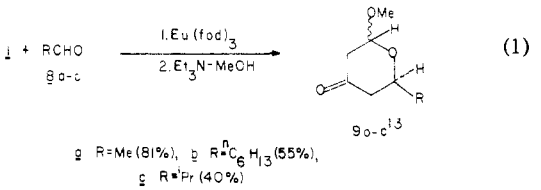
yield route to these silyl enol ethers (**5**) in hand, procedures for their smooth transformation to products of the type **6**[11] or **7**[11] were devised.

In the cyclocondensation reaction of the "parent" diene **1a** with saturated aliphatic aldehydes, endo selectivity is eroded. Aldehydes **8** react with **1a** (eq 1) in the presence of 0.5–5 mol % of $Eu(fod)_3$[12]



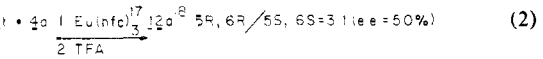

(1)

**9** a R=Me (81%), b R=$^n$C$_6$H$_{13}$ (55%), c R=$^i$Pr (40%)

in chloroform at room temperature. Methanolysis of the crude reaction mixture afforded compounds **9**[11] in the indicated yields as mixtures[13] of methyl acetals. Where studied, it was shown that the composition of the pyranosides reflects the ratio of their precursor silyl enol ethers.

The power of the method for the stereospecific synthesis of carbon-branched pyranose derivates is seen from the reaction of the substituted diene **1b**[14] with aldehydes **4a**, **8a**, and **8b**. Unlike the case with unsubstituted diene **1a**, virtually total endo specificity is maintained in the reaction of **1b** with a range (both aromatic and aliphatic) of aldehydes, giving rise to enol ethers **10**. Thus, three chiral centers are established through this suprafacial[4b,9] endo-cycloaddition process. A fourth center at $C_2$ is controlled through apparent axial protonation of the silyl enol ethers, which gives rise to the methoxyketones **11** (Scheme III).[11,15] Alternatively, the enol ethers **11** can be converted to cis-disubstituted pyrones **12**[11] in the usual way. Of course, for strictly preparative purposes, **11** and **12** could be obtained in higher yield by avoiding purification of the very sensitive vinylogous ortho esters **10**.

We have begun to explore the possibility that a $Eu^{3+}$ salt, bearing chiral ligands, might exhibit topological biases as it orchestrates the cyclocondensation reaction. This proposition has been reduced to practice. While the ultimate potentialities of this method for asymmetric induction will only be revealed after the sort of methodical investigations that are now in progress, the following finding is suggestive:




12a[16] 5R,6R/5S,6S=3:1 (ee=50%) (2)

The various results reported above have ramifications which are of continuing interest to our laboratory.

**Acknowledgment.** This research was supported by NIH Grant A1-16943-03. NMR spectra were obtained through the auspices of the Northeast Regional NSF/NMR Facility at Yale University.

(11) The structure of this compound is consistent with its infrared, NMR, and mass spectra. Spectral data for all new compounds are provided in the supplementary material.

(12) As expected, increases in the amounts of $Eu(fod)_3$ lead to an increased reaction rate. In the case of aldehyde **8a**, 0.5 mol % of catalyst was employed for 14 h (room temperature); for aldehyde **8b**, 5 mol % catalyst and 12 h (room temperature) were used, while in the case of aldehyde **8c** reaction was carried out with 1 mol % of catalyst for 100 h (room temperature).

(13) The cis/trans ratios in compounds **9** were for **9a** 2.8:1, for **9b** 1.2:1, and for **9c** 1.5:1.

(14) Danishefsky, S.; Yan, C.-F.; Singh, R. K.; Gammill, R. B.; McCurry, P. M., Jr.; Fritsch, N.; Clardy, J. *J. Am. Chem. Soc.* **1979**, *101*, 7001.

(15) Traces of another isomer, too minor for isolation, are suggested in the NMR spectra of compounds **12**. It is not clear whether this isomer is that arising from cycloaddition or from $\alpha$-protonation.

(16) Silyl enol ether **11c** was obtained as a ca. 1:1 mixture with the dihydropyrone **13c**. The latter was obtained as a pure compound on treatment of "**11c**" with trifluoroacetic acid (TFA) as shown.

(17) This is the trade name for tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato]europium, which is commercially available from Aldrich.

(18) **12a** was degraded to methyl 2-methyl-3-phenyl-3-hydroxybutyrate as previously[3a] described. The agreement of the optical rotation[19] and NMR ($Eu(hfc)_3$) measurements on this erythro ester serve to define both the sense and magnitude of the asymmetric induction. Details of the NMR method will be provided in the full paper.

(19) Cf.: Evans, D. A.; Bartoli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127 and references therein.

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**Supplementary Material Available:** Infrared, NMR ($^1$H and $^{13}$C), and mass spectral data for all new compounds (3 pages). Ordering information is given on any current masthead page.

## DNA Major–Minor Groove Binding Specificity of Daunorubicin: Anthramycin-Modified and T-4 Bacteriophage DNA Studies

Shau-Fong Yen, Wayne Germon, and W. David Wilson*

*Department of Chemistry and Laboratory for Microbial and Biochemical Sciences Georgia State University, Atlanta, Georgia 30303*

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The major vs. minor groove binding specificity of substituents on intercalating drugs is an important aspect of their interaction with DNA, which is not well understood and for which methods for systematic evaluation are not readily available.[1] With antitumor anthracycline drugs, adriamycin and daunorubicin, for example, fiber diffraction,[2] model building, and drug analogue activity[3] studies have led to proposals for binding of the nonaromatic A ring and its substituents in the major groove. An X-ray crystallographic structure of daunorubicin intercalated into a complementary double-helical nucleotide segment[4] and derivative binding analysis[5] have resulted in proposals for minor groove binding specificity for these drugs. We report here a method for evaluating major vs. minor groove binding specificity for many intercalators and use the method to establish that the A-ring substituents to daunorubicin bind in the minor groove under the solution conditions of these experiments.

Anthramycin (AM) is an antitumor antibiotic that reacts covalently with the 2-amino group of guanine in the minor groove of DNA.[6,7] Work by Kohn and co-workers[6] and by Hurly and co-workers[7] has shown that AM is topologically matched to the minor groove of DNA and covers approximately three base pairs to produce an uncharged adduct with very little perturbation of the double-helix structure. We prepared two samples with different AM to DNA-P ratio and conducted binding and viscometric studies of the interaction of daunorubicin with these modified DNA samples.[8] The binding results, shown in Figure 1A, il-

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(8) Samples I and II were prepared by addition of $3.2 \times 10^{-3}$ and $2.3 \times 10^{-2}$ mmol, respectively, of anthramycin methyl ether to $7.6 \times 10^{-2}$ mmol of sonicated calf thymus DNA in 2.0 mL of PIPES buffer (0.01 M piperazine-*N*,*N*'-bis(2-ethanesulfonic acid), 0.001 M EDTA, pH 7.0). The reaction mixture was stirred at room temperature for 3 h and at 4 °C for 4 h, extracted with octanol, and extensively dialyzed at 4 °C against the desired buffer. The anthramycin to phosphate ratios, determined spectrophotometrically,[7] were 0.0352 and 0.106 for samples I and II, respectively. Samples were also characterized by $^{31}$P NMR, Tm, and viscometric analysis. Binding studies were conducted as previously described.[9]

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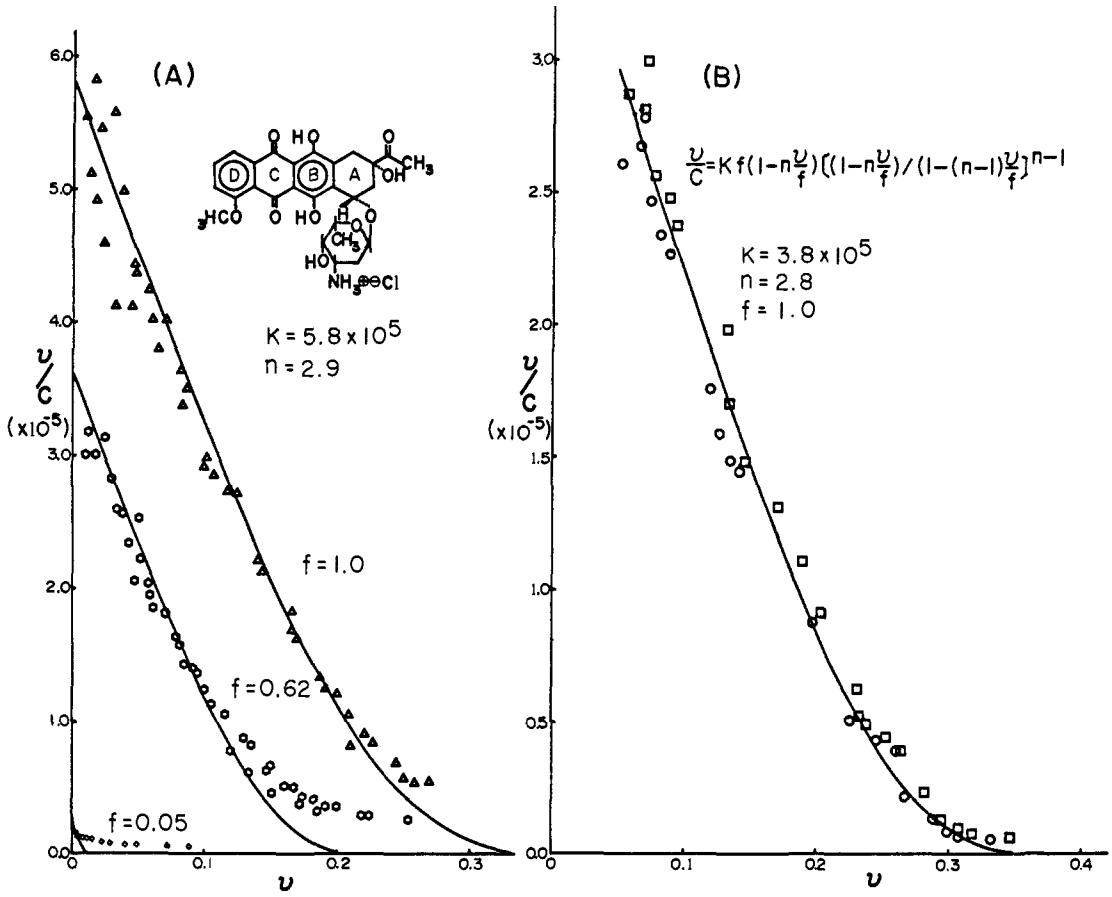


**Figure 1.** Scatchard plots for daunorubicin binding to several DNA samples. The symbols represent individual data points, and the lines are best fit values from eq 1: (A) curves from top to bottom are for unmodified DNA and samples I and II, respectively; (B) data points for T4 DNA are shown as squares while the nonglucosylated DNA results are shown as circles. The line in B is drawn with $K = 3.8 \times 10^5$, $n = 2.8$, and $f = 1.0$. This binding constant for T4 DNA is lower, as expected, than for the more G·C rich calf thymus DNA.[11] Experiments in A were conducted by using spectrophotometric methods while B represents equilibrium dialysis measurements.[9] All experiments were conducted at 30 °C in PIPES buffer containing 0.2 M NaCl at pH 7.2.

lustrate a dramatic decrease in daunorubicin binding as the fraction of AM-modified base pairs is increased. The binding results were analyzed by using the neighbor exclusion model of McGhee and von Hipple[9,10] modified to include blocking of sites on DNA:

$$\nu/C = Kf(1 - n\nu/f)[(1 - n\nu/f)/(1 - (n-1)\nu/f)]^{n-1} \quad (1)$$

where $\nu$ is the molar ratio of ligand bound per base pair, $C$ is the unbound ligand concentration, $K$ is the intrinsic binding constant, $n$ is the number of potential binding sites (base pairs) covered by a bound ligand, and $f$ is the fraction of sites that are available for binding (e.g., not blocked with AM). For native DNA $f = 1.0$, $K = 5.8 \times 10^5$, and $n = 2.9$ (Figure 1A) in agreement with other studies under similar conditions.[11] Binding results to the AM-blocked DNA samples are also shown in Figure 1A. The lines are drawn by using the same $K$ and $n$ values as for unmodified DNA and $f$ values of 0.62 for sample I and 0.05 for sample II. The lines fit the binding results well at low $\nu$ values, but there is clear evidence for a second binding mode with a lower binding constant at higher $\nu$ values. We have investigated binding of a range of intercalators to AM-blocked DNA and have found that binding inhibition seems to be correlated with the size of the intercalator groups that must fit into the minor groove. With proflavine, for example, which has been proposed, on the basis of X-ray diffraction experiments, to have only a small protrusion of the acridine ring into the minor groove (reviewed in ref 12), the inhibition to binding is a factor of 25–30 times less than for daunorubicin. With ethidium, which has substituents that are of smaller size than daunorubicin but that have also been proposed to lie in the minor groove,[12,13] the inhibition is still a factor of 10–15 times less than for daunorubicin. The inhibition obtained with proflavine probably occurs due to a combination of a slight protrusion of the acridine ring into the minor groove and some disruption of anthramycin–DNA contacts.

Viscometric titrations (not shown) were used to calculate the helix-length increase of the DNA samples on binding daunorubicin.[14,15] A dramatic reduction in the length increase was obtained with the AM-modified DNA samples. A calculation of the reduction in available base pairs using the ratio of the maximum viscosity increases of modified DNA divided by the viscosity increase of unmodified DNA indicated reductions of approximately 15% for sample I and 80% for sample II. The $f$ values discussed above indicate reductions of approximately 40% and 95% in available binding sites for samples I and II, respectively. If AM blocks three base pairs,[7] reductions in available base-pair binding sites of 21% and 63% are calculated for samples I and II, respectively, if only direct blocking of base pairs is considered. The difference between the viscosity and binding study calculations probably occurs due to the secondary binding mode, which was not considered in determining the $f$ values but which apparently can affect the maximum viscosity changes on daunorubicin binding. Differing sensitivity to partial blocking of neighboring

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sites in the modified DNA may also contribute to these differences. All of these results clearly show that AM modification of the DNA minor groove greatly limits daunorubicin binding.

Wild type T4 DNA has glucose residues covalently attached to cytosine in the major groove.[16] The glucose adduct is uncharged, does not significantly perturb the double-helix structure, and should be a steric probe for the major groove. We have isolated both this DNA[17] and a nonglucosylated sample.[18] In contrast to the results with AM-modified DNA samples, binding of daunorubicin to the glucosylated DNA is quite similar to binding to the nonglucosylated T4 mutant DNA (Figure 1B). Viscometric titrations with the glucosylated DNA are not significantly different than with the nonglucosylated DNA samples (not shown), and it is clear that the glucose residue in the major groove has a negligible effect on daunorubicin binding to DNA. These results taken together demonstrate that daunorubicin strongly prefers an intercalation complex in which the A-ring substituents are located in the DNA minor groove.

**Acknowledgment.** This research was supported by National Institutes of Health Grants GM 30267 and RR 09201. The anthramycin methyl ether used in this work was generously supplied by Dr. W. E. Scott of Hoffmann-La Roche Inc.

**Registry No.** Daunorubicin, 20830-81-3.

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## Diffuse Reflectance Infrared and Photoluminescence Spectra of Surface Vanadyl Groups. Direct Evidence for Change of Bond Strength and Electronic Structure of Metal–Oxygen Bond upon Supporting Oxide

Masakazu Iwamoto,* Hiroshi Furukawa, Kazuto Matsukami, Toshihisa Takenaka, and Shuichi Kagawa

*Department of Industrial Chemistry, Faculty of Engineering Nagasaki University, Nagasaki 852, Japan*
*Received February 8, 1983*

In the present communication, evidence is presented demonstrating that the bond strength and electronic structure of metal–oxygen bonds in supported metal oxides are dependent on the kinds of carriers and contents, with V=O double bonds in vanadium oxide as an example. Although much effort has so far been made to clarify surface structures and properties of catalytically active components supported on various carriers, results, as reported in the present study, have never reported. The present work will be useful for an understanding of catalytic reactions including photocatalysis and for solid inorganic chemistry.

The absorption bands of V=O double bonds in various supported vanadium oxides, which were changed along with the carriers and contents, are summarized in Table I.[1] The bond lengths listed in Table I were calculated on the basis of the correlation between the wavenumbers of V=O bonds and their bond lengths.[2] Byström et al.[3] and Bachmann et al.[4] have reported

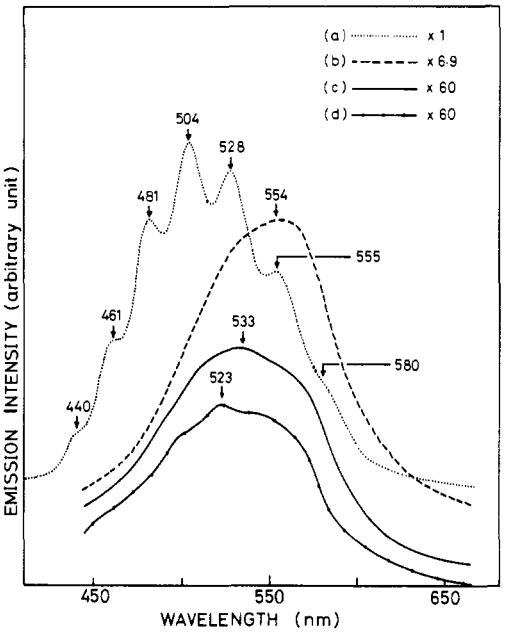


**Figure 1.** Phosphorescence spectra of 3.3 wt % $V_2O_5/SiO_2$ (a), 5.1 wt % $V_2O_5/MgO$ (b), 5.3 wt % $V_2O_5/\gamma$-$Al_2O_3$ (c), and 5.1 wt % $V_2O_5/\alpha$-$Al_2O_3$ (d) at 77 K. The spectra were recorded at 77 K after evacuation of the samples at 673 K. Excitation wavelengths were listed in Table I. Slit widths for excitation and emission were 5.0 and 1.5 nm, respectively.

1.58 Å for the V=O bond length in $V_2O_5$ crystals by their X-ray analyses, which is slightly longer than the present value determined by the diffuse reflectance IR technique. As shown in Table I, there are two kinds of V=O species in supported vanadium oxides. One has a length of 1.55–1.58 Å, the other of 1.68–1.70 Å. By considering that lengths of V–O single bonds in $V_2O_5$ crystals are 1.78–2.02 Å,[3,4] it follows that the latter V=O species is weaker in bond strength than that in the $V_2O_5$ lattice but it still retains the property of a double bond.

Generally, the strengths of metal–oxygen bonds decrease with decreasing electronegativity of metal ions.[5] The addition of electron-donating metals such as alkaline metals into pure $V_2O_5$ has indeed been reported to cause a red shift of the stretching band of V=O groups.[6] A similar red shift has been observed in the solid solutions of $V_2O_5$–$MoO_3$ because the charge of vanadium ions has been changed in part of 4+ from the usual 5+ owing to the presence of 6+ molybdenum ions in the $V_2O_5$ lattice.[7] Therefore, the bands at 912–954 $cm^{-1}$ presumably result from V=O species in which the charges of vanadium ions are less than 5+. Magnesia is known to be a typical basic oxide,[8] and the V=O stretching band appeared at 922 $cm^{-1}$ on the oxide. It is probable that silica gel has both basic and acidic sites on the surface. The $V^{4+}$ ions were confirmed in a separate ESR experiment to exist in the $V_2O_5/TiO_2$ sample without any reduction treatment,[9] which is the reason for the appearance of the V=O band at 912 $cm^{-1}$.

(1) Supported vanadium oxides were prepared by the following impregnation method. Silica gel (Fuji Davison Chemical, ID type) or other supports were soaked in an ammonia–aqueous solution of ammonium metavanadate, and water was evaporated on a water bath. The sample obtained was then calcined in air at 873 K for 5 h. The $V_2O_5$ content was determined by an atomic absorption spectroscopy after the sample was dissolved in a concentrated HCl + $HNO_3$ solution. Diffuse reflectance IR and photoluminescence spectra were measured by using a Nicolet 7199C FTIR spectrometer at 300 K and a Hitachi 650-10s fluorescence spectrophotometer at 77 K, respectively.
(2) On the basis of bond lengths and wavenumbers of vanadyl groups in $VOCl_3$, $V_2O_5$, $VOSO_4 \cdot 5H_2O$, $(NH_4)_2[VO(NCS)_4 \cdot H_2O] \cdot 4H_2O$, and $V_2O_4 \cdot 2H_2O$, one can obtain the following linear correlation, bond length (Å) = 2.751 − 0.001 15 × wavenumber ($cm^{-1}$).
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