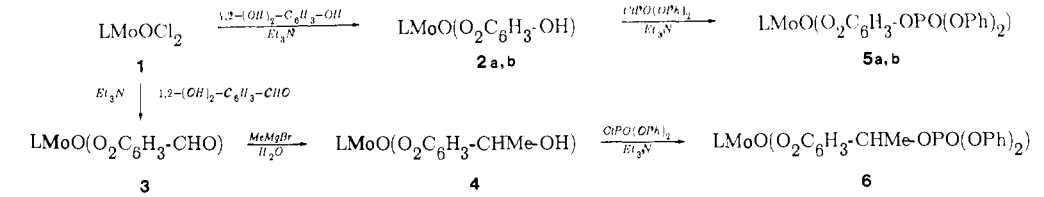
Scheme I



amount of triethylamine in refluxing toluene.[8] Phosphorylation of the free hydroxyl group of **2a,b** and **4** with diphenylchlorophosphate in refluxing toluene in the presence of triethylamine provides **5a,b** and **6** in ~90% yield.[9]

The ^{31}P NMR spectra for **5a,b** and **6** (Figure 1) show substantial differences in both chemical shift and line width. The ^{31}P resonances for **5a** (−12.26 ppm) and **5b** (−15.16 ppm) are deshielded (downfield) relative to $PO(OPh)_3$ at −16.80 ppm. However, the most striking difference between **5a** and **5b** is the large difference in their line widths. The broad line for **5a** (207 Hz) indicates rapid relaxation of the ^{31}P nucleus by the unpaired electron on the Mo(V) center of the complex. For **5b** the broadening is much smaller (24 Hz). The chemical shift of **6** (−4.09 ppm) is significantly more deshielded than **5a**, **5b**, and than free benzyldiphenylphosphate at −11.55 ppm. The line width of **6** (10 Hz) is similar to that of a free phosphate triester, and the relatively poor signal-to-noise ratio for **6** suggests slow relaxation of the ^{31}P nucleus in this compound. The general dependence of the ^{31}P NMR linewidths on the Mo···P distance[7] is consistent with dipolar relaxation being the dominant process, but variations in spin density at the 3- and 4-positions on the catechol ring may also contribute to the observed line widths.

To our knowledge this is the first study of the broadening of ^{31}P NMR resonances by oxo–molybdenum(V) centers in discrete complexes. The observed line widths are consistent with those expected[10] for slow electron relaxation[11] and rapid molecular rotation.

These preliminary results demonstrate that ^{31}P NMR can be used to probe the interaction between an oxo-molybdenum(V) center and a pendant phosphate group and that the ^{31}P chemical shift and line width are both sensitive to the overall structure of the intervening ligand. Thus, ^{31}P NMR holds promise for probing the molybdenum–phosphate interactions of I. Recent EPR studies of solutions of the liberated molybdenum cofactor[12] show that the Mo(V) state of I is experimentally accessible.

The steric constraints of the ligands in **5a,b** and **6** preclude coordination of the phosphate group to the molybdenum atom. However, molecular modeling calculations on the proposed molybdenum cofactor I show that its phosphate group could actually coordinate to the molybdenum atom if a vacant coordination site were available. More detailed NMR studies of these initial models and of other models for the molybdenum–phosphate interactions of I are in progress.

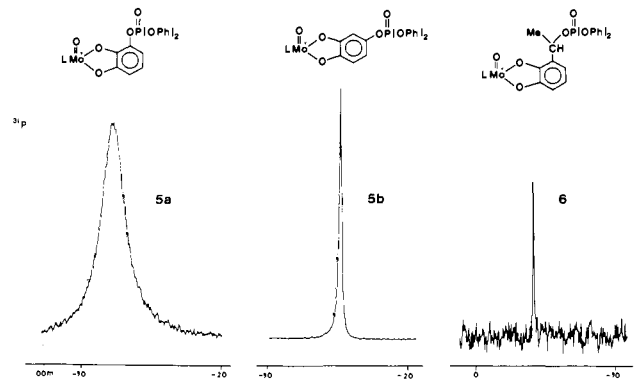


Figure 1. ^{31}P NMR spectra of the Mo(V) complexes **5a**, **5b**, and **6** (43.6 mMol) in $CHCl_3$ at 20 °C recorded on a Bruker WM-250 (4400 scans).

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Supplementary Material Available: Table of infrared data, EPR data, ^{31}P NMR data, elemental analyses, and cyclic voltammetric data (1 page). Ordering information is given on any current masthead page.

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(9) To 1 mmol of the hydroxy-substituted catechol complex (**2a**, **2b** or **4**) dissolved in 30 mL of toluene are added 0.15 mL (1.1 mmol) of triethylamine and 0.23 mL (1.1 mmol) of diphenylchlorophosphate. The mixture is refluxed for 15 h (30 h in the case of **4**), and the products are purified by chromatography on silica gel and recrystallization from dichloromethane/hexane to yield olive-green air stable microcrystals. All compounds give satisfactory elemental analysis. The physical properties—electronic spectra, EPR spectra, IR spectra—are available as Supplementary Material and are nearly identical with those of LMoO(cat).[8]

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σ-Assisted Exchange Interactions in Linear Adducts of Nitroxides with Dirhodium Tetrakis(trifluoroacetate)

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Recent reports on bis-nitroxyl adducts of tetrakis(trifluoroacetato)dirhodium,[1,2] ($Rh_2(tfac)_4$), show that efficient interactions between the two ligand based radicals are mediated by the Rh–Rh bond.

As part of our studies concerning the coordination chemistry of the nitronyl and imino nitroxides,[3,4] we have synthesized a series of discrete bis-nitroxyl complexes as well as extended linear adducts of these free radicals with $Rh_2(tfac)_4$. The O-bonded nitronyl complexes show moderate antiferromagnetic nitroxyl–nitroxyl interactions, while the N-bonded imino adducts exhibit either weak antiferro- or ferromagnetic couplings. The structural features of

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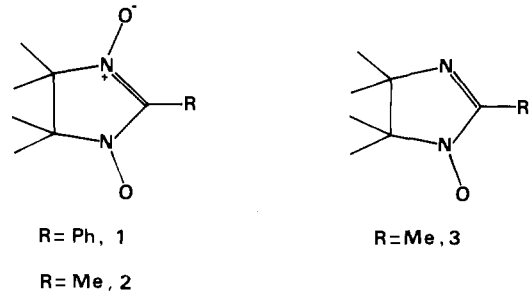

Figure 1. Chemical structures of the nitronyl (**1** and **2**) and imino (**3**) nitroxides.

these compounds strongly suggest that the spin–spin coupling mechanism through the dirhodium core mainly involves an orbital of σ symmetry.

The nitronyl,[5] **1** and **2**, and imino,[6] **3**, nitroxides (Figure 1) have two conjugated coordination sites. These sites are equivalent in **1** and **2** while in **3** only $^1/_3$ of the spin density is located on the imino–nitrogen atom.[6] The ability of these free radicals to behave as bridging ligands in multinuclear assemblies is limited only by steric factors. Thus the reaction of $Rh_2(tfac)_4$ with **1** affords a discrete 2:1 adduct **4**, whereas an extended linear complex **5** is formed with **2**. The stoichiometries 2:1, **6** (discrete adduct), and 1:1, **7** (linear compound), of the two complexes obtained with **3** depend on the relative proportions of the reagents.

The structures of the four complexes have been determined by single-crystal X-ray diffraction techniques.[7] The structures of the two bis adducts, **4** and **6**, display the typical centrosymmetric rhodium carboxylate dimer core[2] coordinated at each axial site by an oxygen atom with a Rh–O distance of 2.239 (3) Å in **4** or by an imino–nitrogen atom with a Rh–N distance of 2.237 (4) Å in **6**. The two extended linear adducts display similar local properties, but the center of the Rh–Rh bond no longer is a center of symmetry for the molecule. Critically important differences in the structures of the O- and N-bonded compounds are reflected in the dihedral angles between the $Rh–O_4$ plane and the nitroxyl mean plane. Coordination by an oxygen lone pair leads to a Rh–O–N angle close to 120°, while coordination by the imino–nitrogen lone pair requires the nitroxide (C–N–C) plane to be nearly orthogonal to the $Rh–O_4$ plane (83.6° in **6**, 88.5° in **7**). In all four compounds, the different fragments have the usual[2,3,4,9] bond lengths and angles.

Variable temperature (4.2–300 K) magnetic susceptibility data were collected for the four complexes.[10] For the two O-bonded adducts the expected[2] fairly large antiferromagnetic interactions of $2J = -167$ cm^{-1} for **4** and $2J = -197$ cm^{-1} for **5** were observed. In contrast, the two Rh–N bonded complexes exhibit quite different magnetic properties; a weak antiferromagnetic interaction

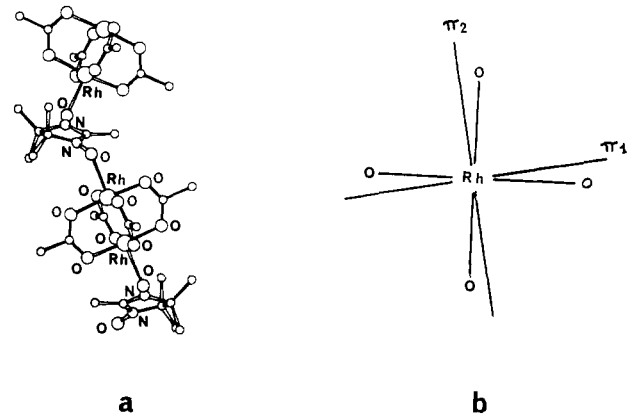

Figure 2. (a) Drawing of the molecular structure of compound **5**. (b) Schematic representation of the direction of the projections of the π^* orbitals of the axially bound nitroxides on the RhO_4 plane.

of $2J = -11$ cm^{-1} was found in **6**, but **7** showed a ferromagnetic coupling of $2J = +4$ cm^{-1}.

Evidence for the *intra*molecular nature of the exchange interactions in nitroxyl–rhodium complexes with very similar *inter*molecular contacts[13] has been extensively and convincingly discussed.[2] Because the $2J$ values in **6** and **7** are so small, we must consider both inter- and intramolecular interactions, but, more importantly, we have to explain the unexpectedly weak exchange coupling in these two compounds compared to the Rh–O bonded analogues.

Unfortunately, the electronic structure of the $Rh_2(O_2CR)_4L_2$ fragment is not fully understood. Experimental work[14–17] as well as theoretical calculations[18–21] have shown that the energy level ordering of the molecule depends on the nature of the axial ligand L and of the carboxyl group, and HOMO's of various symmetries (π^*, δ^*, σ) have been proposed for the Rh–Rh fragment. The characteristic structural features of compounds **4–7** now provide us with the information needed to analyze this question in new terms for the $Rh_2(tfac)_4$ nitroxyl adducts.

To relate the structural characteristics to the bonding between the Rh_2 core and the ligands, it is convenient to divide each nitroxide (O- or N-bonded) π^* SOMO[22] into a σ_z component collinear with the Rh–Rh bond and a π component parallel to the $Rh–O_4$ plane. In the O-bonded adducts with Rh–O–N angles close to 120°, the nitroxide σ_z and π components are nearly equivalent. Therefore, depending on the Rh–Rh energy level ordering, both $Rh\pi^*–NO\pi$ and $Rh\sigma–NO\sigma_z$ overlap can be involved in the nitroxyl–nitroxyl magnetic coupling. In the previously reported centrosymmetric adducts,[2] the large antiferromagnetic coupling has been accounted for by $Rh\pi^*–NO\pi^*$ back bonding. Although this mechanism is in agreement with the properties of compound

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4, the other adducts, 5–7, afford new geometrical schemes. The extended linear O-bonded compound 5 deserved special mention since the two nitroxide π components are no longer parallel, as found in the centrosymmetric adducts but orthogonal (91.2 (6)°) as shown in Figure 2. Owing to this orthogonality, a Rhπ*–NOπ overlap cannot be responsible for the coupling of the nitroxide ligands. However, there is no symmetry limitation for the interaction of a Rh σ orbital with the two σ_z components of the nitroxide groups, and we suggest that, in all cases studied so far, it is this mechanism which is reponsible for the magnitude of the observed couplings.

Further strong support for this mechanism comes from the magnetic behavior of the two remaining complexes 6 and 7. In these adducts, containing one or two axially bonded nitrogen atoms, owing to the near orthogonality of the nitroxide least-squares plane and the Rh–O_4 plane, the nitroxide σ_z components are nearly zero. Therefore, the large π component would give a large interaction with a Rh–Rh HOMO of π symmetry. With a Rh–Rh σ HOMO, the overlap is symmetry forbidden, and the nitroxyl–nitroxyl coupling is expected to be very weak (positive or negative) as observed.

The magnetic behavior of this series of rhodium–nitroxide complexes clearly demonstrates that the interligand interaction is highly geometry dependent. Although Rhπ*–NOπ* back bonding has been made responsible[23] for some of the observed properties of similar compounds, local symmetry considerations clearly show that the magnetic behavior of complexes 4–7 is better explained by a nitroxyl–nitroxyl coupling mechanism involving a σ Rh–Rh orbital.

Acknowledgment. Helpful comments by Professors O. Kahn, D. Gatteschi, and U. Mueller-Westerhoff are gratefully acknowledged.

Supplementary Material Available: Listing of atomic positional parameters for compounds 4–7 (2 pages). Ordering information is given on any current masthead page.

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Models for a Hypothetical Mechanism of Action of the Anticancer Agent Vinblastine

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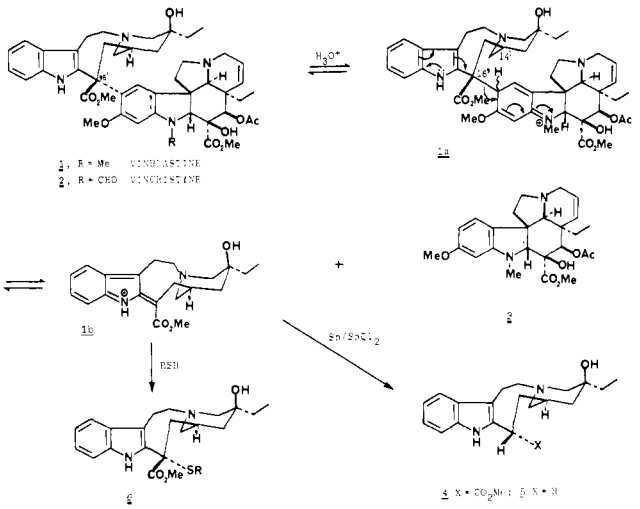
Vinblastine 1 and vincristine 2 are used in combination cancer chemotherapy for the treatment of a wide range of tumors.[1] While a large number of cytotoxic agents are commonly associated with DNA binding and/or intercalation and alkylation, thus inhibiting protein synthesis, there are no suggestions as to how vinblastine 1 might operate at the molecular level.[2] Apparently, vinblastine 1 and vincristine 2 bind to the protein tubulin and modify the accessibility of certain cysteine –SH groups, in particular two –SH groups, although it is not known which two.[3] It should be noted that a large number of antitumor agents have been shown to act by S-alkylation of an –SH function in target enzymes or coenzymes.[4]



In vitro, vinblastine 1 prevents the uptake of thymidine into DNA and uridine into RNA, processes that are dependent upon thymidylate synthetase, which utilizes –SH addition to C-6 (U).[5] Vinblastine 1 and vincristine 2 show markedly different toxicities. The former exhibits bone marrow depletion, whereas the latter is associated with neuropathy.[6] Given that the only difference between the two molecules is N^1–CH_3 1 and N^1-CHO 2, this substituent must exert a significant effect. Apparently, in vivo, vincristine undergoes considerably less metabolism than vinblastine.[7]

In this paper we present chemical evidence that vinblastine models can act as alkylating agents toward thiols. It is known that reductive cleavage of 1 with use of $Sn/SnCl_2/HCl$ gives vindoline 3 and velbanamine 5, which arises from hydrolysis and decarboxylation of carbomethoxyvelbanamine 4.[8] This process is best explained by a reversible ipso protonation[9] of vinblastine 1 to form the arenium ion 1a, which can undergo fragmentation into the iminium ion 1b and vindoline 3. The iminium ion 1b is reduced to carbomethoxyvelbanamine 4.[10]

This degradation initiated the intriguing idea that under enzymatically controlled conditions vinblastine 1 can undergo ipso protonation to give 1a and then 1b, which can scavange thiol groups to give adducts such as 6. As a corollary to this, vincristine 2 is deactivated toward ipso protonation by the N^1–CHO group and cannot function as an alkylating agent.

When the vinblastine model 7[11] was treated with aqueous TFA/*n*-BuSH/THF at 70 °C the adduct 9 (R = *n*-Bu) was isolated in 86% yield, along with *m*-methoxy-*N*,*N*-dimethylaniline. In a separate experiment 9 (R = *n*-Bu) was dissolved in neat TFA/*n*-BuSH/26 °C for 4.5 h, and the reduced product 10 was isolated in 68% yield. Exposure of 7 to concentrated HCl/*n*-

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0002-7863/87/1509-7929$01.50/0