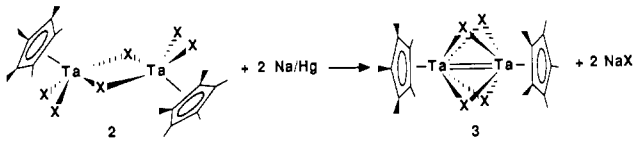

2 3 (3)

N_2O, and product characterizations are in progress. The high reactivity of **2**, as also noted for **3**,[5,7,8] suggests that it should prove to be a useful synthon for the preparation of other Ta(IV) and, through oxidative addition, Ta(V) organometallics.

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Supplementary Material Available: Tables of crystallographic data collection parameters, atomic coordinates, bond lengths (non-hydrogen atom), and bond angles (non-hydrogen atom) (4 pages). Ordering information is given on any current masthead page.

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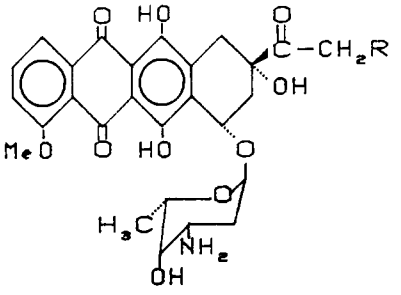
Structural Model for the Binding of Iron by Anthracycline Drugs

Sir:

The anthracycline drugs daunorubicin (R = H) and doxorubicin (R = OH) (structure **1**) have been in clinical use for nearly 2 decades in the treatment of various human cancers.[1-4] Recently,



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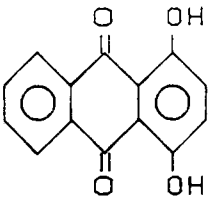
these drugs have also been found to inhibit the infectivity and replication of human immunodeficiency virus (HIV) in vitro and may find applicability as antiviral agents in the treatment of acquired immune deficiency syndrome (AIDS) and AIDS-related complex (ARC).[5-7] The popularity of these drugs in cancer chemotherapy stems in part from their potency against a wide range of maligancies, but is tempered by toxic side effects, which include cardiotoxicity.[4] Despite the widespread use of the drugs and many years of intensive investigation, little information is available concerning their in vivo cytotoxicity. One possibility involves coordination of iron to form a catalyst for the production of reactive oxygen species including hydroxyl radicals,[1,8-13] which could account for all of the known cytotoxic effects of the drugs (including damaging DNA[1,14-18] and cell membranes[1,19-21]) as well as account for their cardiotoxicity.

The drugs are recognized as good iron chelators,[22-24] capable of acquiring iron from ferritin[25] or from transferrin in acidic intracellular compartments.[26] The hydroxyquinone groups found in both drugs have been shown by resonance Raman spectroscopic experiments to play a role in binding metals,[27-29] yet no complex of this type has been structurally characterized. We wish to report the synthesis of complexes of daunorubicin and doxorubicin with Fe(salen),[30] their characterization in solution using spectroscopic techniques, and the structural characterization by single-crystal X-ray diffraction of a model of these complexes employing 1,4-dihydroxy-9,10-anthraquinone, or quinizarin (Qz) (structure **2**),



quinizarin (**2**)

to model the interaction of the drugs with Fe(salen). The complex, $[Fe(salen)]_2Qz$, is the first structurally characterized complex with direct structural relevance to iron binding by anthracycline drugs.

The combination of anaerobic solutions of daunorubicin hydrochloride or doxorubicin hydrochloride in dry acetonitrile containing 1 mM Et_3N with a solution of Fe(salen)OAc in the same solvent mixture, gives rise to spectra like that shown in Figure 1. In addition to the strong absorbance near 480 nm present in the solution of the drug itself, new bands at 593 and 643 nm are observed. These bands are assigned to ligand-to-metal charge-transfer (LMCT) transitions on the basis of resonance Raman data (using a 633-nm excitation) that reveal several peaks in the

(1) Myers, C.; Gianni, L.; Zweier, J.; Muindi, J.; Sinha, B. K.; Eliot, H. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **1986**, *45*, 2792–2797.
(2) Arcamone, F. *Med. Res. Rev.* **1984**, *4*, 153–188.
(3) Naff, M. B.; Plowman, J.; Narayanan, V. L. In *Anthracycline Antibiotics*; El Khadem, H. S., Ed.; Academic Press: New York, 1982; pp 1–57.
(4) Young, R. C.; Ozols, R. F.; Myers, C. E. *Clin. Rev.* **1981**, *305*, 139–153.
(5) Nakashima, H.; Yamamoto, N. *J. Antibiot.* **1987**, *40*, 396–399.
(6) Wondrak, E. M.; Löwer, J.; Kurth, R. *J. Antimicrob. Chemother.* **1988**, *21*, 151–161.
(7) De Clercq, E. *Arzneim.-Forsch.* **1985**, *35*, 1007–1008.
(8) Lown, J. W. *Adv. Free Radical Biol. Med.* **1985**, *1*, 225–264.
(9) Gianni, L.; Zweier, J. L.; Levy, A.; Myers, C. E. *J. Biol. Chem.* **1985**, *260*, 6820–6826.
(10) Zweier, J. L.; Gianni, L.; Muindi, J.; Myers, C. E. *Biochim. Biophys. Acta* **1986**, *884*, 326–336.
(11) Zweier, J. L. *J. Biol. Chem.* **1984**, *259*, 6056–6058.
(12) Doroshow, J. H. *Cancer Res.* **1983**, *43*, 4543–4551.
(13) Doroshow, J. H. *Biochem. Biophys. Res. Commun.* **1986**, *135*, 330–335.
(14) Sugioka, K.; Nakano, H.; Nakano, M.; Tero-Kubota, S.; Ikegami, Y. *Biochim. Biophys. Acta* **1983**, *753*, 411–421.
(15) Muindi, J. R. F.; Sinha, B. K.; Gianni, L.; Myers, C. E. *FEBS Lett.* **1984**, *172*, 226–230.
(16) Eliot, H.; Gianni, L.; Myers, C. *Biochemistry* **1984**, *23*, 928–936.
(17) Gutteridge, J. M. C.; Toeg, D. *FEBS Lett.* **1982**, *149*, 228–232.
(18) Gutteridge, J. M. C.; Quinlan, G. J. *Biochem. Pharmacol.* **1985**, *34*, 4099–4103.
(19) Muindi, J.; Sinha, B. K.; Gianni, L.; Myers, C. *Mol. Pharmacol.* **1985**, *27*, 356–365.
(20) Goormaghtigh, E.; Ruysschaert, J. M. *Biochim. Biophys. Acta* **1984**, *779*, 271–288.
(21) Praet, M.; Pollakis, G.; Goormaghtigh, E.; Ruysschaert, J. M. *Cancer Lett.* **1984**, *25*, 89–96.
(22) Myers, C. E.; Gianni, L.; Simone, C. B.; Klecker, R.; Greene, R. *Biochemistry* **1982**, *21*, 1707–1713.
(23) Kiraly, R.; Martin, R. B. *Inorg. Chim. Acta* **1982**, *67*, 13–18.
(24) May, P. M.; Williams, G. K.; Williams, D. R. *Inorg. Chim. Acta* **1980**, *46*, 221–228.
(25) Demant, E. J. F. *FEBS Lett.* **1984**, *176*, 97–100.
(26) Demant, E. J. F.; Nørskov-Lauritsen, N. *FEBS Lett.* **1986**, *196*, 321–324.
(27) Dutta, P. K.; Hutt, J. A. *Biochemistry* **1986**, *25*, 691–695.
(28) Beraldo, H.; Garnier-Suillerot, A.; Tosi, L.; Lavelle, F. *Biochemistry* **1985**, *24*, 284–289.
(29) Beraldo, H.; Garnier-Suillerot, A.; Tosi, L. *Inorg. Chem.* **1983**, *22*, 4117–4124.
(30) salen = bis(salicylaldehyde) ethylenediimine.

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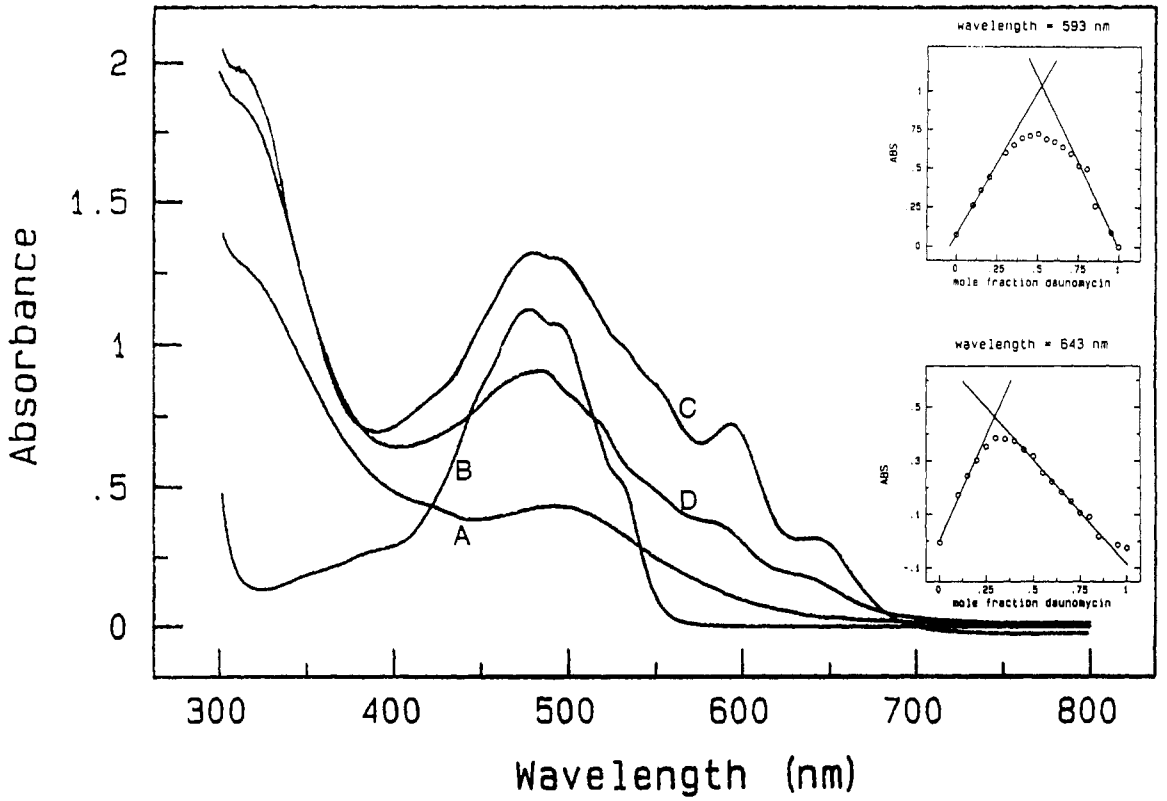

Figure 1. Electronic absorption spectroscopic data: (A) 1.0 mM Fe(salen)OAc in CH_3CN using a 0.1-cm path length cell; (B) 0.90 mM daunorubicin hydrochloride in CH_3CN using a 0.1 cm path length cell; (C) 1:1 daunorubicin hydrochloride/Fe(salen)OAc mixture (0.1 mM in each) in 1 mM Et_3N/CH_3CN solution using a 1.0-cm path length cell; (D) 1.0 mM $[Fe(salen)]_2Qz$ in CH_2Cl_2 using a 0.1-cm path length cell. The insets are the Job plots generated from absorbance data at 593 (top) and 643 nm (bottom) for mixtures of Fe(salen)OAc and daunomycin hydrochloride, holding the total concentration of these two reagents to 0.20 mM in 1 mM Et_3N/CH_3CN solution.

1200–1300-cm^{-1} region (C–O stretching vibrations) associated with these absorptions[31-33] and in analogy with the charge-transfer spectra of iron phenolate and catecholate complexes.[32-34] The use of Job's method[35] reveals that the band at 593 nm is associated with a 1:1 complex of the drugs with Fe(salen)OAc and that the 643-nm band corresponds to a 1:2 stoichiometry that is suggestive of a bridging role for the drugs involving binding of Fe(salen) by both hydroxyquinone groups. In contrast, solutions of simple ferric complexes of the drugs reveal only one such transition at ca. 600 nm.[10]

Quinizarin is a molecule that has been used to model the chelation of metals by the anthracycline drugs.[23] To explore the nature of the complexes formed between the drugs and Fe(salen), we also employed Qz to model the dihydroxyquinone group found in the drugs. The preparation of $[Fe(salen)]_2Qz$ was carried out in flame-dried glassware under N_2 by using dry, anaerobic solvents and standard Schlenk techniques. A solution of Qz (1.45 g, 6.0 mmol) in room-temperature ethyl acetate was added to a solution of Fe(salen)OAc (1.0 g, 2.6 mmol) in refluxing acetonitrile. When the mixture was cooled overnight, a black microcrystalline product was obtained. The product was ground to a fine powder and dried in vacuo over P_4O_{10}.[36] The electronic absorption spectrum obtained for CH_2Cl_2 solutions of this compound strongly resemble those obtained from mixtures of Fe(salen)OAc and the drugs (Figure 1). Crystals suitable for X-ray diffraction studies were obtained via vapor-phase diffusion of benzene into dichloromethane solutions of the complex.

The structure of $[Fe(salen)]_2Qz$ is summarized by Figure 2.[37] Both iron centers display distorted octahedral geometry with the best equatorial planes defined by the oxygen atoms of the quinizarin and an oxygen and a nitrogen atom from a salen. Coordination to the quinizarin causes the salen ligands to adopt a nonplanar cis-β configuration.[38] The idealized molecular symmetry is C_s, with the iron centers displaying opposite handedness. For both centers, the shortest bonds are to the salen oxygen atoms (average = 1.926 (5) Å), while the longest bonds are to the nitrogen atoms (average = 2.133 (6) Å). The bonds to the quinizarin oxygen atoms have an intermediate value (average = 2.033 (5) Å). Angles about Fe(1) between cis ligands range from 74.2 (2) to 105.0 (2)°, while angles involving trans ligand atoms range from 159.7 (2) to 165.8 (2)°. The corresponding values for Fe(2) are 75.6 (2)–112.4 (2)° and 157.0 (2)–164.8 (2)°.

While the geometry about the iron atoms is very similar for both iron centers, their dispositions relative to the quinizarin group are different. Fe(2) is in the plane of the quinizarin group, where

(31) Maroney, M. J. Unpublished results.
(32) Pyrz, J. W.; Roe, A. L.; Stern, L. J.; Que, L., Jr. *J. Am. Chem. Soc.* **1985**, *107*, 614–620.
(33) Que, L., Jr. *Coord. Chem. Rev.* **1983**, *50*, 73–108.
(34) Heistand, R. H.; Lauffer, R. B.; Fikrig, E.; Que, L., Jr. *J. Am. Chem. Soc.* **1982**, *104*, 2789–2796.
(35) Connors, K. A. In *Binding Constants*; John Wiley and Sons: New York, 1987; pp 24–28.
(36) Anal. Calcd for $[Fe(salen)]_2Qz$: C, 62.61; H, 3.88; N, 6.35. Found: C, 61.64; H, 4.20; N, 6.16.
(37) Data were obtained for a crystal of dimensions 0.25 × 0.48 × 0.60 mm. Crystal data: monoclinic space group $P2_1/n$ (alternate setting of $P2_1/c$-No. 14), a = 17.626 (4) Å, b = 11.295 (3) Å, c = 21.563 (5) Å, β = 97.52 (2)°, Z = 4, and $\mu_{Mo\,K\alpha}$ = 8.7 cm^{-1}. A total of 4848 independent reflections ($+h,+k,\pm l$) were measured on an Enraf-Nonius CAD4 diffractometer (23 ± 2°, $\theta - 2\theta$ scan mode, graphite monochromated Mo K$\bar{\alpha}$ radiation, λ = 0.71073 Å, $2\theta_{max}$ = 43°). An empirical absorption correction based on ψ scans was applied (from 0.87 to 1.00 on I). The structure was solved by direct methods and was refined by full-matrix least-squares techniques (function minimized = $\sum w(|F_o| - |F_c|)^2$, $w^{1/2} = 2F_o(Lp)/\sigma_I$). The non-hydrogen atoms of the complex were refined anisotropically. Hydrogen atoms were included in idealized positions as fixed isotropic scatterers. Residual electron density was interpreted as a disordered dichloromethane of solvation. The four independent non-hydrogen atoms of this moiety (two positions for one of the Cl atoms in half-occupancy) were treated as isotropic scatterers. The final agreement factors were R = 0.062 and R_w = 0.088 for the 3581 reflections with $I > 3\sigma_I$. All computations were done on a MicroVAX II computer using the Enraf-Nonius SDP system of programs.
(38) Sargeson, A. M.; Searle, G. H. *Inorg. Chem.* **1965**, *4*, 45–52.

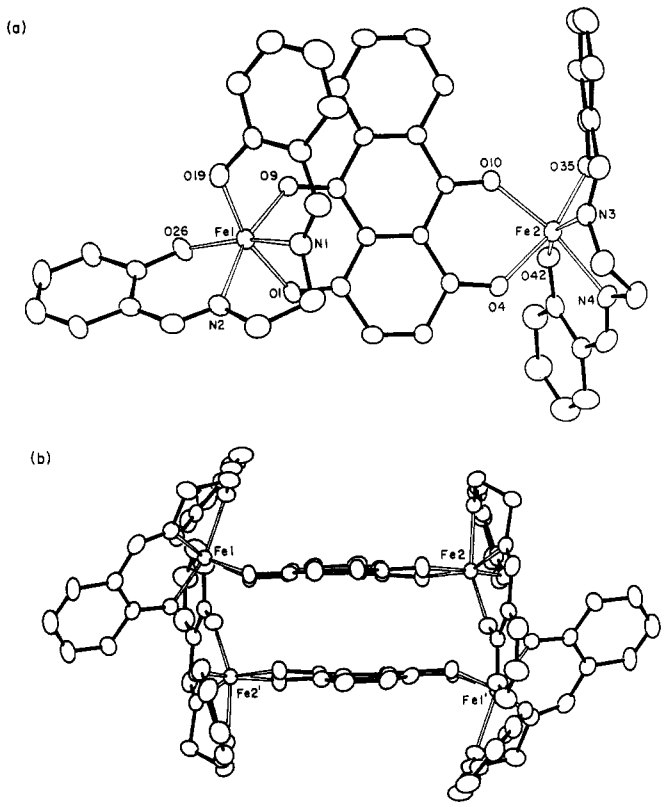

Figure 2. ORTEP plots of $[Fe(salen)]_2Qz$ with thermal ellipsoids at the 30% probability level with hydrogen atoms omitted for clarity: (a) plot showing the geometry of the complex; (b) plot showing the stacking interaction between the quinizarin moieties of inversion-related pairs of complexes.

the atoms of the six-membered chelate ring with quinizarin are coplanar to within ±0.048 (6) Å. However, Fe(1) is displaced 0.627 (1) Å from the plane defined by the other five atoms (±0.011 (6) Å) of its corresponding six-membered chelate ring in a direction toward N(1). This displacement can be viewed as a result of rotating the equatorial plane defined by atoms O(1), O(9), O(19), and N(2) by ca. 24° about an axis containing O(1) and O(9).

The difference between the disposition of the iron centers appears to be due to the fact that inversion-related pairs of molecules exist in the solid state as stacked dimers. The quinizarin planes of the dimers, required by symmetry to be parallel, are separated by a distance of slightly less than 3.4 Å, where the overlap involves the non-oxygen bearing ends of the fused ring systems. The equatorial plane of each Fe(1) atom is tipped away from the inversion related molecule. Even in the presence of this distortion, there are van der Waals contacts between the halves of the dimer, which involve atoms of nonequivalent salen ligands. Thus, the stacking interaction appears to preclude equivalence of the two iron centers. The association of two quinizarin ligands may be similar to the self-association of molecules of daunorubicin that has previously been observed for solutions of this drug.[39-42] The π-complex described is apparently strong enough to drive Fe(1) out of plane and may be responsible for the observation of two LMCT transitions in the electronic absorption spectrum of the compound if it persists in solution.

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(39) Martin, S. R. *Biopolymers* **1980**, *19*, 713-721.
(40) Chaires, J. B.; Dattagupta, N.; Crothers, D. M. *Biochemistry* **1982**, *21*, 3927-3932.
(41) Barthalemy-Clavey, V.; Maurizot, J. C.; Dimicoli, J. L.; Sicand, P. *FEBS Lett.* **1974**, *46*, 5-10.
(42) Eksborg, S. *J. Pharm. Sci.* **1978**, *67*, 782-785.

Supplementary Material Available: Atomic coordinates for non-hydrogen atoms (Table S1), anisotropic thermal parameters (Table S2), hydrogen atom parameters (Table S3), and bond lengths and bond angles (Table S4) (13 pages); a table of observed and calculated structure factor amplitudes (25 pages). Ordering information is given on any current masthead page.

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Synthesis and Characterization of a Trinuclear Polyoxomolybdate Containing a Reactive $[MoO_3]$ Unit, $[(n\text{-}C_4H_9)_4N]_2[Mo_3O_7(CH_3C(CH_2O)_3)_2]$, and Its Conversion to the Methoxy Derivative $[(n\text{-}C_4H_9)_4N][Mo_3O_6(OCH_3)(CH_3C(CH_2O)_3)_2]$

Sir:

The effectiveness of early-transition-metal oxides as heterogeneous catalysts,[1-4] together with the difficulty of characterizing surface-bound intermediates for these systems, has prompted a number of investigations of the coordination chemistry of analogous polyoxoanion derivatives with organic substrate molecules.[5,6] Structurally characterized examples of polyoxomolybdate complexes incorporating simple organic substrate units include $[Mo_8O_{26}(HCO_2)_2]^{6-}$,[7] $[Mo_8O_{24}(OCH_3)_4]^{4-}$,[8] $[Mo_4O_{14}(OH)CH_2]^{3-}$,[9] and $[Mo_4O_8(OC_2H_5)_2(CH_3C(CH_2O)_3)_2]$,[10] while detailed studies of polyoxoanion interconversions have been reported for systems based on $[Nb_2W_4O_{19}H]^{3-}$[11] and $[MoO_2(OR)(P_3O_9)]^{2-}$.[12] In common with the vast majority of polyoxometalate structures,[13] the metal centers of these coordination complexes exhibit ligation to a number of bridging oxygen donors and either to two terminal oxo groups or to a single terminal oxo unit, to give the $[MO_2]^{2+}$ or $[MO]^{4+}$ core, respectively. Although molybdenum bound to three terminal oxo groups ($[MoO_3]$) and weakly bound to the bulk by additional bridging oxo interactions provides a reasonable

(1) Cheng, W.-H.; Chowdhry, U.; Ferretti, A.; Firment, L. E.; Groff, R. P.; Machiels, C. J.; McCarron, E. M.; Ohuchi, F.; Staley, R. H.; Sleight, A. W. In *Heterogeneous Catalysis, Proceedings of the 2nd Symposium of IUCCP of Department of Chemistry, Texas A&M*; Shapiro, B. L., Ed.; Texas A&M University Press: College Station, TX, 1984; p 165.
(2) Machiels, C. J.; Chowdry, U.; Staley, R. H.; Ohuchi, F.; Sleight, A. W. In *Catalytic Conversions of Synthetic Gas and Alcohols to Chemicals*; Herman, R. G., Ed.; Plenum Press: New York, 1984.
(3) Graselli, R. K.; Burrington, J. D. *Adv. Catal.* **1981**, *30*, 133.
(4) Liu, H.-F.; Liu, R.-S.; Liew, K. Y.; Johnson, R. E.; Lunsford, J. H. *J. Am. Chem. Soc.* **1984**, *106*, 4117.
(5) Day, V. W.; Klemperer, W. G. *Science* **1985**, *228*, 533.
(6) Pope, M. T. *Heteropoly and Isopoly Oxometalates*; Springer-Verlag: New York, 1983.
(7) Adams, R. D.; Klemperer, W. G.; Liu, R.-S. *J. Chem. Soc., Chem. Commun.* **1979**, 256.
(8) McCarron, E. M., III; Harlow, R. L. *J. Am. Chem. Soc.* **1983**, *105*, 6179.
(9) Day, V. W.; Fredrich, M. F.; Klemperer, W. G.; Liu, R.-S. *J. Am. Chem. Soc.* **1979**, *101*, 491.
(10) Wilson, A. J.; Robinson, W. T.; Wilkins, C. J. *Acta Crystallogr.* **1983**, *C39*, 54.
(11) Day, V. W.; Klemperer, W. G.; Schwartz, C. *J. Am. Chem. Soc.* **1987**, *109*, 6030.
(12) Klemperer, W. G.; Mainz, V. V.; Wang, R.-C.; Yang, S. *Abstracts of Papers*, Third Chemical Congress of the North American Continent, Toronto, June 1988; American Chemical Society: Washington, DC, 1988; INOR 265. Day, V. W.; Klemperer, W. G.; Schwartz, C.; Wang, R.-C. In *Surface Organometallic Chemistry: The Molecular Approach to Surface Science and Catalysis*; Basset, J. M., Gates, B., Eds.; Reidel: Dordrecht, Holland, in press.
(13) Schroder, F. A. *Acta Crystallogr.* **1975**, *B31*, 2294.

0020-1669/89/1328-0175$01.50/0