] led to **8**[4a] in 88% overall yield from **6**.

Application of our newly developed lactam annulation methodology[6] commenced with conversion of **8** to thiolactam **9**[4a,b] in quantitative yield via Lawesson's reagent.[7] Compound **9** was transformed into **10**[4a] (77% yield) through a three-step sequence: (i) ester hydrolysis (1 N sodium hydroxide–methanol); (ii) mixed anhydride formation (acid; isobutyl chloroformate, *N*-methylmorpholine–THF); and (iii) diazo ketone formation (mixed anhydride; diazomethane–ether).[8] Treatment of **10** with rhodium(II) acetate in benzene under reflux gave a crude product (presumed to be **11** but not characterized), which was directly treated with W-2 Raney Ni in acetone.[9] There was thus obtained the dihydropyridone **12**[4a] in 65% yield.

Attention was now directed toward elaborating the azonine ring system by a novel fragmentation sequence.[10,11] Treatment of **12** with trimethyloxonium fluoroborate generated an iminium salt,

(3) (a) McCoy, L. L. *J. Am. Chem. Soc.* **1958**, *80*, 6568. (b) Garcia, J.; Vilarrasa, J.; Bordas, X.; Banaszek, A. *Tetrahedron Lett.* **1986**, *27*, 639.

(4) The structure of this compound is supported by (a) NMR, infrared, and mass spectral measurements and (b) combustion analysis within 0.45% of theory.

(5) (a) Hubert, J. C.; Wijinberg, J. B. P. A.; Speckamp, W. N. *Tetrahedron* **1975**, *31*, 1437. (b) Chamberlin, A. R.; Chung, J. Y. L. *J. Am. Chem. Soc.* **1983**, *105*, 3653.

(6) For our first report on this process, see: Fang, F. G.; Prato, M.; Kim, G.; Danishefsky, S. J. *Tetrahedron Lett.* **1989**, *30*, 3625. That annulation was in fact developed for purposes of the indolizomycin synthesis.

(7) Pederson, B. S.; Sheibye, S.; Lawesson, S.-O. *Bull. Soc. Chim. Belg.* **1978**, *87*, 229.

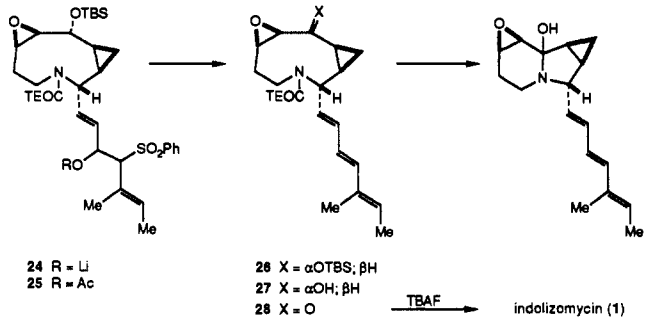
(8) Leary, R.; Larsen, D.; Watanabe, H.; Shaw, E. *Biochemistry* **1977**, *16*, 5857.

(9) The assignment of structure **11** as the presumed intermediate rests on analogy.[6] This compound was not fully characterized.

(10) We view this reaction as an oxa vinylogue of an interesting amine dealkylation reaction described by Hobson and McCluske.[11] To our knowledge, this type of sequence has not hitherto been applied to the synthesis of medium-ring heterocycles.

(11) Hobson, J. D.; McCluske, J. G. *J. Chem. Soc. C* **1967**, 2015. For a recent review of amine dealkylaton, see: Cooley, J. H.; Evain, E. J. *Synthesis* **1989**, 1.

Scheme IV



which was reduced directly with sodium borohydride to give the crude enol ether **13** (Scheme III). Reaction of this material with 2-(trimethylsilyl)ethyl chloroformate (**14**, TEOC-Cl)[12] in benzene at room temperature afforded enone **15**[4a,b] in 30% overall yield from **12**. Nucleophilic epoxidation of **15** (30% H_2O_2; NaOH–methanol) afforded a mixture of epoxy ketones in 93% yield, differing only in the configuration at the oxide bond α to the keto group.[13] Treatment of the mixture with hydrazine[14] (methanol–cat. acetic acid; room temperature) afforded a single allylic alcohol, **17**.[4a,b] Epoxidation (*m*-chloroperbenzoic acid–methylene chloride)[15] afforded **18**[4a,b] which was protected as its TBS ether **19**[4a,b] (43% overall from **16**).

Oxidation of **19** (ozone, methylene chloride–methanol) followed by workup with dimethyl sulfide gave rise to aldehyde **20**,[4a,b] which was subjected to the action of (methoxymethylene)triphenylphosphorane. Photooxygenation of *E*–*Z* mixture **21**[16] followed by reduction of the resultant hydroperoxide with triphenylphosphine afforded enal **22**[4a] (53% overall from **19**). The setting for installation of the triene functionality was now at hand.

Reaction of lithio sulfone **23**[17] with aldehyde **22** (THF; -78 °C) was followed by direct acetylation of the presumed lithium alkoxide **24** (Scheme IV) with acetic anhydride. The mixture of acetoxy sulfone diastereomers **25**, when treated with 5% sodium amalgam, afforded triene **26**[4a] (77% yield from **22**). It was possible to selectively cleave the oxygen-bound silyl group of **26** (1 N periodic acid–THF)[18] to give alcohol **27**,[4a] which upon treatment with 1 equiv of tetra-*n*-propylammonium perruthenate[19] afforded keto urethane **28**[4a] (74% overall from **26**). Upon fluoride ion (TBAF) induced removal of the TEOC group, there was obtained, after two chromatographic purifications,[20] *dl*-indolizomycin in 29% yield. The ^{1}H NMR spectrum (500 MHz) was in agreement with the ^{1}H NMR spectrum (400 MHZ) of the natural product provided by Dr. Ikeda.[21] The structure was further confirmed by high-resolution and low-resolution mass spectroscopy as well as by ultraviolet measurements (λ_{max}^{MeOH} = 267 nm; reported value = 268 nm). The stereochemistry of both the allyl and epoxy groups has further been established by crystallographic determinations on congeners of the systems shown here.[22] Though a direct comparison with an authentic sample was not possible,[23] the claim of a total synthesis of indolizomycin can be asserted with complete confidence.[24]

Acknowledgment. This work was supported by NIH Grant CA 28824. NMR spectra were obtained through the auspices of the Northeast Regional NSF/NMR Facility at Yale University, which was supported by NSF Chemistry Division Grant CHE 7916210. We also thank Gayle Schulte of the Yale University Instrumentation Center for crystallographic determination on analogues of structures shown here.

Supplementary Material Available: Copies of NMR spectra for compounds **1** (natural and synthetic), **6–10**, **12**, **15–22**, and **25–28** (20 pages). Ordering information is given on any current masthead page.

(12) It was important to use freshly prepared TEOC-Cl (from the reaction of 2-(trimethylsilyl)ethanol and 20% phosgene in toluene); cf.: Shute, R. E.; Rich, D. H. *Synthesis* **1987**, 346.
(13) Zimmerman, H. E.; Singer, L.; Thayagarajan, B. S. *J. Am. Chem. Soc.* **1959**, *81*, 108.
(14) Wharton, P. S.; Bohlen, D. H. *J. Org. Chem.* **1961**, *26*, 3615.
(15) Itoh, T.; Jitsukawa, K.; Kaneda, K.; Teranishi, S. *J. Am. Chem. Soc.* **1979**, *101*, 159.
(16) Rousseau, G.; Le Perchec, P.; Conia, J. M. *Synthesis* **1978**, 67.
(17) Kocienski, P. J.; Lythgoe, B.; Waterhouse, I. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1045.
(18) The special feature of the periodic acid may be its optimal pH as opposed to its oxidizing properties.
(19) Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *J. Chem. Soc., Chem. Commun.* **1987**, 1625.
(20) A short silica gel column removed debris arising from the TBAF. Additional contaminants arising from the silica gel were removed by prep-plate chromatography. Decomposition during this purification procedure is responsible for the rather modest yield of **1**.
(21) We thank Dr. Ikeda of the Institute of Microbiotic Chemistry in Tokyo for the ^{1}H NMR (400 MHz) and the ultraviolet spectra of indolizomycin.
(22) In addition to spectral agreement of synthetic and naturally derived indolizomycin, the structures were supported by key crystallographic measurements. X-ray crystal structures were obtained for the FMOC analogue of **15** and the methoxycarbonyl analogue of **18**. Thus the stereochemical relationship of the cyclopropane, epoxide, and allyl functionalities is fully established. The crystallographic data as well as all other supporting data and experimental procedures are found in the Ph.D. thesis of Guncheol Kim, Yale University, 1989, and will be described in due course.
(23) The fully synthetic material exhibited instability similar to that described for the natural product. Its decomposition does not lead to a well-defined product. After several hours at room temperature, under neutral conditions, substantial decomposition has occurred.
(24) We note that the synthesis per se does not establish the stereochemistry of the carbinolamine linkage. This matter has been previously considered.[1] Although the presumption is that the hydroxyl group is β in the antipode shown here, it has not been proven.

Spectroscopic Studies of the Mixed-Valent [Fe(II),Fe(III)] Forms of the Non-Heme Iron Protein Hemerythrin: Iron Coordination Differences Related to Reactivity

James M. McCormick and Edward I. Solomon*

Department of Chemistry, Stanford University
Stanford, California 94305

Received September 25, 1989

Hemerythrin (Hr), the binuclear non-heme iron, oxygen transport protein,[1-3] can exist in the following three oxidation states: [Fe(III),Fe(III)] in oxy and met derivatives,[4-12] [Fe(II),

(1) Okamura, M. Y.; Klotz, I. M. *Inorganic Biochemistry*; Eichorn, G. L., Ed.; Elsevier: New York, 1973; pp 320–343.
(2) Kurtz, D. M., Jr.; Schriver, D. F.; Klotz, I. M. *Coord. Chem. Rev.* **1977**, *24*, 145–178.
(3) Klippenstein, G. L. *Am. Zool.* **1980**, *20*, 39–51.
(4) (a) Okamura, M. Y.; Klotz, I. M.; Johnson, C. E.; Winter, M. R. C.; Williams, R. J. P. *Biochemistry* **1969**, *8*, 1951–1958. (b) York, J. L.; Beardan, A. J. *Biochemistry* **1970**, *9*, 4549–4554. (c) Garbett, K.; Johnson, C. E.; Klotz, I. M.; Okamura, M. Y.; Williams, R. J. P. *Arch. Biochem. Biophys.* **1971**, *142*, 547–583.
(5) Moss, T. H.; Moleski, C.; York, J. L. *Biochemistry* **1971**, *10*, 840–842.
(6) Dawson, J. W.; Gray, H. B.; Hoenig, H. E.; Rossman, G. R.; Schredder, J. M.; Wang, R.-H. *Biochemistry* **1972**, *11*, 461–465.
(7) Clark, P. E.; Webb, J. *Biochemistry* **1981**, *20*, 2628–4632.
(8) Gay, R. R.; Solomon, E. I. *J. Am. Chem. Soc.* **1978**, *111*, 1972–1973.
(9) Reem, R. C.; McCormick, J. M.; Richardson, D. E.; Devlin, F. J.; Stephens, P. J.; Musselman, R. L.; Solomon, E. I. *J. Am. Chem. Soc.* **1989**, *111*, 4688–4704.
(10) (a) Stenkamp, R. E.; Sieker, L. C.; Jensen, L. H. *J. Am. Chem. Soc.* **1984**, *106*, 618–622. (b) Stenkamp, R. E.; Sieker, L. C.; Jensen, L. H.; McCallum, J. D.; Sanders-Loehr, J. *Proc. Natl. Acad. Sci. U.S.A.* **1985**, *82*, 713–716.
(11) (a) Hendrickson, W. A.; Co, M. S.; Smith, J. L.; Hodgson, K. O.; Klippenstein, G. L. *Proc. Natl. Acad. Sci. U.S.A.* **1982**, *79*, 6255–6259. (b) Elam, W. T.; Stern, E. A.; McCallum, J. D.; Sanders-Loehr, J. *J. Am. Chem. Soc.* **1982**, *104*, 6369–6373. (c) Elam, W. T.; Stern, E. A.; McCallum, J. D.; Sanders-Loehr, J. *J. Am. Chem. Soc.* **1983**, *105*, 1919–1923. (d) Zhang, K.; Stern, E. A.; Ellis, F.; Sanders-Loehr, J.; Shiemke, A. K. *Biochemistry* **1988**, *27*, 7470–7479.

0002-7863/90/1512-2005$02.50/0 © 1990 American Chemical Society