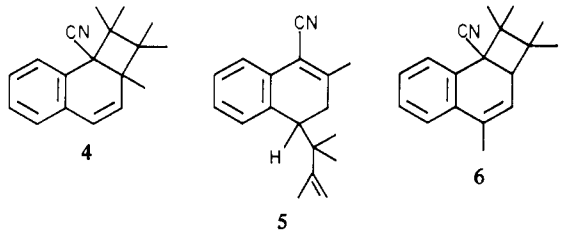
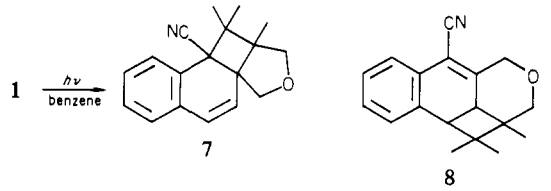


4 5 6

8, in the approximate ratio 20:1. The ratio was determined by GLC, and the compounds were separated by column chromatography.[14]



7 8

The structure of photoproduct **7**, mp 141.5–142.5 °C, was established by single-crystal X-ray diffraction. Crystal data: $C_{18}H_{19}NO$, monoclinic, space group $P2_1/c$, C_{2h}^5 (No. 14), a = 12.088 (3) Å, b = 8.162 (2) Å, c = 15.152 (3) Å, Z = 4. A total of 2378 independent reflections in $2\theta_{Mo K\alpha} \leq 55°$ was collected on a Syntex $P2_1$ automated diffractometer using the θ–2θ scan mode and graphite-monochromated Mo radiation. Initial coordinates for the nonhydrogen atoms were obtained by direct methods (MULTAN). Full-matrix least-squares refinement of the structural parameters and a scale factor, using anisotropic temperature factors for the nonhydrogen atoms and isotropic temperature factors for the hydrogen atoms, led to R_1 = 0.064 and R_2 = 0.060.[15] Bond lengths and bond angles within the structure are normal. The structure is shown in Figure 2.

The structure of **8**, mp 119–120 °C, was assigned from its spectra.[16] Important features are as follows: IR 2217 cm^{-1} (conjugated CN); ^1H NMR (FT, 80 MHz, $CDCl_3$) δ 7.0 (m, aromatics), 3.85, 2.95 (AB quartets, J = 9.8 Hz, area 2, bridgehead methines), centered at δ 3.73 (J = 10.0 Hz, area 2, allylic CH_2), centered at δ 3.15 (J = 5.0 Hz, area 2, CH_2). Methyl groups appeared at δ 0, 0.59, and 1.1 (s, each area 3).

Quantum yields of formation of the cycloadducts **4**, **6**, and **7** were measured.[17] Limiting quantum yields (infinite TME concentration) were 0.020 for **4** and 0.51 for **6**. Thus, the methyl group in 2-methyl-1-naphtonitrile is exerting a significant steric effect on collapse of exciplex to product. The quantum yield for formation of **7** was 0.68. Since **1** is a 2-alkylnaphthonitrile, the much higher quantum yield of **7** vs. **4** shows that the order introduced in the reactant by the three-atom chain significantly favors exciplex collapse to product.

Exciplex decay and collapse to product should have the same activation energy,[5a] and indeed Caldwell has found that both are activated processes in several systems.[18] Clearly, the three-atom link in **1** must be influencing the choice which the system makes on crossing from the excited- to the ground-state surface at the pericyclic minimum.[19,20]

(14) The technique of W. C. Still, M. Kahn, and A. Mitra, *J. Org. Chem.*, **43**, 2923 (1978), was employed.

(15) $R_1 = \sum||F_o| - |F_c||/\sum|F_o|$, $R_2 = \{\sum w(|F_o| - |F_c|)^2/\sum wF_o^2\}^{1/2}$.

(16) Mass spectra and ^{13}C NMR spectra of **4**–**8** were also consistent with the assigned structures, and satisfactory analyses were obtained.

(17) Irradiation was at 313 nm, using a monochromator, beam splitter, and ferrioxalate actinometry. Product assay was by GLC (1.2 m × 4 mm of 3% OV-1 on 80/100 mesh WHP), using phenanthrene or 4,4′-dichlorobenzophenone as internal standard.

(18) R. A. Caldwell and D. Creed, *Acc. Chem. Res.*, **13**, 45 (1980), and references therein.

(19) Triplet formation does not account for the inefficiency in collapse of 2-methyl-1-naphthonitrile–TME exciplex. No triplets were detected from this system or from **1**, using biacetyl phosphorescence as monitor.[20] Also, the efficiency of exciplex fluorescence is 0.1 or smaller.

(20) F. Wilkinson and J. T. Dubois, *J. Chem. Phys.*, **39**, 377 (1963).

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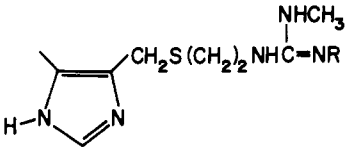
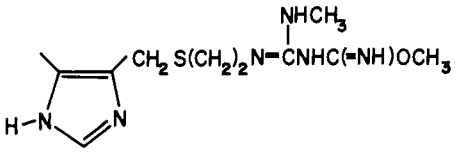
Copper(II) Complexes of the Antiulcer Drug Cimetidine

Sir:

One of the most potent histamine H_2 receptor antagonists is cimetidine (**1**), marketed under the trade name Tagamet,[1] which is used for the treatment of peptic ulcer.[2-4] The drug is taken



1 R = CN
2 R = $CONH_2$



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orally and reaches the H_2 receptors via the blood stream. Since micromolar levels of loosely bound Cu(II) are present in blood serum,[5] the drug may exist as a Cu(II) chelate under in vivo conditions. This realization along with a report that Cu(II) dramatically increases specific cimetidine binding to rat brain histamine H_2 receptors[6] and the fact that certain Cu(II) coordination compounds show antiulcer activity prompted us to explore the copper binding properties of **1**. We have found that the drug readily reacts with the cation to produce blue and green Cu(II) complexes. While the green compound contains the unaltered drug (**1**), the blue complexes possess forms of cimetidine which have been modified by a copper-catalyzed solvolysis (by water or methanol) of the nitrile function (**2** and **3**). In this report we describe the synthesis, spectroscopic characterization, and X-ray crystallographic analyses[8] of the green (**4**) and blue (**5**) Cu(II)

(1) Marketed by Smith, Kline and French, Philadelphia, PA.

(2) Durant, G. J.; Emmett, J. C.; Ganellin, C. R.; Miles, P. D.; Parsons, M. E.; Prain, H. D.; White, G. R. *J. Med. Chem.* **1977**, *20*, 901.

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complexes of cimetidine.

The interactions which occur between the drug and Cu(II) in solution were easily followed spectrophotometrically. Incremental addition of 0.14 M $Cu^{II}(ClO_4)_2$ to a 10^{-3} M aqueous solution of **1** at pH 7.0, followed at 615 nm, resulted in the formation of a single species. The complex which forms exhibited the stoichiometry $Cu^{II}(\mathbf{1})_2$ and had absorption maxima at 337 and 606 nm. Combining concentrated hot aqueous solutions (90 °C) of $Cu^{II}(ClO_4)_2$ and **1** in a 1:2 ratio and cooling ultimately resulted in the crystallization of a green complex (**4**) which analyzed[9] for the hydrate of $Cu^{II}(\mathbf{1})_2(ClO_4)_2$. The compound was sparingly soluble in water, and while an absorption maximum was observed at 606 nm, it slowly shifted with time.

A similar metal titration in CH_3OH showed the formation of $[Cu^{II}(\mathbf{1})_2]^{2+}$ with absorption maxima at 344 and 615 nm, but as additional Cu(II) was added to the solution, the first-formed complex disappeared to form a new species having an apparent stoichiometry of $[Cu^{II}(\mathbf{1})]^{2+}$ (λ_{max} 333, 695 nm). Attempts to isolate this intermediate complex were prevented by its slow conversion in CH_3OH (8 h, 20 °C) to a blue compound. Combining concentrated hot (65 °C) methanolic solutions of $Cu^{II}(ClO_4)_2$ and **1** in a 1:1 molar ratio, cooling, and allowing to stand overnight resulted in the crystallization of a blue complex analyzing for $Cu^{II}(\mathbf{1})(ClO_4)_2 \cdot CH_3OH$[9] and having absorption properties[10] identical with those of the blue species observed in the metal titration. X-ray structural analysis[8] ultimately showed that the blue complex contains a modified form of **1** and it should be formulated as $Cu^{II}(\mathbf{3})(ClO_4)_2$ (**5**).[11]

In the absorption spectrum of cimetidine two bands are observed in solution at 197 and 215 nm arising from $\pi \rightarrow \pi^*$ transitions in the imidazole and guanidine moieties, respectively. In the solid-state spectrum no inflections are observed. Analysis of the absorption spectra of **5**[10] in H_2O and methanol showed the presence of a weak d–d transition in the visible region of the spectrum at 570 nm and strong transitions in the region 200–350 nm. The major difference between solution and mull spectra is the appearance of an additional resolved band at 220 nm in solution.[10] Analogy with numerous Cu(II) thioether complexes[12] suggests assignment of the band near 300 nm to an S → Cu(II) charge-transfer transition. However, the bands at 220 and 240 nm as well as absorptions in the region of ~300 nm can all be explained on the basis of being imidazole → Cu(II) charge-transfer transitions. Fawcett et al.[13] have reported σ(Im) →, π(Im) →, and π(Im) → Cu(II) bands near 220, 260, and 330 nm, respectively, for a number of imidazole–copper complexes. We have been unable to determine whether the band at 308 nm in the spectrum of **5** has one or two components. Solutions of **4** showed two peaks in the region 330–350 nm,[10] but due to the instability of the compound in solution, reliable values of peak positions and intensities were not possible to obtain. While the nitrile absorption is absent in the IR spectrum of **5**, it occurs as a strong band at 2200 cm^{-1} in the spectrum of **4** shifted by 20 cm^{-1} to higher energy relative to that of **1**. Shifts of this magnitude have been observed for nitrile functions bound to transition-metal ions.[14]

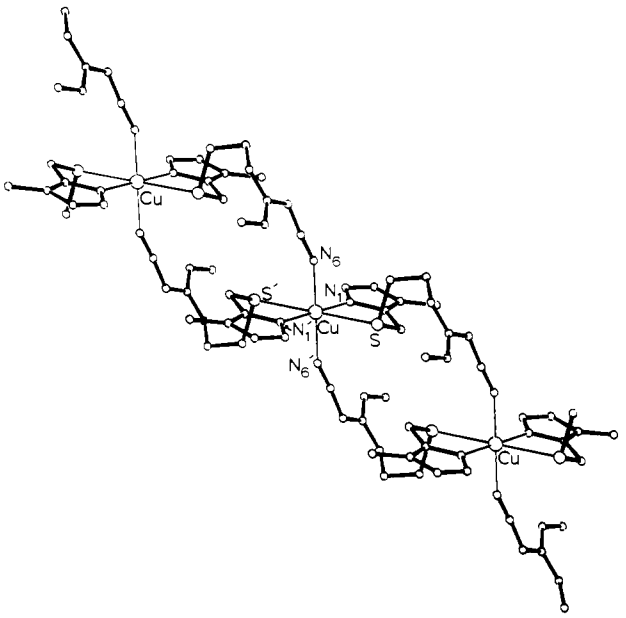

Figure 1. ORTEP drawing for three subunits of the cationic polymer of green $[Cu^{II}(\mathbf{1})_2]_n^{2n+}$ (**4**) as observed in the solid state for its perchlorate salt. Each Cu atom occupies a crystallographic inversion center.

^1H and ^{13}C NMR studies of **1** in the presence of Cu(II) clearly implicate the imidazole and some portion of the cyano guanidine moiety of **4** as being involved in metal chelation in solution.[15] Addition of small amounts of Cu(II) to **1** in CD_3OD results in selective broadening of the ^1H NMR resonance due to H-2 of the imidazole (δ 7.47).[16] The proton resonances due to the two methyl groups (Im, 4-CH_3, δ 2.21; NCH_3, δ 2.79) experience the least broadening. ^{13}C NMR resonances due to the imidazole ring carbons and the nitrile carbon were selectively broadened upon addition of Cu(II) to **1** in CD_3OD. At a Cu:**1** ratio of 1:350 only the resonances due to the guanidine (δ 161.80) and *N*-methyl (δ 28.66) carbon atoms are observed, and at a ratio of 1:100 only the latter remains. These results suggest binding of the imidazole and nitrile functions of **1** to Cu(II) in solution.

The EPR spectrum of the blue complex $Cu^{II}(\mathbf{2})(ClO_4)_2$ (**5**) is well resolved, in contrast to that of the green complex, with hyperfine splitting due to at least two nitrogen atoms being observed on $g_\perp$. The EPR parameters are substantially different from those found for the green compound[17] and correspond to a significantly

(8) Single crystals of green $Cu^{II}(\mathbf{1})_2(ClO_4)_2$ (**4**) and blue $Cu^{II}(\mathbf{3})(ClO_4)_2$ (**5**) are both monoclinic, space group $p2_1/c$-C^5_{2h} (no. **14**), with a = 12.264 (3) Å, b = 8.529 (3) Å, c = 15.947 (4) Å, β = 94.45 (2)° and Z = 4 for **4** and a = 11.698 (3) Å, b = 7.387 (2) Å, c = 23.670 (4) Å, β = 94.53 (2)° and Z = 2 (formula units) for **5**. Three-dimensional X-ray diffraction data were collected on a computer-controlled four-circle Syntex P1 autodiffractometer [3799 independent reflections of **4** having $2\theta < 55°$ and 6983 independent reflections of **5** having $2\theta < 63.7°$ (Mo K$\bar{\alpha}$)] by using graphite-monochromated Mo K$\bar{\alpha}$ radiation and full (1° wide) ω scans. The solid-state structure of **5** was solved by using the "heavy atom" technique and that of **4** by a combination of direct methods (MULTAN) and difference Fourier syntheses. The resulting structural parameters have been refined to convergence [R(unweighted, based on F) = 0.043 and 0.053, respectively, for 2066 (**4**) and 5244 (**5**) independent reflections having $I > 3\sigma(I)$] by using unit weighted full-matrix least-squares techniques with anisotropic thermal parameters for all nonhydrogen atoms and isotropic thermal parameters for all hydrogen atoms of both compounds. Full experimental details and comprehensive comparisons for the solid-state structural analyses of **4** and **5** will be published elsewhere.

(9) Anal. Calcd for **4**, $C_{20}H_{34}N_{12}O_9S_2Cl_2Cu$: C, 30.58; H, 4.37; N, 21.42; Cl, 9.03; Cu, 8.10. Found: C, 30.81; H, 4.29; N, 21.67; Cl, 9.12; Cu, 7.93. Calcd for **5**, $C_{11}H_{20}N_6O_9SCl_2Cu$: C, 24.14; H, 3.69; N, 15.37. Found: C, 24.33; H, 3.78; N, 15.28.

(10) **1**: *A* (H_2O, pH 6), 197, 215 nm. **4**: Solid state (halocarbon mull) 240, 354, 631 nm; *A* (H_2O, pH 6), 220, 337, 606 nm; *A* (CH_3OH), 220, 344, 615 nm. **5**: Solid state (halocarbon mull), ~240, 310, 566 nm; *A* (H_2O, pH 6) (ϵ), 220 (~10000), 245 (sh), 308 (2600), 570 (130) nm; *A* (CH_3OH) (ϵ), 220 (~10000), 245 (sh), 308 (3100), 570 (140) nm.

(11) Ethanol gives similar results to methanol in that a blue complex with similar spectral characteristics was obtained, although the rate of solvolysis was slower.

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(15) **1**: ^1H NMR (CD_3OD, 80 MHz) δ 2.21 (3 H, s, 4-CH_3), 2.68 (2 H, t, J = 6.5 Hz, SCH_2CH_2), 2.79 (3 H, s, NCH_3), 3.34 (2 H, t, J = 6 Hz, $NHCH_2$), 3.72 (2 H, s, SCH_2), 7.47 (1 H, s, H-2); ^{13}C NMR (CD_3OD, 20 MHz) proton-coupled spectra: δ 10.06 (q, J_{CH} = 127 Hz, 4-CH_3), 27.23 (t, J_{CH} = 140 Hz), 28.66 (q, J_{CH} = 127 Hz, NCH_3), 31.54 (t, J_{CH} = 217 Hz), 42.07 (t, J_{CH} = 130 Hz), 120.01 (s, CN), 127.57 (s, Im), 130.57 (s, Im), 134.56 (d, J_{CH} = 220 Hz, C-2, Im), 161.80 (s, C=N). All shifts are relative to Me_4Si.

(16) ^1H NMR ($\Delta\nu_{1/2}$ in CD_3OD at Cu, ratios of 0, 0.0004, 0.001) δ 2.21, $\Delta\nu_{1/2}$ 3.4, 5.2, 8.5 Hz; δ 2.79, $\Delta\nu_{1/2}$ 3.1, 3.4, 3.7 Hz; ν 7.47, $\Delta\nu_{1/2}$ 4.0, 22.4 Hz, unobserved.

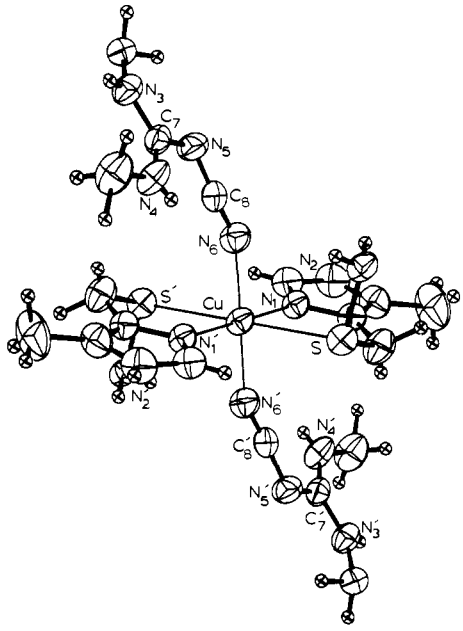

Figure 2. Perspective ORTEP drawing for one of the octahedral $[Cu^{II}(1)_2]^{2+}$ (**4**) subunits of Figure 1. Nonhydrogen atoms are represented by thermal vibration ellipsolids drawn to encompass 50% of the electron density; hydrogen atoms are represented by arbitrarily small spheres for purposes of clarity. Atoms labeled with a prime are related to those without a prime by the crystallographic inversion center at the Cu atom.

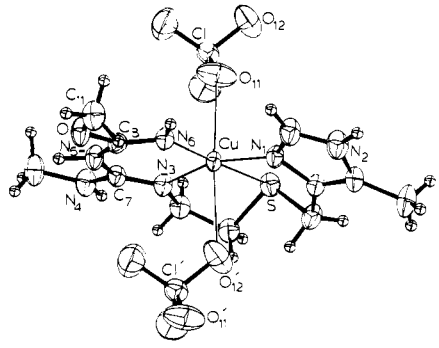

Figure 3. Perspective ORTEP drawing for one of the octahedral $[Cu^{II}(3)(ClO_4)]^{1+}$ subunits in the cationic solid-state $[Cu^{II}(3)(ClO_4)]_n^{n+}$ polymer of **5**. Nonhydrogen atoms are represented by thermal vibration ellipsoids drawn to encompass 50% of the electron density; hydrogen atoms are represented by arbitrarily small spheres for purposes of clarity. Atoms of the perchlorate group labeled with a prime are related to those labeled without a prime by translation of one unit cell along $\bar{b}$.

greater in-plane crystal field strength. This is also confirmed by the appliction of the rule of average environment to the positions of the d–d bands of **5**.[18]

The X-ray diffraction studies of **4** and **5** reveal a solid-state structure composed of polymeric cationic Cu(II) complexes and anionic perchlorate groups. The cationic unit of **4** is an infinite polymer (Figure 1) of centrosymmetric octahedral Cu(II) subunits like that shown in Figure 2 which are generated by a bridging tridentate cimetidine ligand. The cationic unit of **5** is also an infinite polymer (Figure 3) which is formed by bidentate perchlorate anions bridging nearly square-planar dicationic Cu(II) complexes of the neutral tetradentate methoxyimine ligand (**3**). The bridging perchlorate Cu–O interactions in **5** are weak with bond lengths of 2.505 (6) and 2.805 (7) Å.

The planar (to within 0.03 Å) guanidyl portion of the organic ligand exists in different tautomeric forms in the two complexes: N_3 is protonated in **4** while N_5 is protonated in **5**. As a result, the gaunidyl double bond is between C_7 and N_5 in **4** and between C_7 and N_3 in **5**. Bond lengths and angles of interest in **4** include Cu–N_1, 1.972 (4) Å; Cu–N_6, 2.036 (5) Å; Cu–S, 2.700 (1) Å; C_7–N_3, 1.333 (7) Å; C_7–N_4, 1.321 (8) Å; C_7–N_5, 1.351 (7) Å; C_8–N_6, 1.159 (7) Å; S–Cu–N_1, 78.8 (1)°; S–Cu–N_6, 93.2 (1)°; N_1–Cu–N_6, 91.7 (2)°; C_7–N_5–C_8, 119.2 (5)°; N_5–C_8–N_6, 172.5 (6)°. Bond lengths and angles of interest in **5** include Cu–N_1, 1.962 (5) Å; Cu–N_3, 1.954 (5) Å; Cu–N_6, 1.944 (6) Å; Cu–S, 2.353 (2) Å; Cu–O_{11}, 2.505 (6) Å; Cu–O_{12}, 2.805 (7) Å; C_7–N_3, 1.289 (8) Å; C_7–N_4, 1.344 (9) Å; C_7–N_5, 1.384 (8) Å; C_8–N_6, 1.255 (9) Å; C_8–O, 1.325 (7) Å; C_{11}–O, 1.456 (8) Å; N_5–C_8–N_6, 124.0 (5)°; N_5–C_8–O, 107.6 (5)°; C_8–O–C_{11}, 119.4 (5)°; O_{11}–Cu–O_{12}, 174.1 (2)°; S–Cu–N_6, 176.7 (2)°; N_1–Cu–N_3, 163.2 (2)°; bond angles subtended at Cu by atoms occupying cis octahedral coordination sites range from 78.1 to 99.5°.

The mechanism by which metal-assisted solvolysis of a nitrile function occurs is not well understood.[19] However, in an effort to determine if this reaction would occur for **1** under simulated physiological conditions, the reactivity of **4** was explored. Addition of **1** equiv of **1** to an aqueous solution of **4** at pH 7.0 at 25 °C caused only a small change in the absorption spectrum of the solution over a period of several days. However, heating the above solution for 4 h at 80 °C resulted in a blue solution which spectroscopically was nearly identical with **5**.[20] Purging this solution with H_2S to percipitate the Cu(II) as CuS followed by workup yielded an impure oil. ^{13}C NMR spectral data indicate a structure for the oil consistent with the amide **2**.[21] This amide is also produced in the absence of metal by mild acid hydrolysis of cimetidine.[2]

Although the conditions necessary for modifying the drug are severe by biological standards and thus are not likely to occur in vivo, the tendency of the drug to bind Cu(II) suggests that metal interactions may be important for the biological activity of cimetidine. Future studies with the drug will concentrate on determining the strength of the metal interactions and on establishing the existence of Cu(II) complexes under physiological conditions.

(17) X-band EPR at 90 K in frozen aqueous (pH 5.8) solutions. **4**: $g_{\parallel} = 2.332$, $g_{\perp} = 2.078$, $|A_{\parallel}(Cu)| = 0.0147$ cm^{-1}. **5**: $g_{\parallel} = 2.199$, $g_{\perp} = 2.052$, $|A_{\parallel}(Cu)| = 0.0191$ cm^{-1}, $|A_{\perp}(N)| = 0.0016$ cm^{-1}.

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(20) *A* (CH_3OH) (ϵ), 310 (3140), 612 (150) nm.

(21) **3**: ^{13}C NMR (CD_3OD, 20 MHz) proton-coupled spectra δ 10.06 (q, $J_{CH} = 130$ Hz, 4-CH_3), 25.24 (t), 29.62 (q, $J_{CH} = 140$ Hz, NCH_3), 31.70 (t), 42.44 (t), 127.68 (s, Im), 129.05 (s, Im), 134.61 (d, $J_{CH} = 220$ Hz, C-2, Im), 155.61 (s, CO), 157.45 (s, C=N).

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Received July 28, 1980

Coordination Stabilization of Organic Intermediates. Crystal Structure of $\{[(en)_2Co(SCH_2CH_2NH_2)]_2I\}(NO_3)_5 \cdot 4H_2O$, a Stable Complex of Iodine(I)

Sir:

Under appropriate conditions the oxidation of thiols coordinated to cobalt(III) leads to stable, S-bonded, coordinated sulfenic acids which may be isolated and characterized.[1] Since noncoordinated

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