nearly as well as the respective bleomycins (bleomycin A$_2$ (**1b**)).[7] They have been shown to mediate DNA strand scission with the same sequence specificity as the respective bleomycins;[5d] following anaerobic activation with C$_6$H$_5$IO both bleomycin and deglyco-bleomycin converted *cis*-stilbene to *cis*-stilbene oxide.[5c,7] For the present study we employed an analogue of deglycobleomycin (compound **2**[8]) lacking the putative DNA binding domain, as well

2   **3**
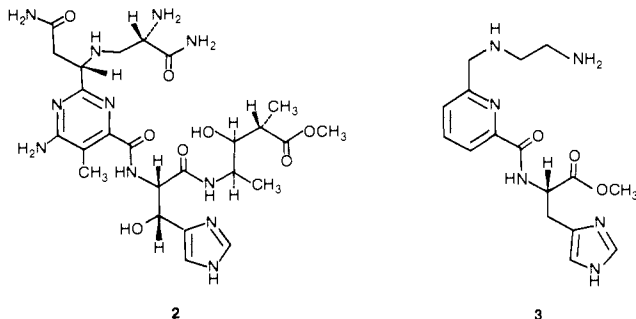
as a structurally simpler analogue (**3**) reported by Hénichart et al.[10]

Shown in Figure 1 is the attempted cleavage of SV40 form I DNA using **2** and **3** in the presence of Fe(II) and O$_2$.[11] At concentrations of Fe^{II}·**2** (lanes 11–14) and Fe^{II}·**3** (lanes 15–18) up to 50 μM, no conversion to form II (nicked circular) DNA or form III (linear duplex) DNA was noted beyond that produced by Fe(II) alone (lanes 7–10). In contrast, Fe(II)–deglyco-bleomycin produced extensive DNA degradation when tested over the same concentration range (lanes 3–6).

Although the lack of activity of Fe(II) + **2** or **3** in DNA strand scission seemed likely to be due to the absence of the putative DNA binding domain, it was also possibly due to lack of Fe(II) binding by **2** or **3** or to an inability to activate or transfer oxygen. Accordingly, the formation of Fe^{II}·**2** and Fe^{II}·**3** was established by spectral determination,[12] and each was utilized for the attempted epoxidation of *cis*-stilbene following activation with C$_6$H$_5$IO, a transformation already established for bleomycin[5c] and deglyco-bleomycin.[7] When employed at 0.57 mM concentration, Fe^{III}·**2** and Fe^{III}·**3** both effected epoxidation of *cis*-stilbene; the yields were ~150% in each case, based on added ligand.[13] Similar yields of *trans*-epoxide were obtained when Fe^{II}·**2** or Fe^{II}·**3** were incubated in the presence of *cis*-stilbene + O$_2$ + ascorbate. This confirmed the activation and transfer of oxygen by **2** and **3** in more traditional bimolecular reactions and served to define those structural components of BLM required for oxygen activation.

One remarkable feature of *cis*-stilbene oxidation by **2** and **3** was the finding that *trans*-stilbene oxide was the predominant

product. Previous studies using cytochrome P-450 and related model compounds containing ligated Fe have shown the cis isomer of stilbene to be the preferred substrate for epoxidation and *cis*-stilbene oxide to be the predominant product.[14] Analogous findings for three metallobleomycins[2e,5c] and two metallode-glycobleomycins[7] have reinforced these observations, as well as the mechanistic similarities between bleomycin and cytochrome P-450 as regards oxygen activation and transfer. The present finding parallels the observation by Valentine and co-workers that *trans*-stilbene oxide was produced from *cis*-stilbene via the agency of Cu(NO$_3$)$_2$ + C$_6$H$_5$IO.[15] It seems reasonable to suggest that the stereoselectivity noted previously for *cis*-stilbene finds its basis in the greater steric accessibility of this isomer to the bulky ep-oxidizing agents.[16]

(7) Aoyagi, Y.; Suguna, H.; Murugesan, N.; Ehrenfeld, G. M.; Chang, L.-H.; Ohgi, T.; Shekhani, M. S.; Kirkup, M. P.; Hecht, S. M. *J. Am. Chem. Soc.* **1982**, *104*, 5237.

(8) Prepared by DCC-mediated coupling of BOC-pyrimidoblamic acid[9] with methyl (2*S*,3*S*,4*R*)-4-(L-*erythro*-β-hydroxyhistidylamino)-3-hydroxy-2-methylvalerate,[7] followed by deblocking (CF$_3$COOH, CH$_3$SCH$_3$, 25 °C, 1 h).[7]

(9) Umezawa, Y.; Morishima, H.; Saito, S.; Takita, T.; Umezawa, H.; Kobayashi, S.; Otsuka, M.; Narita, M.; Ohno, M. *J. Am. Chem. Soc.* **1980**, *102*, 6631. (b) Arai, H.; Hagmann, W. K.; Suguna, H.; Hecht, S. M. *Ibid.* **1980**, *102*, 6633.

(10) Hénichart, J.-P.; Houssin, R.; Bernier, J.-L.; Catteau, J.-P. *J. Chem. Soc., Chem. Commun.* **1982**, 1295.

(11) Reaction mixtures (40 μL) containing 15 μM SV40 DNA, 1–50 μM Fe(NH$_4$)$_2$(SO$_4$)$_2$, and 1–50 μM **1a**, **2**, or **3** in 20 μM sodium cacodylate, pH 7.0, were incubated at 25 °C for 1 h. The reaction was terminated (1 mM EDTA) and samples were loaded onto 1.2% agarose gels containing 1 μg/mL ethidium bromide for electrophoretic analysis (16 h at 40 V in 40 mM Tris-OAc, 5 mM NaOAc, 1 mM EDTA, pH 7.8).

(12) For both **2** and **3**, the addition of Fe(II) in increasing concentrations up to 1 equiv caused increased absorption at the observed λ_{max} (282 and 268 nm, respectively), analogous to changes noted for BLM.

(13) An anaerobic solution (O$_2$-free argon) containing 0.12 μmol of **2** or **3** and 5 μg of Fe(ClO$_4$)$_3$ (0.12 μmol) in 25 μL of H$_2$O was incubated (10 min, 25 °C) and then treated with *cis*-stilbene (2 mg, 11.1 μmol) in 135 μL of CH$_3$OH. Iodosobenzene (0.8 mg, 3.6 μmol) was added dropwise (50 μL CH$_3$OH) over a period of 10 min. After an additional 1 h at 25 °C, the reaction was subjected to extractive workup and analyzed by HPLC.[2e]

(14) (a) Groves, J. T.; Nemo, T. E.; Myers, R. S. *J. Am. Chem. Soc.* **1979**, *101*, 1032. (b) Groves, J. T.; Nemo, T. E. *Ibid.* **1983**, *105*, 5786.

(15) Franklin, C. C.; Van Atta, R. B.; Fan Tai, A.; Valentine, J. S. *J. Am. Chem. Soc.* **1984**, *106*, 814.

(16) Consistent with this suggestion was the observation that variation in porphyrin or olefin substitution significantly altered chiral induction during the epoxidation of prochiral olefins: Groves, J. T.; Myers, R. S. *J. Am. Chem. Soc.* **1983**, *105*, 5791.

(Ethylene)ethylnickel Cyanide Complex Intermediate in Catalytic Hydrocyanation of Ethylene. Reductive Elimination by an Associative Process

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Contribution No. 3609
Central Research & Development Department
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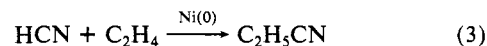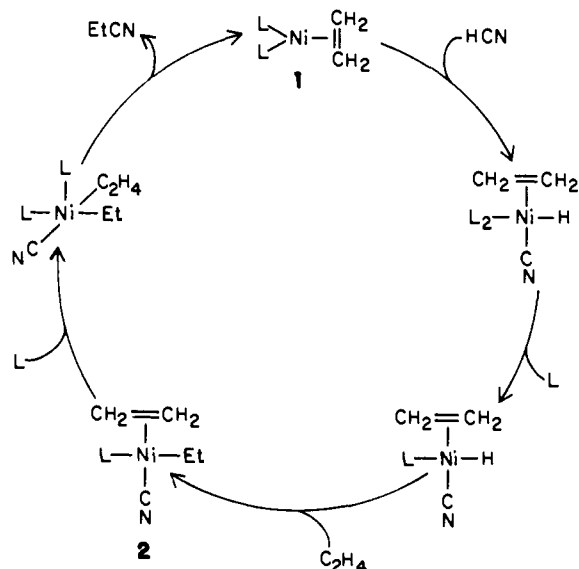*Experimental Station, Wilmington, Delaware 19898*
Received October 1, 1984

The reaction of (ethylene)bis(tri-*o*-tolyl phosphite)nickel, (C$_2$H$_4$)L$_2$Ni(0) [L = P(O-*o*-tolyl)$_3$] (**1**), with ethylene and hydrogen cyanide at −40 °C produces (C$_2$H$_4$)L(CN)(C$_2$H$_5$)Ni(II) (**2**) quantitatively (eq 1). Reaction of **2** with tri-*o*-tolyl phosphite
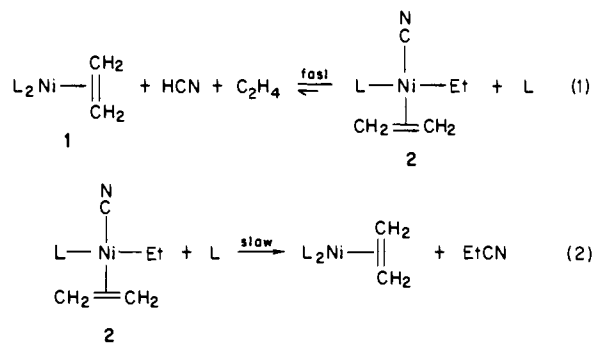
(L) causes reductive elimination of propionitrile and regenerates **1** (eq 2).

As part of our continuing studies of olefin hydrocyanation, we carried out kinetic measurements of the previously reported nickel-catalyzed hydrocyanation of ethylene,[1] eq 3, at low temperature utilizing proton NMR spectroscopy. Starting with the ethylene complex **1** rather than the [(*o*-tolyl-O)$_3$P]$_3$Ni previously

$$HCN + C_2H_4 \xrightarrow{Ni(0)} C_2H_5CN \qquad (3)$$

(1) Tolman, C. A.; Seidel, W. C.; Druliner, J. D.; Domaille, P. J. *Organometallics* **1984**, *3*, 33–38.

Scheme I

employed as catalyst, we were surprised to find an apparent second-order rate dependence on the initial concentration of **1**,[2] with a large negative entropy of activation [at –40 °C, $k = 7.6 \pm 0.8 \times 10^{-4}$ L/(mol s); $\Delta H^{\ddagger} = 8.9 \pm 0.9$ kcal/mol; $\Delta S^{\ddagger} = -34 \pm 4$ eu].[3] The reaction rate is independent of ethylene and hydrogen cyanide concentrations.

Examination of the system by ^{31}P NMR spectroscopy[4] revealed that, upon addition of HCN in the presence of excess ethylene at –40 °C, the resonance of **1** at 141.4 ppm is quantitatively replaced by four new singlets at 129.8, 118.1, 117.7, and 116.9 ppm with areas in a relative ratio of 1.00:0.14:0.80:0.06. The signal at 129.8 ppm is assigned to free (o-tolyl-O)$_3$P. These signals persist until HCN and/or ethylene are consumed. Reexamination of the proton spectrum reveals a multiplet at δ 0.61 assigned to a Ni–C$_2$H$_5$ species,[1] a singlet at δ 2.03 assigned to coordinated ethylene, and a broad singlet at δ 2.09 assigned to the methyls of (o-tolyl-O)$_3$P, both coordinated and uncoordinated. The ^{13}C NMR spectrum at –50 °C using ^{13}C^{12}CH$_4$-enriched ethylene[5] shows signals assigned to a Ni–C$_2$H$_5$ unit at 14.1 and 11.7 ppm, the latter a doublet with $J_{CP} = 35$ Hz, indicating coupling to one phosphorus in a trans position,[5] as well as a signal for coordinated ethylene at 58.9 ppm.

On the basis of these data, the intermediate species are assigned the isomeric structures of **2a–c** with **2a** being the predominant
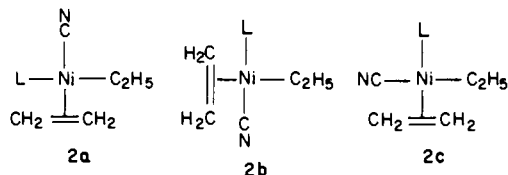
isomer based on the carbon–phosphorus coupling constant.[5] Whether all isomers participate in catalysis is unclear, but

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(2) Measurements were obtained on a Nicolet NT-360 MHz NMR spectrometer at 360.961 MHz. T_1 measurements were obtained for all species from –50 to –10 °C and pulse delays set accordingly. Samples were prepared in a Vacuum Atmosphere drybox in toluene-d_8 with concentration of **1** ranging from 0.01 to 0.10 M and concentrations of HCN and C$_2$H$_4$ generally about 0.26 and 0.20 M, respectively. CH$_2$Cl$_2$ (0.50 M) was used as an internal standard for proton spectra.

(3) Second-order rate constants were obtained from **1** (0.05 M in toluene-d_8) at –10, –20, –30, –40, and –50 °C. Activation parameters were estimated by nonlinear least-squares analysis of the experimental data.

(4) ^{31}P NMR spectra were obtained on a Nicolet 360-MHz NMR spectrometer at 146.14 MHz or on a Nicolet 300-MHz instrument at 121.68 MHz. T_1 measurements were obtained at ambient temperature and pulse delays set accordingly. Samples were prepared as in ref 2. Chemical shifts are referenced to external phosphoric acid.

(5) ^{13}C NMR spectra were those described in ref 1 and were obtained both with ^{13}C^{12}CH$_4$ and ^{13}C$_2$H$_4$ at –50 °C on the Nicolet 360-MHz instrument at 90.80 MHz. Chemical shifts are referenced to tetramethylsilane.

equilibration among the isomers appears to be faster than the catalytic reaction.

The apparent second-order rate dependence on **1** results from the production of **2** and free ligand which must recombine in the final slow step to produce propionitrile and **1**. Indeed, we have confirmed the second-order rate law,

$$d[\text{EtCN}]/dt = k[\mathbf{2}][\text{L}]$$

where k is the same second-order rate constant described above; the rate law is obeyed over at least tenfold concentration changes in each component. We propose the mechanism shown in Scheme I.

The rate dependence on the ligand concentration and the large negative entropy of activation suggest that a five-coordinate nickel species is formed prior to reductive elimination of propionitrile. This proposal is consistent with earlier observations on reductive elimination of organonitrile[6] and supports the recent theoretical analysis of Tatsumi et al.;[7] they suggest that reductive elimination from five-coordinate nickel species will usually be preferred over three- or four-coordinate counterparts primarily because of the stability of the nickel fragment produced. In our case, the generated fragment is an isolable complex whose stability must contribute greatly to the driving force of the reaction.

In light of proposals that oligomerization and polymerization of ethylene on nickel catalysts proceed through a (C$_2$H$_4$)Ni–C$_2$H$_5$-containing intermediate,[8] it is interesting to note that no butenes or hexenes or hydrocyanation products thereof are detected under our reaction conditions.

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(6) Favero, G.; Turco, A. *J. Organomet. Chem.* **1976**, *105*, 389. Favero, G.; Gaddi, M.; Morvillo, A.; Turco, A. *Ibid.* **1978**, *149*, 395. Favero, G.; Morvillo, A.; Turco, A. *Ibid.* **1978**, *162*, 99.

(7) Tatsumi, K.; Nakamura, A.; Komiya, S.; Yamamoto, A.; Yamamoto, T., submitted for publication.

(8) Jolly, P. W. In "Comprehensive Organometallic Chemistry"; Wilkinson, G., Stone, F. G. A., Abel, E. W., Eds.; Pergamon Press: New York, 1982; Vol. 8, pp 615–647.

Useful Approach for Determination of the Structure of Organosulfur Compounds: Sulfur-33 High-Resolution FT-NMR

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While the NMR spectra of many different nuclei have proved useful in organic structure determination, sulfur-33 NMR spectroscopy has been conspicuously absent. The vast importance of organosulfur chemistry demands an examination of this untapped tool. We show here that the combination of sulfur-33 line-width and chemical-shift data is a powerful diagnostic indicator. Compounds of the type R(SO$_2$)R' are usually amenable to ^{33}S NMR studies, which can provide relatively routine, unambiguous structural information not available from ^{13}C and ^{1}H NMR experiments. Compounds of the type RSR, RS(O)R, and RS(O)OR generally have line widths that are too broad (1000–5000 Hz) for routine ^{33}S NMR experiments. In the course of studies designed to explore the chemistry of acyl sulfones,[1] the carbomethoxy

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(1) Trost, B. M.; Quayle, P. *J. Am. Chem. Soc.* **1984**, *106*, 2469–2471.