Oxidation of Molybdenum Dithiolene Complexes Yields Thiophene Analogues of Urothione and Molybdopterin Form B

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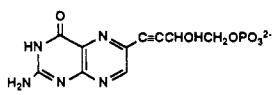
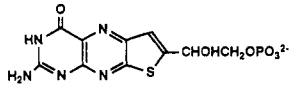
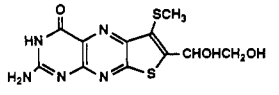
Molybdopterin is the pterin component of the molybdenum cofactor [Mo-co] required by oxomolybdenum enzymes such as xanthine oxidase, sulfite oxidase, and nitrate reductase.[1] Destruction of Mo-co by various oxidative methods yields many different pterin products, and several of these products are unique to Mo-co.[2] The identification of two degradation products and the metabolic product of Mo-co, form A, form B, and urothione,[3] respectively, ultimately led to a proposed structure for molybdopterin.[4] A dithiolene group is one unusual feature of this structure, and its presence has been supported by subsequent chemical and spectroscopic means.[5] The initial report of the



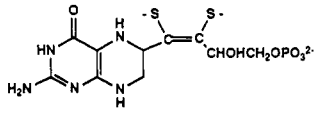
Form A



Form B



Urothione



molybdopterin

molybdopterin structure suggested that the dithiolene group served to bind the Mo atom. Results from recent resonance Raman studies on Mo dithiolene model complexes and on Mo-co from flavin-free dimethyl sulfoxide reductase support this idea.[6]

The alkyne group in form A suggests a strategy for a chemical synthesis of Mo-bound molybdopterin. Dithiolene ligands are known products from reactions of molybdenum tetrasulfide complexes and electron-deficient acetylenes.[7] We[8] and others[9] have studied reactions of metal tetrasulfides with acetylenes substituted by nitrogen heterocycles to investigate whether N-heterocycles are sufficiently electron-deficient to activate the acetylene bond. Acetylenes substituted by both quinoxaline and pterin are successful in these reactions and form dithiolene complexes in good yields. We now report that oxidative degradation of Mo (quinoxalyl)dithiolene complexes produces quinoxalylthiophene molecules structurally related to both urothione and

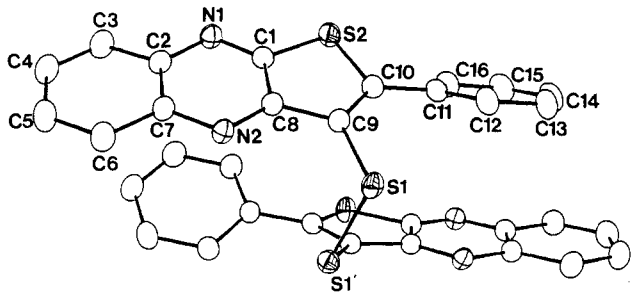
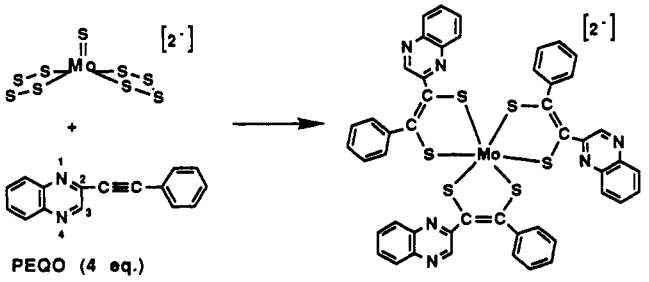


Figure 1. ORTEP drawing of one molecule of compound **2**.

form B. Quinoxalylthiophene formation from these new Mo (quinoxalyl)dithiolene complexes is the first evidence to support the proposed transformation of a dithiolene ligand of Mo-co to the thiophenes urothione and form B.

$[TEA]_2[Mo(S_9)]$ reacts with 2-(phenylethynyl)quinoxaline (PEQO) under conditions[10] similar to those of other literature syntheses for Mo dithiolenes[11] to give $[TEA]_2[Mo(S_2PEQO)_3]$ (**1**) in ca. 60% yield.[12] Like other Mo tris(dithiolene) complexes,[13]



compound **1** exhibits two reversible couples, at +210 mV and −230 mV in acetonitrile vs Ag/AgCl.[14] These potentials indicate that the corresponding Mo(V)- and Mo(VI) tris[(quinoxalyl)dithiolene] complexes should be chemically accessible using mild oxidants. Iodine oxidation of **1** yields both $[TEA][Mo^V(S_2PEQO)_3]$ and $Mo^{VI}(S_2PEQO)_3$ in amounts that depend on the reaction conditions.[15] In addition to oxidized molybdenum

(1) Burgmayer, S. J. N.; Stiefel, E. I. *J. Chem. Educ.* **1985**, *62*, 443.
(2) Johnson, J. L.; Hainline, B. E.; Rajagopalan, K. V. *J. Biol. Chem.* **1980**, *255*, 1783.
(3) Johnson, J. L.; Rajagopalan, K. V. *Proc. Natl. Acad. Sci. U.S.A.* **1982**, *79*, 6856.
(4) Johnson, J. L.; Hainline, B. E.; Rajagopalan, K. V.; Arison, B. H. *J. Biol. Chem.* **1984**, *259*, 5414.
(5) Kramer, S. P.; Johnson, J. L.; Ribeiro, A. R.; Millington, D. S.; Rajagopalan, K. V. *J. Biol. Chem.* **1987**, *262*, 16357.
(6) (a) Subramanian, P.; Burgmayer, S. J. N.; Richards, S.; Szalai, V.; Spiro, T. G. *Inorg. Chem.* **1990**, *29*, 3849. (b) Gruber, S.; Kilpatrick, L.; Bastian, N.; Rajagopalan, K. V.; Spiro, T. G. *J. Am. Chem. Soc.* **1990**, *112*, 8179.
(7) (a) Draganjac, M.; Coucouvanis, D. *J. Am. Chem. Soc.* **1983**, *105*, 139. (b) Coucouvanis, D.; Hadjikyriacou, A.; Toupadakis, A.; Koo, S.-M.; Ileperuma, O.; Draganjac, M.; Salifoglou, A. *Inorg. Chem.* **1991**, *30*, 754. (c) Ansari, M. A.; Chandrasekaran, J.; Sarkar, S. *Inorg. Chim. Acta* **1987**, *133*, 133. (d) Halbert, T.; Pan, W.-H.; Stiefel, E. I. *J. Am. Chem. Soc.* **1983**, *105*, 5476.
(8) (a) Soricelli, C. L.; Szalai, V. A.; Burgmayer, S. J. N. Abstracts of the 4th Chemical Congress of North America and the 202nd National Meeting of the American Chemical Society, New York, 1991.
(9) Pilato, R. S.; Erikson, K. A.; Greaney, M. A.; Stiefel, E. I.; Goswami, S.; Kilpatrick, L.; Spiro, T. G.; Taylor, E. C.; Rheingold, A. L. *J. Am. Chem. Soc.*, in press.

(10) In a typical preparation performed under purified nitrogen, $[TEA]_2[MoS_9]$ (3.06 mmol, 1.97 g) was dissolved in warm (70 °C) acetonitrile. PEQO (12.4 mmol, 2.86 g) was added, and the resulting slurry was refluxed at 80 °C for 5 h. The product precipitates from the reaction solution maintained at room temperature overnight. The blue-black solid was isolated by filtration and washed with three 15-mL portions of acetonitrile and three 15-mL portions of ethyl ether. The dark teal-blue solid can be recrystallized from a ternary solvent mixture of DMF, methylene chloride, and diethyl ether. Yield: 2.56 g (68%). Soricelli, C. L.; Szalai, V. A.; Burgmayer, S. J. N., manuscript to be submitted to *Inorg. Chem.*
(11) (a) Coucouvanis, D.; Hadjikyiacou, A.; Toupadakis, A.; Koo, S.-M.; Ileperuma, O.; Draganjac, M.; Salifoglou, A. *Inorg. Chem.* **1991**, *30*, 754. (b) Draganjac, M.; Simhon, E.; Chan, L. T.; Kanatzidis, M.; Baenziger, N.; Coucouvanis, D. *Inorg. Chem.* **1982**, *21*, 3321.
(12) Mo tris(dithiolene) complexes derived from 3,4-quinoxalinedithiol have been previously reported: Garner, et al. *J. Chem. Soc., Dalton Trans.* **1987**, *297*, 2267. The (3,4-)quinoxaline substitution in these complexes, however, is structurally different from the 6-pterinyldithiolene proposed for Mo-co.
(13) Eisenberg, R. *Prog. Inorg. Chem.* **1970**, *12*, 295.
(14) The rest potential measured is −300 mV, and $\Delta E_{c,a}$ = 60 mV for both Mo^{IV}/Mo^V and Mo^V/Mo^{VI} couples. Under our experimental conditions, the internal reference couple ferrocene/ferrocenium had a reduction potential of +451 mV.
(15) Addition of a methylene chloride solution of iodine to **1** in methylene chloride at −50 °C followed by addition of diethyl ether precipitates $[NEt_4]Mo^V(S_2PEQO)_3$ as an olive-green powder in ca. 50% yield. Performing the iodine oxidation of **1** in acetonitrile at room temperature causes an immediate color change from blue-black to green. $Mo^{VI}(S_2PEQO)_3$ and compound **2** coprecipitate from this solution. Compound **2** can be separated from the Mo(VI) complex by recrystallization from chloroform/acetonitrile, giving **1** as yellow crystals and $Mo(S_2PEQO)_3$ as a grass-green solid. The rest potential measured prior to cyclic voltammetric scans for the Mo(V) complex is −150 mV and for the Mo(VI) complex is +370 mV. Details of other physical properties are in the supplementary material.

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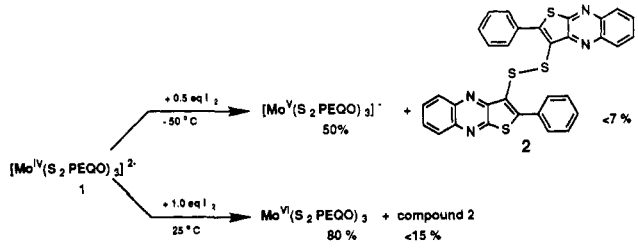
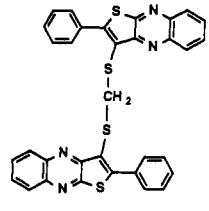
compounds, a third product, compound **2**, was isolated from I_2 oxidation. **2** is yellow and has an infrared spectrum very similar to that of the S_2PEQO dithiolene ligand, but it contains no molybdenum. The ^{1}H NMR spectrum of **2** shows that all protons of S_2PEQO are intact with the exception of H3.[16] This information led us to speculate that compound **2** was a thiophene derivative of the $[S_2PEQO]^{2-}$ ligand, a hypothesis proven correct by an X-ray crystal structure analysis.[17]



A view of the molecular structure of 2-phenylthieno[2,3-*b*]-quinoxaline **2** in Figure 1 reveals the fate of S_2PEQO ligand oxidation. A thiophene ring fused to quinoxaline is formed from cyclization of the β-thiolate at quinoxaline C3. Oxidation of the α-thiolate causes formation of a disulfide bond to a second quinoxalylthiophene moiety. A crystallographic C_2 axis passes through the midpoint of the disulfide bond and relates one quinoxalylthiophene plane to its molecular partner. Bond distances and angles within this molecule are unremarkable since they reproduce values previously reported.[18]

Compound **2** is obtained from **1** using a variety of oxidants (I_2, Ce^{IV}, O_2, and S_8) as well as from solutions of the Mo(V) and Mo(VI) tris(dithiolene) complexes after long exposure to the atmosphere. In fact, we have not yet accomplished an oxidation of $[TEA]_2[Mo(S_2PEQO)_3]$ that does not yield some of compound **2**. Our continued study of these reactions seeks to determine if formation of **2** proceeds through a particular Mo oxidation state and if quinoxaline N-coordination aids a dithiolene cis–trans isomerization that must precede thiophene ring closure.

A second degradation product, compound **3**, has been obtained in small amounts from recrystallization attempts using impure Mo (quinoxalyl)dithiolene complexes. Our preliminary[19] report on this material presents its structure determinated from ^{1}H and ^{13}C NMR and X-ray analysis. As depicted schematically, **3** is also a thiophene derivative of quinoxaline wherein the exocyclic sulfur is bridged to a second (3-thiothieno)quinoxaline by a methylene group.



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Decomposition products **2** and **3** isolated from Mo complexes having S_2PEQO dithiolene ligands demonstrate for the first time that thiophene cyclization is a likely decomposition result from such dithiolene complexes. The isolation of both the disulfide-bridged and the S-alkylated products indicates multiple decomposition pathways as has been observed for Mo-co decomposition leading to two fused pterin thiophene compounds, urothione and form B. These results provide the needed experimental support to link the known structures of urothione and form B to the proposed pterinyldithiolene unit in Mo-co.

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Registry No. 1, 137516-72-4; **2**, 137516-68-8; **3**, 137516-69-9; PEQO, 75163-23-4; $[TEA]_2[Mo(S_9)]$, 76581-48-1; $[TEA][Mo^V(S_2PEQO)_3]$, 137516-74-6; $Mo^{VI}(S_2PEQO)_3$, 137516-75-7.

Supplementary Material Available: Listings of analytical and physical properties, crystallographic collection and solution data, atom positions, thermal parameters, and bond distances and angles for **2** (5 pages); tables of observed and calculated structure factors for **2** (19 pages). Ordering information is given on any current masthead page.

(16) ^{1}H NMR in $CDCl_3$ (δ, ppm) 8.06 (m, 2 H) and 7.78 (m, 2 H) (quinoxaline); 7.36 (m, 2 H), 7.00 (m, 2 H), and 6.92 (m, 1 H) (phenyl).

(17) Crystals of compound **2** possess an orthorhombic cell in space group *Pbcn* (Z = 4) with parameters a = 14.93 (7) Å, b = 12.50 (8) Å, c = 14.07 (7) Å for a volume of 2627.4 Å^3. Using 1893 data where $I > 3\sigma(I)$ for 182 variables, refinement produced final agreement factors R_1 = 0.037 and R_2 = 0.052. Details are in the supplementary material.

(18) (a) Gronowitz, S. *The Chemistry of Heterocyclic Compounds*; Taylor, E. C., Ed.; Wiley-Interscience: New York, 1991; Vol. 44, Part 4, pp 31–37. (b) Barlin, G. *The Chemistry of Heterocyclic Compounds*; Taylor, E. C., Ed.; Wiley-Interscience: New York, 1982; Vol. 41, p 8.

(19) Formation of compound **3** is currently under study to duplicate its production from deliberate decomposition of $Mo(S_2PEQO)_3$ complexes. Physical details (^{1}H and ^{13}C NMR data, UV spectral data, and preliminary X-ray parameters) are available in the supplementary material.

Novel Enediynes Equipped with Triggering and Detection Devices. Isolation of *cis*-Diol Models of the Dynemicin A Cascade

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The discovery of the enediyne anticancer antibiotics[1] (e.g., neocarzinostatin chromophore,[2] calicheamicin γ_1^I,[3] esperamicin A,[4] dynemicin A[5]) with their novel molecular structures, fascinating mode of action, and important biological activity sparked a great deal of excitement and research in the areas of chemistry, biology, and medicine.[1] Reports from these laboratories included the first designed mimics[6] of these enediyne natural products and the design and synthesis of a series of dynemicin A models equipped with acid, base, and photosensitive triggering devices[7,8]

(1) For a review, see: Nicolaou, K. C.; Dai, W.-M. *Angew. Chem., Int. Ed. Engl.*, in press.

(2) Edo, K.; Mizugaki, M.; Koide, Y.; Seto, H.; Furihata, K.; Otake, N.; Ishida, N. *Tetrahedron Lett.* **1985**, *26*, 331.

(3) Lee, M. D.; Dunne, T. S.; Siegel, M. M.; Chang, C. C.; Morton, G. O.; Borders, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 3464. Lee, M. D.; Dunne, T. S.; Chang, C. C.; Ellestad, G. A.; Siegel, M. M.; Morton, G. O.; McGahren, W. J.; Borders, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 3466.

(4) Golik, J.; Clardy, J.; Dubay, G.; Groenewold, G.; Kawaguchi, H.; Konishi, M.; Krishnan, B.; Ohkuma, H.; Saitoh, K.; Doyle, T. W. *J. Am. Chem. Soc.* **1987**, *109*, 3461. Golik, J.; Dubay, G.; Groenewold, G.; Kawaguchi, H.; Konishi, M.; Krishnan, B.; Ohkuma, H.; Saitoh, K.; Doyle, T. W. *J. Am. Chem. Soc.* **1987**, *109*, 3462.

(5) Konishi, M.; Ohkuma, H.; Matsumoto, K.; Tsuno, T.; Kamei, H.; Miyaki, T.; Oki, T.; Kawaguchi, H.; VanDuyne, G. D.; Clardy, J. *J. Antibiot.* **1989**, *42*, 1449. Konishi, M.; Ohkuma, H.; Tsuno, Y.; VanDuyne, G. D.; Clardy, J. *J. Am. Chem. Soc.* **1990**, *112*, 3715.

(6) Nicolaou, K. C.; Zuccarello, G.; Ogawa, Y.; Schweiger, E. J.; Kumazawa, T. *J. Am. Chem. Soc.* **1988**, *110*, 4866. Nicolaou, K. C.; Ogawa, Y.; Zuccarello, G.; Kataoka, H. *J. Am. Chem. Soc.* **1988**, *110*, 7247.

(7) (a) Nicolaou, K. C.; Hwang, C.-K.; Smith, A. L.; Wendeborn, S. V. *J. Am. Chem. Soc.* **1990**, *112*, 7416. (b) Nicolaou, K. C.; Smith, A. L.; Wendeborn, S. V.; Hwang, C.-K. *J. Am. Chem. Soc.* **1991**, *113*, 3106. For related synthetic studies in the dynemicin A area, see: (c) Porco, J. A., Jr.; Schoenen, F. J.; Stout, T. J.; Clardy, J.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 7410. (d) Wender, P. A.; Zercher, C. K. *J. Am. Chem. Soc.* **1991**, *113*, 2311. (e) Magnus, P.; Fortt, S. M. *J. Chem. Soc., Chem. Commun.* **1991**, 544. (f) Nishikawa, T.; Isobe, M.; Goto, T. *Synlett* **1991**, 393. (g) Nishikawa, T.; Ino, A.; Isobe, M.; Goto, T. *Chem. Lett.* **1991**, 1271.

0002-7863/91/1513-9878$02.50/0