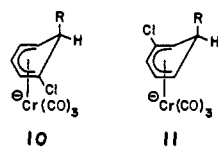donors (water, trifluoroacetic acid) but which are in rapid equilibrium with the starting materials, **1** and **2**. Addition of methyl iodide to the dynamic mixture of **1, 2, 3, 10,** and **11** leads to selective reaction of **1** (to


form pivaloylnitrile) and a shift in the equilibrium back to **2**, consistent with efficient recovery of chlorobenzene (entry 3, Table I).

The nature of the intermediates produced by protonation is not completely clear; a possible scheme is suggested in eq 2 using intermediate **11** as an example.
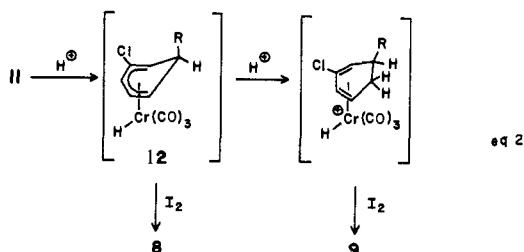
This pathway is consistent with the very low incorporation of deuterium into **8** (and **7**) when D_2O is used as the quenching agent. The dihydro analogs of **7** and **8** then arise by protonation on the carbon ligand in **12** to give intermediates which react with iodine to produce **9**, consistent with high incorporation of deuterium into **9** and with the higher proportion of **9** (and isomers) formed when a strong acid is used as quenching agent (entry 4, Table I).

Direct quenching with iodine (entry 5, Table I) again gives a mixture of **6, 7,** and **8**, consistent with oxidation of the proposed intermediates **4, 10,** and **11**, respectively; this reaction may be providing the best measure of the equilibrium mixture of early intermediates. In addition, the quenching with iodine provides a suggestion of a potentially useful synthetic reaction, where an aryl ring hydrogen is replaced by a nucleophile *via* coordination to chromium.[9] Similarly, the substitution for hydrogen *with* reduction observed as a minor process during quenching with proton sources (entries 4 and 5, Table I) points to potential applications in synthesis. For example, work in progress has shown that these processes are much more efficient for π-benzenechromium tricarbonyl (eq 3).[10] Further ex-
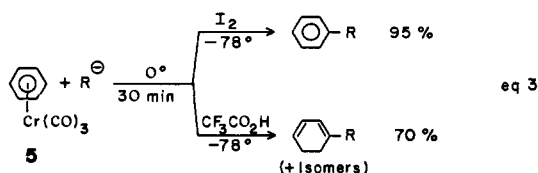
(9) A related conversion involving *n*-butyl- and *tert*-butyllithium with complex 2 may also involve nucleophilic addition although the mechanism is obscure. *Cf.* R. J. Card and W. S. Trahanovsky, *Tetrahedron Lett.*, 3823 (1973).

(10) M. F. Semmelhack and H. T. Hall, to be submitted for publication.

amples of these processes and direct observation of the intermediates involved are currently under study.[11]

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Reactions of Vinyl Ethers with Cobalamins and Cobaloximes

Sir:

We recently reported[1] that cobaloximes and cobalamins reacted with vinyl ethers, in the presence of alcohols, to give acetals containing cobalt–carbon σ-bonds. On the basis of these, and earlier[2] experiments, we suggested that the reactions proceeded *via* the intermediary of a Co(III)–olefin π-complex. Schrauzer, *et al.,*[3] then reported that they were unable to confirm our results and concluded that the reactions we reported did not in fact take place. It was further concluded[3] that the biochemical implications our reactions suggested were also invalid.

We wish to report, for a second time, that both cobaloximes and cobalamins react as their Co(III) complexes with vinyl ethers, in the presence of alcohols and bases, to give the corresponding cobalt(III) alkyl complexes (Scheme I). The experimental details,[4] for

Scheme I
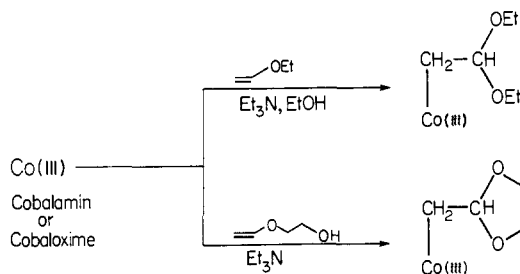
the reactions we reported in our earlier communication,[1] are given below.

Reaction between bromo(pyridine)cobaloxime and ethyl vinyl ether was accomplished as follows. To a deaerated solution of bromo(pyridine)cobaloxime (0.9 g, 2.0 mmol) in dry methylene dichloride (35 ml), over Drierite, was added triethylamine (0.31 g, 3.2 mmol, twice distilled from 1-naphthyl isocyanate), absolute ethanol (4.7 g, 100 mmol), and ethyl vinyl ether (7.53 g,

(1) R. B. Silverman and D. Dolphin, *J. Amer. Chem. Soc.,* **95,** 1686 (1973).

(2) R. B. Silverman, D. Dolphin, and B. M. Babior, *J. Amer. Chem. Soc.,* **94,** 4028 (1972).

(3) W. J. Michaely and G. N. Schrauzer, *J. Amer. Chem. Soc.,* **95,** 5771 (1973).

(4) We wish to thank Professor Alan Davison (MIT) for confirming our experimental procedures. After this confirmation, Professor Schrauzer informed us that he too had repeated the experiments and confirmed our observation we reported[1] for the reactions between cobaloximes and vinyl ethers.

100 mmol). The mixture was then allowed to stand in the dark until the reaction was complete[5] (3 days). The desiccant was removed by filtration, and the solvent was removed, below 35°, under reduced pressure. The yellow-brown residue was triturated with water (10 ml, containing one drop of triethylamine) and filtered to give a yellow-orange solid (0.77 g). This solid was recrystallized from methylene dichloride–cyclohexane. The product,[6] 2,2-diethoxyethyl(pyridine)cobaloxime (orange crystals), was then stirred in water (10 ml) for 20 min. This procedure removes formylmethylcobaloxime, which is the major impurity: nmr $\delta_{TMS}^{CDCl_3}$ 1.09(t, J = 7 Hz, 6 H), 1.55 (d, J = 5 Hz, 2 H), 2.13 (S, 12 H), 3.15–3.6 (m, 4 H), 4.27 (t, J = 5 Hz, 1 H), 7.32, 7.77, 8.58 (3m, 5 H); ir$_{cm^{-1}}^{KBr}$ 1565 (C=N), 1235, 1085 (N—O), 1040 (C—O), 520 (Co—N).

The product from the above reaction may be hydrolyzed on silica gel as follows. The crude product from the above reaction was dissolved in a small volume of methylene dichloride and chromatographed on silica gel (2.3 × 25 cm, Woelm activity II) eluting with methylene dichloride containing 5% pyridine. The orange band was collected and the solvent was evaporated. Recrystallization from methylene dichloride–cyclohexane afforded formylmethyl(pyridine)cobaloxime as shiny orange crystals: nmr $\delta_{TMS}^{CDCl_3}$ 1.83 (d, J = 5 Hz, 2 H), 2.23 (S, 12 H), 7.32, 7.77, 8.50 (3m, 5 H), 9.33 (t, J = 5 Hz, 1 H); ir$_{cm^{-1}}^{KBr}$ 2820, 2725 (C—H), 1655 (C=O), 1560 (C=N), 1238, 1089 (N—O). Anal. Calcd for $C_{15}H_{22}CoN_5O_5$: C, 43.80; H, 5.39; N, 17.03. Found: C, 44.07; H, 5.49; N, 17.13.

Reaction between hydroxocobalamin and ethyl vinyl ether was accomplished as follows. To a deaerated solution of hydroxocobalamin (50 mg, 3.3 × 10^{-5} mol) in absolute ethanol (5 ml) was added triethylamine (10 mg, twice distilled from 1-naphthyl isocyanate) and ethyl vinyl ether (0.25 g, 2.3 mmol). The reaction mixture was allowed to stand in the dark, at room temperature until the reaction was complete[7] (2 days). The product, 2,2-diethoxyethylcobalamin, which crystallized directly from the reaction mixture, was collected by filtration to give shiny burgundy needles.[8]

The reaction between bromo(pyridine)cobaloxime and 2-hydroxyethyl vinyl ether was accomplished as follows. To a deaerated solution of bromo(pyridine)cobaloxime (224 mg, 0.5 mmol) in dry methylene dichloride (8 ml) was added triethylamine (83 mg, 0.8 mmol, twice distilled from 1-naphthyl isocyanate) and 2-hydroxyethyl vinyl ether[9] (1.9 ml, 25 mmol). The brown solution was allowed to stand in the dark at

room temperature until the reaction was complete[10] (3 days). The mixture was then concentrated at room temperature on a rotary evaporator and taken down to dryness under high vacuum. The residue was stirred with water (5 ml, containing 1 drop of triethylamine), and filtered to give a yellow solid which was recrystallized from methylene dichloride–cyclohexane to give the product 1,3-dioxa-2-cyclopentylmethyl(pyridine)cobaloxime as shiny orange needles:[6] nmr $\delta_{TMS}^{CDCl_3}$ 1.46 (d, J = 5 Hz, 2 H), 2.14 (S, 12 H), 3.6–3.9(m, 4H), 4.79 (t, J = 5 Hz, 1 H), 7.32, 7.77, 8.58 (3m, 5 H); ir$_{cm^{-1}}^{KBr}$ 1560 (C=N), 1233 1083 (N—O), 1030 (C—O), 517 (Co—N). Anal. Calcd. for $C_{13}H_{16}CoN_5O_5$: C, 44.84; H, 5.76; N, 15.38. Found: C, 44.67; H, 5.67; N, 15.27.

Reaction between hydroxocobalamin and 2-hydroxyethyl vinyl ether was accomplished as follows. To a deaerated solution of hydroxocobalamin (50 mg, 3.3 × 10^{-5} mol) in deionized water (5 ml) was added triethylamine (10 mg twice distilled from 1-naphthyl isocyanate) and 2-hydroxyethyl vinyl ether[9] (0.25 ml, 3 mmol). The red solution was allowed to stand in the dark at room temperature until the reaction was complete[7] (2 days). The reaction mixture was concentrated and a drop of triethylamine added. Acetone was then added until the solution turned cloudy. After 1 day, the product[8] 1,3-dioxa-2-cyclopentylmethylcobalamin (40 mg) was collected as bright red needles.

We proposed[2] that these reactions could be envisaged as proceeding via a Co(III) olefin π-complex (1) (Scheme II). Schrauzer, et al.,[3] questioned the existence of

Scheme II
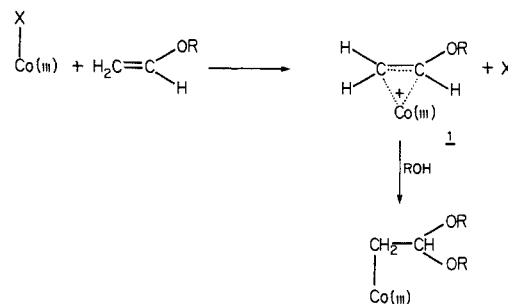
such π-complexes, claiming that the Co(III) ion is unable to form sufficiently stable dπ–pπ bonds with organic π-electron systems and that the CH₂=CH– moiety in vinyl ethers could not be regarded as sufficiently strongly σ bonding to coordinate with the Co(III) ion in corrins or cobaloximes. We wish to point out, however, that the bonding between a transition metal and an unsaturated organic ligand (whether it be carbon monoxide, cyanide, or an olefin) is synergic.

Thus many stable transition metal–olefin complexes[11] are formed with the metal in a low oxidation state (electron rich) and olefins such as tetracyanoethylene (electron deficient). There is no reason to suppose that synergic bonding cannot function in the opposite sense, and we propose that the reverse situation, high oxidation state of the metal and electron rich olefins,

(5) The reaction was followed by nmr spectroscopy, observing a decrease in the signal at 2.37 ppm of the methyl protons in the dimethylglyoximato ligand of the starting material, and an increase in the signal at 2.10 ppm of the product.

(6) The acetals prepared from the cob(III)aloxime and vinyl ethers were identical with the acetals prepared from the cob(I)aloxime and the corresponding bromoacetal.

(7) The reactions between hydroxocobalamin and vinyl ethers were followed by observing the decrease in the absorption at 350 nm and by tlc on cellulose plates (Brinkmann Celplate-22 without indicator) using 1-butanol:ethanol:water (10:3:7) containing 0.5% concentrated NH$_4$OH as eluent. In this chromatographic system the R_f values were: hydroxocobalamin, 0.22; 2,2-diethoxyethylcobalamin, 0.61; and 1,3-dioxa-2-cyclopentylmethylcobalamin, 0.56.

(8) The acetals prepared from hydroxocobalamin and vinyl ethers were identical with those prepared from B$_{12a}$ and the corresponding bromoacetal.

(9) H. S. Hill and L. M. Pidgeon, J. Amer. Chem. Soc., 50, 2718 (1928).

(10) Reaction followed as in ref 5; the product absorbed at 2.09 ppm.

(11) M. Herberhold, "Metal π-Complexes," Vol. II, Part I, Elsevier, New York, N. Y., 1972.

might also give rise to stable transition metal–olefin π complexes.

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Figure 1. (a) Hydroxocobalamin was reduced by $NaBH_4$ to $B_{12}(s)$ and then alkylated with 3-chloro-1,2-propanediol. The product was desalted (D. Dolphin, *Methods Enyzmol.*, **18c**, 34 (1971)) and applied to silica gel plates, which were developed in 1-propanol: water:concentrated ammonia (100:99:1). The resulting 2,3-dihydroxypropylcobalamin (2) ran as a broad band with R_f = 0.3–0.5 and was eluted and oxidized with meta periodate in aqueous ammonia.[6] (The oxidation was followed by measuring release of formaldehyde by a modification of the method described in E. R. Frisell, L. A. Meech, and C. G. MacKenzie, *J. Biol. Chem.*, **207**, 709 (1954).) The formylmethylcobalamin was separated from hydroxocobalamin (also a product in the oxidation reaction) by passing the mixture through a column of Bio-Gel P-2 (200–400 mesh) in aqueous ammonia. (b, c) Preparation of 1,3-dioxa-2-cyclopentylmethylcobalamin (3) from hydroxocobalamin and 2-hydroxyethyl vinyl ether is described in the preceding paper. See R. B. Silverman and D. Dolphin, *J. Amer. Chem. Soc.*, **96**, 7094 (1974). The same product is obtained from the bromoacetal 4 and $B_{12}(s)$. Partial hydrolysis of the acetal to formylmethylcobalamin occurred after 48 hr at pH 9.0 in 0.025 M Borax–0.1 N HCl buffer (R. C. Weast, Ed., "Handbook of Chemistry and Physics," 46th ed., The Chemical Rubber Co., Cleveland, Ohio, 1965, p D-73). The product was separated from hydroxocobalamin and the starting acetal by chromatography on cellulose plates. (d) Hydroxocobalamin and ethyl vinyl ether were allowed to stand at room temperature for 6 days in 95% ethanol. On chromatography,[5] formylmethylcobalamin and 2,2-diethoxyethlcobalamin were resolved in the ratio of about 4 to 1.

Formylmethylcobalamin

Sir:

It has been postulated that formylmethylcobalamin (1) is an intermediate in the enzymic conversion of ethylene glycol to acetaldehyde in a coenzyme-B_{12} dependent reaction.[1,2] The synthesis of this compound has recently been reported as well as some of its chemical properties.[3] We have also synthesized this compound and have found significant differences in its chemical properties from those reported. Since this compound has been proposed as an intermediate in a reaction of considerable interest, we now report the properties of the compound we have observed.

Formylmethylcobalamin was synthesized in four different ways, which are outlined in Figure 1. Each synthetic scheme resulted in the same product. The methods of synthesis establish the structure of the compound as formylmethylcobalamin. The product was characterized through its uv and visible absorption spectrum[4] and the R_f value in several chromatographic systems.[5] The rates of acid hydrolysis of the compound prepared by any of the above routes were identical (see below). Acetaldehyde and hydroxocobalamin were quantitatively identified after acid hydrolysis (acetaldehyde by glc and hydroxocobalamin by its optical spectrum). The same products were qualitatively identified after aerobic and anaerobic photolysis.[6]

The properties of formylmethylcobalamin, which we have observed, differ from those reported previously in two respects. It was reported that the nmr spectrum of formylmethylcobalamin showed a triplet at 9.01 ppm (solvent not stated).[3] The compound which we have shows a broad triplet at 8.22 ppm[7] (in D_2O).

The broadening may be due to the interaction with the diastereotopic methylene protons. The diastereotopic nature of the methylene protons of cobalamin has previously been reported.[8,9]

It was also reported that formylmethylcobalamin is acid stable,[3] and an optical spectrum of this compound at pH 5.8 was shown. We find that formylmethylcobalamin is acid sensitive. The rate of decomposition at various pH values for formylmethylcobalamin synthesized through two different routes is shown in Table I. Note that $t_{1/2}$ at pH 5.8 is 3 min.[10] The rate law for decomposition is $d[\text{formylmethylcobalamin}]/dt = -k[\text{formylmethylcobalamin}][H_3O^+]$, where k = 2040 $M^{-1}\ sec^{-1}$.

(1) R. H. Abeles, *Advan. Chem. Ser.*, No. **100**, 346 (1971).
(2) T. J. Carty, B. M. Babior, and R. H. Abeles, *J. Biol. Chem.*, **246**, 6313 (1971).
(3) G. N. Schrauzer, W. J. Michaely, and R. J. Holland, *J. Amer. Chem. Soc.*, **95**, 2024 (1973).
(4) The spectrum was typical of an alkylcobalamin, $\lambda_{nm}^{H_2O}$ ($\epsilon \times 10^{-3}$): 262 (26.3), 278 (23.3), 288 sh (20.0), 334 (15.1), 370 (13.9), 430 (5.42), 496 sh (6.54), 526 (8.37), 550 sh (7.12).
(5) Formylmethylcobalamin has an R_f value of 0.51 on Brinkmann cellulose plates developed in 1-butanol:ethanol:water (10:3:7) containing 0.5% concentrated aqueous ammonia. Products from all synthetic routes also cochromatographed when the plates were developed in *n*-butyl alcohol:isopropyl alcohol:water (7:6:7) containing 0.5% concentrated aqueous ammonia (R_f = 0.54) or *sec*-butyl alcohol:methanol:water (55:15:30) containing 0.5% concentrated aqueous ammonia (R_f = 0.45).
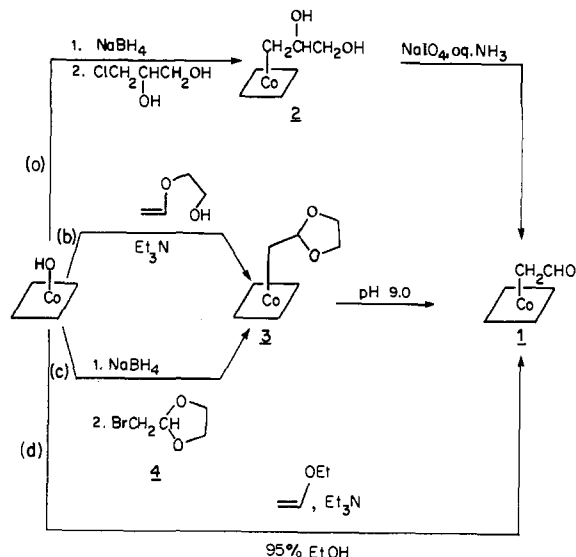(6) T. J. Carty, Ph.D. Thesis, Brandeis University, 1973.
(7) The methine proton of aliphatic aldehydes normally appears in the region δ 9–10. A value of 8.22 for formylmethylcobalamin is consistent with the shielding, and consequent upfield shift, experienced by protons on the β-carbon of an alkylcobalamin.
(8) J. D. Brodie and M. Poe, *Biochemistry*, **11**, 2534 (1972).
(9) J. D. Brodie and M. Poe, *Biochemistry*, **10**, 914 (1971).
(10) Acetate buffers, prepared by mixing 0.1 M solutions of sodium acetate and acetic acid, were used for runs with pH <6; phosphate buffers, prepared by mixing 0.1 M solutions of mono- and dibasic sodium phosphate, were used for runs with pH >6.