1019 (1973); D. Sellmann, *ibid.*, **13**, 639 (1974). In the infrared spectrum of the complex, $N_2H_2[Cr(CO)_5]_2$, the N_2H_2 bridging ligand is assigned a cis configuration. NH stretching frequencies of 3480 and 3250 cm^{-1} are observed. These frequencies are not in conflict with the present results for *cis*-methyldiazene and the predictions for *cis*-diazene, since complexation engages the unshared electron pairs in bonding and modifies the strengths of the bonds in the *cis*-diazene ligand.

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Sulfur 2p Photoelectron Spectra of 1,8-Bis(2′-pyridyl)-3,6-dithiaoctane and Its Copper(II) Complex. Possible Interpretation of the S_{2p} 168-eV Peak in Blue Copper Proteins

Sir:

X-ray photoelectron spectroscopy (XPES) could provide a simple, direct method of determining sulfur-copper coordination in metalloproteins. In principle, if a shift in the S_{2p} peak in the spectrum of the apoprotein from the same peak in the spectrum of the copper protein could be detected, then, qualitatively at least, sulfur-copper coordination would be implicated. Such studies have been reported on the blue protein, plastocyanin,[1] and on oxyhemocyanin.[2] The plastocyanin study suggested that a 4-5-eV shift in the S_{2p} peak occurred upon sulfur-copper coordination (from 164 to 168-169 eV) and, since only a major signal at 164 eV was observed for oxyhemocyanin, it was assumed that there is no sulfur-copper coordination in this protein.

Experience suggests that a 4-eV shift in the S_{2p} peak upon copper coordination is unreasonably large, since the energy of the S_{2p} peak seems to be largely determined by the formal oxidation state of the sulfur atom, spanning only 7 eV in transferring from S^{2-} to SO_4^{2-}.[3] Similar observations have been made before on a number of occasions,[4-7] and one group has proposed[6] that the 168-eV S_{2p} peak in the plastocyanin spectrum is due to SO_4^{2-} or some other oxidized sulfur impurity. However, careful examination of the experimental facts has shown[2] that the 168-eV S_{2p} signal is a property of Co(II) or Cu(II) binding to apoplastocyanin. Clearly, the exact origin of the plastocyanin 168-eV S_{2p} signal must be elucidated if further XPS studies on proteins are contemplated.

The purpose of this communication is to describe an XPES study of the ligand 1,8-bis(2′-pyridyl)-3,6-dithiaoctane and its copper(II) complex[7] (Figure 1), where we show that a high energy S_{2p} binding peak (~168 eV) can be generated in the copper complex but that it is caused by copper-catalyzed radiation damage.

A comparison of the S_{2p} signal of the free ligand and its copper(II) complex obtained under normal conditions (~20-min X-ray exposure at 25 °C) is shown in Figure 1A, B. Clearly, no significant shift of the S_{2p} binding energy upon metal coordination is observed. However, a broad shoulder in the region 167-169 eV can be distinguished in Figure 1B that is not present in 1A. Since this shoulder is in precisely the region where the high energy binding peak of plastocyanin was observed, it was important to determine its origin.

Exposure of the complex to the X-ray source for 12 h gave the spectrum shown in Figure 1C. As can be seen, this exposure causes a dramatic increase in the intensity of the high-energy binding peak. The sample is visibly damaged after this treatment. Importantly, similar exposure of the free ligand did *not* give a high-energy binding peak. Finally, a 30-s exposure of the complex to an argon-ion etching beam causes complete changeover of the 164-eV peak to the one at 168 eV (Figure 1D). Again, no such effect is observed for the uncomplexed ligand.

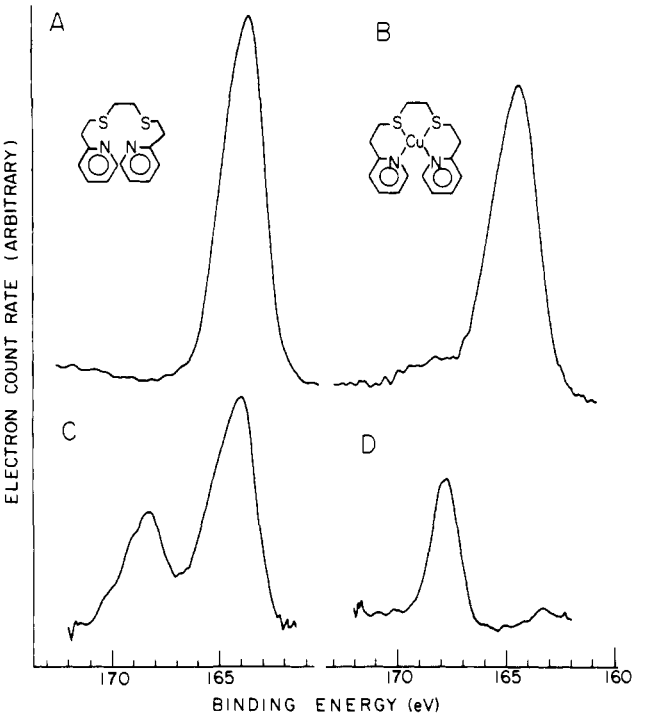

Figure 1. XP S_{2p} spectra of ligand (A), copper complex (B), after 12-h exposure to source beam (C), and complex after 10-s exposure to a 10-μA argon-ion beam. Samples were run on a McPherson ESCA 36 X-ray photoelectron spectrometer in the Mg Kα (250 W) mode.

It is clear from these results that very little shift of the S_{2p} binding peak occurs upon copper coordination to sulfur and that the higher energy peak arises from other sources. The position of the 168-eV peak corresponds to a sulfur atom at the oxidation level of a sulfone,[3] which implies that radiation-induced surface oxidation has occurred, but, as we have shown, this oxidation occurs *only in the presence of ligated copper*, an observation that bears directly on attempts to correlate the results obtained for apo- and metalloproteins.

The high binding peak (168 eV) observed in plastocyanin and in other blue proteins[2] could be due to the effect described here[9] or it could possibly be a charge-transfer satellite, as proposed by Larsson.[10] Measurements of S_{2s} binding energies are being made on several blue protein samples in an attempt to resolve the issue.[11] It also should be emphasized that the absence of a pronounced high-energy S_{2p} peak in the oxyhemocyanin spectrum[2] does not conclusively rule out sulfur ligation, as there are ~20 sulfur atoms per copper pair in these proteins,[12] and it would be difficult to see a signal attributable to only a few of these. In view of the latter comment, as well as the uncertainty in the interpretation of the 168-eV S_{2p} peak in plastocyanin, it is our opinion that it would be unwise to infer copper-sulfur coordination in proteins based solely on XPE spectroscopic measurements.

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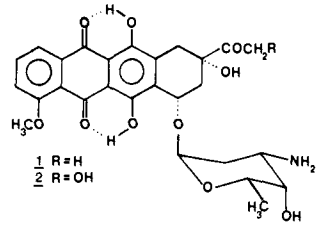
Anthracyclines and Related Substances. 2. An Efficient and Regiospecific Synthesis of *dl*-7,9-Dideoxydaunomycinone[1]

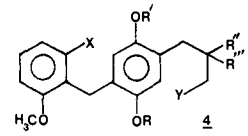
Sir:

Of the group of compounds that comprise the anthracyclines,[2] two substances, namely daunomycin[3] (**1**) and adriamycin[4] (**2**), have achieved preeminence as antitumor agents, despite the fact that they frequently induce an irreversible cardiomyopathy. This has initiated a search for partially or totally synthetic derivatives that might lack this side effect.[5]



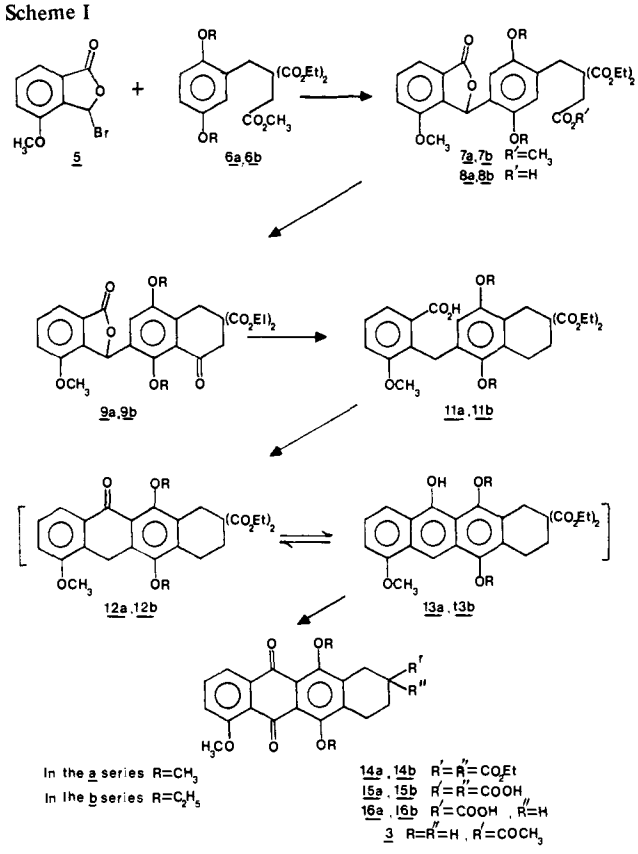
However efforts aimed at the total syntheses of **1** and **2** frequently have been plaqued[6] by the problem of regioisomerism posed by the relationship of the C-4 methoxyl and the substituents on ring A. In cases where this problem has been solved, the methods[7] appear to lack efficiency or alternatively, seem inapplicable to large-scale work. We now describe an efficient synthesis (20% overall yield) of *dl*-7,9-dideoxydaunomycinone (**3**), a compound whose conversion into the aglycones of **1** and **2** is known.[6b,8] The procedure is regiospecific and is adaptable to bulk preparative work.

The overall method of construction follows a convergent B + D → BD → ABD → ABCD pattern and called initially for the synthesis of an intermediate belonging to the class represented by **4** (X and Y being suitably functionalized carbon

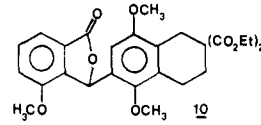


atoms). The crucial step in the synthesis of molecules of this type is a new Friedel-Crafts *alkylation* which directly introduces a phthalido residue (an inductively deactivating group[9]) into the aromatic nucleus destined to be ring B. In the case under consideration the reaction of 3-bromo-4-methoxyphthalide **5** (obtained almost quantitatively by the action of *N*-bromosuccinimide on 4-methoxyphthalide[10]) with the triester **6a** ($SnCl_4$, CH_2Cl_2, 25 °C, 6 h) led to **7a**[11] in 94% yield: mp 135–137 °C. Selective hydrolysis of the terminal methyl ester of **7a** (Scheme I) (1.3 equiv[12] of KOH, THF-CH_3OH-

Scheme I



H_2O) gave **8a** in 96% yield as needles, mp 105–109 °C, from aqueous methanol. Cyclization[13] ($(CF_3CO)_2O$, CF_3CO_2H, 25 °C, 12 h, 91%) of **8a** led to the ketolactone **9a**, mp 149–151 °C. Reduction (Et_3SiH/CF_3CO_2H, 25 °C, 48 h) of **9a** initially gives the lactonic tetralin **10**, mp 143 °C, and at 25 °C this can be isolated easily in high (93%) yield. However, after 2 weeks



at 25 °C or more rapidly (24 h) at 50 °C, the lactone was also reductively cleaved and there was obtained (92%) the dimorphic carboxybenzyltetralin **11a**, mp 117–118 (blades) and 134–136 °C (needles). The cyclization ($(CF_3CO)_2O/CF_3CO_2H$, 25 °C, 30 min, ~88%)) of **11a** occurred with great ease and afforded a tautomeric mixture of the 9-anthrone (**12a**) and the 9-hydroxyanthracene **13a**, in which the latter predominated. Generally these compounds were not isolated. Instead the reaction mixture was diluted with a little water and Jones reagent[14] was added at 0 °C. This led to the quinone **14a**

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