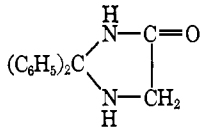
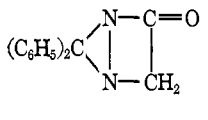
158–159° (83%); ir, 3175, 1760 cm^{-1}; nmr, δ 4.62 (1 H, singlet), 4.92 (1 H, singlet), 6.9–7.7 (15 H, aromatic multiplet)]. The rate of inversion of the benzhydryl grouping of N_1 of compound Ia was measured utilizing the method of Mannschreck.[4,5] In dimethyl-d_6 sulfoxide compound Ia had k_c = 102.8 sec^{-1} and $\Delta G^{\ddagger}$ = 18.4 kcal/mol with a coalescence temperature (T_c) of 97°.

Reduction of azomethine imide Ia with Raney nickel in ethanol gave α-diphenylmethylaminoacetamide (mp 109–110.5°), which was prepared independently from ethyl α-diphenylmethylaminoacetate[6] and ammonia; its formation from Ia follows a well-established precedent for N–N bond cleavage of both acyclic[7,8] and cyclic[9,10] acylhydrazides. However, catalytic reduction of azomethine imide Ia with deactivated Raney nickel[11] gave 2,2-diphenyl-4-imidazolidinone (III) [mp 165–166.5° (67%); ir, 3410, 3100, 1680 cm^{-1}; nmr, δ 3.96 (2 H, singlet), 6.34 (1 H, broad N–H), 7.43 (10 H, complex



III

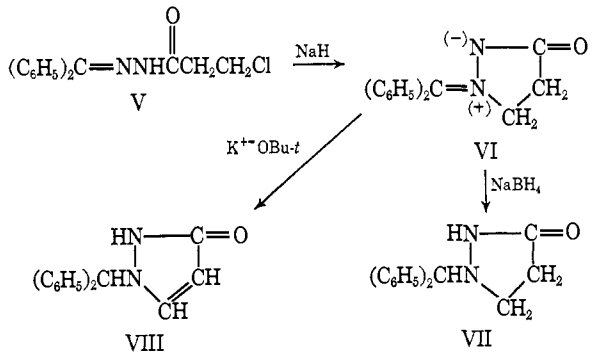


IV

aromatic multiplet); *m/e* 238]. The structure of III was confirmed by dilute acid hydrolysis to benzophenone and glycinamide hydrochloride.

The formation of III from the azomethine imide Ia suggests the possible intermediacy of the bicyclodiaziridine valence bond tautomer IV, which was previously implicated as an intermediate in the pathway to Ia from the chloroacetylhydrazone of benzophenone.[2]

Our new route to cyclic azomethine imides[2] has been extended to the use of the homologous β-chloropropionylhydrazone of benzophenone (V), which yielded VI with sodium hydride in benzene. The structure of VI was confirmed by its spectroscopic and chemical properties. Mass spectroscopy and microanalysis confirmed its molecular formula as $C_{16}H_{14}N_2O$ (*m/e* 250), mp 228–230° dec (77%). Its uv spectrum (ethanol) showed maxima at 240 mμ (ε 13,400) and 335 mμ (ε 23,600); its ir spectrum, in contrast with that of Ia, revealed a carbonyl band at 1685 cm^{-1}, consistent with a five-membered cyclic lactam. Finally, its nmr spectrum showed two triplets at δ 2.59 and 4.12 (J = 7 Hz, with further fine splitting) and a complex eight-proton aromatic multiplet centered at 7.40, with an additional two-proton multiplet at 7.95. Acid hydrolysis of VI in aqueous ethanol gave benzophenone and 3-pyrazolidinone hydrochloride (mp 195° dec, 74%), identical with an authentic sample.[12] Sodium borohydride reduction of VI gave 1-diphenylmethyl-3-pyrazolidinone (VII) [mp 158–160° (66%); ir, 3150, 1680 (split) cm^{-1}; nmr, δ 2.38 (2 H, triplet; J = 8 Hz, with finer splitting), 3.18 (2 H, triplet; J = 8 Hz, with finer splitting), 4.57 (1 H, singlet), 7.0 (broad N–H singlet), 7.34 (10 H, aromatic multiplet)]. Reduction of VI with Raney nickel in ethanol gave β-diphenylmethylaminopropionamide (mp 99–100°).



V

VI

VIII

VII

Treatment of the azomethine imide VI with potassium *t*-butoxide in refluxing benzene resulted in its conversion in 75% yield into an isomer, mp 179–180°. Spectral data [nmr, δ 7.12 (10 H, aromatic multiplet), 6.5 (1 H, singlet), 5.6 and 7.0 (2 H, doublet; J = 3.5 Hz); ir, 2625 (broad), 1675 cm^{-1} (weak); uv, $\lambda_{max}^{ethanol}$ 230 mμ (sh)] showed that this isomeric compound must possess structure VIII. It formed a monobromo derivative and both a hydrochloride and a sodium salt. The mechanism of the conversion of VI to VIII, as well as cycloaddition reactions and further chemical transformations of the cyclic azomethine imides I and VI, will be described in the full paper.

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(12) J. C. Howard, G. Gever, and P. H. L. Wei, *J. Org. Chem.*, 28, 868 (1963).

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The Reaction of Vitamin B_{12a} and of Cobaloximes with Carbon Monoxide. Evidence for Self-Reduction of Vitamin B_{12a} in Neutral Solution[1]

Sir:

Bayston and Winfield[2] recently reported the reduction of vitamin B_{12a} with carbon monoxide in aqueous solution (eq 1). This reaction suggests a unique reactivity

$$2B_{12a} + CO + H_2O \longrightarrow 2B_{12r} + CO_2 + 2H^+ \qquad (1)$$

of the Co(III) ion in vitamin B_{12a}, since conventional Co(III) chelates are known to be unreactive with CO. Cobaloximes(III), *e.g.*, hydroxy(aquo)- or hydroxy(pyridine)bis(dimethylglyoximato)cobalt(III), are likewise not reduced by CO, but if a trace of a cobaloxime(II) is added, reduction to the Co(I) derivatives is observed. The reduction of cobaloximes(III) with carbon monoxide yields the Co(I) nucleophiles under extremely mild conditions and is recommended for the synthesis of sensitive organocobaloximes. The reaction with CO proceeds in a manner typical of autocatalyzed reactions (Figure 1) and appears to be similar to that

(1) Supported by National Science Foundation Grant GB 6174.
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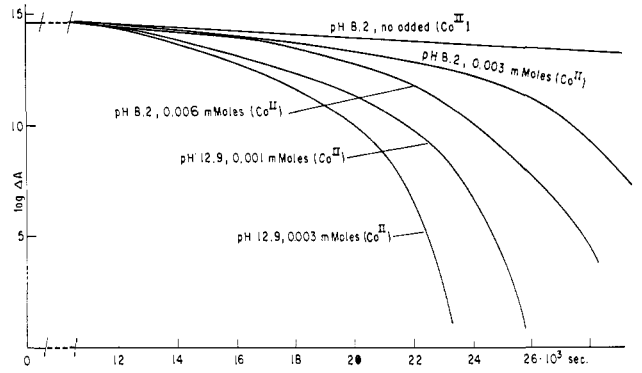


Figure 1. Reduction of hydroxy(aquo)cobaloxime(III) with CO (1 atm, 25°) at pH 8.2 and 12.9 in the presence of various amounts of added bis(aquo)cobaloxime(II). The reaction was followed by measuring the *increase* of absorbance A at 525 mμ. Log $\Delta A = \log (A_\infty - A_t)$.

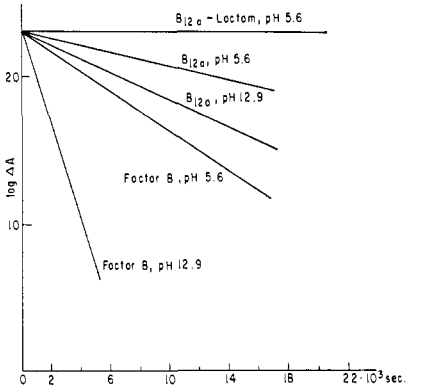
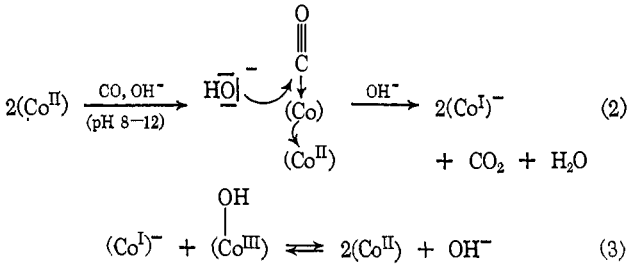


Figure 2. Reduction of vitamin B_{12a}, vitamin B_{12a} lactam, and factor B with CO (1 atm, 25°) at various pH values. The reaction was followed by observing the *decrease* of absorbance A at 525 mμ. Log $\Delta A = \log (A_\infty - A_t)$.

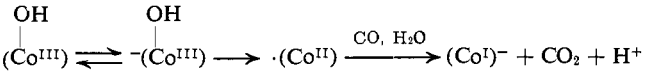
observed for reduction with molecular hydrogen.[3] The carbon monoxide evidently interacts with the Co(II) species present in solution whose concentration increases in the course of the reduction. Since CO is a two-electron donor, the reduction of the cobaloximes to the Co(I) derivatives is seen to involve intramolecular electron-transfer reactions as shown by eq 2 and 3.



Equation 2 is similar to the mechanism proposed for the reduction of Ag^+ or Hg^{2+} by CO in aqueous solution.[4,5] However, we find it preferable to regard the first step as a displacement of the coordinated water rather than an insertion reaction.

The reduction of the cobaloximes is pH dependent. Above pH 8 the Co(I) nucleophiles are formed, but between pH 7 and 8 a slow reduction to the Co(II) derivatives takes place.

Vitamin B_{12a} reacts with carbon monoxide following a pseudo-first-order rate law, at least in the initial stages of reduction.[2] An induction period is not observed. This suggested that vitamin B_{12a} in solution is at equilibrium with a Co(II) derivative formed *via* a self-reduction process. Self-reduction of vitamin B_{12a} was shown to occur slowly in alkaline solution[6–8] but has not been considered to occur in neutral or weakly acidic medium. The self-reduction is pH dependent since it is initiated by the removal of a proton from an activated β position primarily on ring B of the corrin system.[6–8] Subsequent electron transfer to cobalt yields Co(II) or Co(I) derivatives depending on the reaction conditions. Since solutions of vitamin B_{12a} at neutral pH are known to be sensitive to oxygen, it may be assumed that equilibrium amounts of Co(II) species are generated by a process similar to that occurring in alkaline medium. The reduction by CO would hence involve the interaction of CO with a Co(II) derivative, and not the original Co(III) complex, *e.g.*, according to eq 4. The



initially produced vitamin B_{12s} is converted to vitamin B_{12r} on interaction with vitamin B_{12a} by the known[9] reaction 5.

$$B_{12a} + B_{12s} \rightleftharpoons 2B_{12r} \quad (5)$$

Our evidence for the self-reduction of vitamin B_{12a} in solution at room temperature and neutral pH can be summarized as follows. (a) Freshly prepared solutions of vitamin B_{12a} exhibit esr signals similar to those reported[10] for vitamin B_{12r} which are more intense in alkaline than in neutral medium. The esr spectrum in water at pH 7 differs from that of vitamin B_{12r} *by a superimposed free-radical signal at g = 2.029.* (b) On contact with air, the radical species disappear remarkably slowly as they are continuously regenerated. The determined half-life times of the oxidation reaction are 35 hr at pH 5.5 and 7 and 8 hr at pH 10, respectively, if a stream of air is being passed through the solutions at 25°. (c) The oxidized solutions of vitamin B_{12a} show no esr signal and *are not reduced by CO.* Analysis by tlc reveals the presence of significant amounts of pink oxidation products originally absent in the fresh solutions. (d) Factor B in solution is reduced at a faster rate than vitamin B_{12a} (Figure 2). The solutions lose activity over a period of days on contact with air. (e) Vitamin B_{12a} lactam and factor B lactam are reduced by CO much more slowly than vitamin B_{12a} or factor B, respectively (Figure 2), demonstrating the importance of the active β positions in the self-reduction process. (f) The spontaneous formation of Co(II) derivatives in solutions of vitamin B_{12a} causes the generation

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of equilibrium amounts of vitamin B_{12s} under anaerobic conditions. This was demonstrated by adding methyl iodide to a freshly prepared solution of vitamin B_{12a} at pH 7.0 under argon. Methylcobalamin, in yields approaching 18%, was detected after 3 days of standing at 25° (the methylcobalamin was identified by comparison of the R_f values on cellulose with an authentic mixture of vitamin B_{12a} and methylcobalamin, using 1-butanol–acetic acid–water 4:4:1). No methylcobalamin was formed in vitamin B_{12a} solutions at pH 5.5 under otherwise identical conditions.

The reduction of vitamin B_{12a} by CO thus is a consequence of the presence of Co(II) species in the reaction solution and is not indicative of a special reactivity of the Co(III) ion in this corrin derivative. Accordingly, all reactions of vitamin B_{12a} must now be treated with caution unless self-reduction effects are definitely excluded. This applies particularly for the previously reported reaction of vitamin B_{12a} solutions with oxygen, which were interpreted[11] to suggest that vitamin B_{12a} is an oxygen carrier, in fact, the only Co(III) oxygen carrier known. The demonstrated self-reduction of solutions of vitamin B_{12a} makes this view untenable.

Finally, it should be mentioned that the reaction of carbon monoxide with Fe(III) porphyrins was suggested[12] to initially involve a self-reduction to Fe(II) derivatives which were considered to be the catalytically active species.

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Methylcobalt Derivatives of Vitamin B_{12} Model Compounds as Substrates in Enzymatic Methane Formation

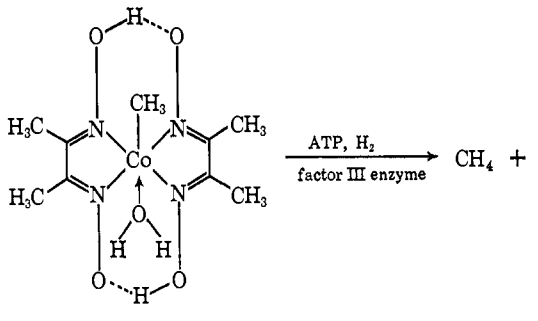
Sir:

Extracts of the methanogenic bacterium MOH[1] catalyze the formation of methane from methylcobalamin according to eq 1.[2-4] This reaction shows an

$$\text{methylcobalamin} \xrightarrow[\text{factor III enzyme}]{\text{ATP, } H_2} CH_4 + \text{vitamin } B_{12r} \quad (1)$$

absolute requirement for adenosine 5′-triphosphate (ATP). The factor III enzyme[4] which is involved in the final methyl transfer reaction leading to the formation of methane from N^5-methyltetrahydrofolic acid and/or methylcobalamin is inhibited by halogenated hydrocarbons such as methylene chloride and chloroform.[5]

We now find that extracts of this bacterium catalyze the formation of methane from a number of methylcobaloxime derivatives, *e.g.*, I (eq 2). The reaction with the cobaloximes shows an absolute requirement for ATP and catalytic amounts of vitamin B_{12r}. This is the first example of a biological system capable of utilizing



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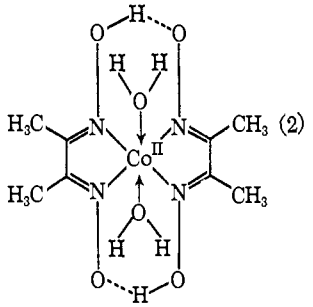

(2)

the simple cobalamin model compounds[6] as substrates. The methyl-Co derivatives of a variety of other cobalt chelates (II–V)[7,8] were tested for their ability to make methane in this bacterial enzyme system. However, only the cobaloximes were found to be active. Most other CH_3-Co compounds were inactive.[9] This demonstrates a unique similarity in properties exhibited between the completely abiogenic methylcobaloximes and methyl-B_{12} derivatives in this biological system. A variety of methylcobaloximes containing different lower axial ligands were tested as well. Table I shows the

Table I. Rates of CH_4 Formation from Methylcobaloximes

Substrate	Spec act. of CH_4 enzyme[a]
Methylcobalamin	15.20
Methyl-Co-(aquo)bis(dimethylglyoxime)	10.60
Methyl-Co-(aquo)bis(diphenylglyoxime)	9.60
Methyl-Co-(pyridine)bis(diphenylglyoxime)	9.50
Methyl-Co-(pyridine)bis(dimethylglyoxime)	8.40
Methyl-Co-(benzimidazole)bis(dimethylglyoxime)	3.50
Methyl-Co-(triphenylphosphine)bis(dimethylglyoxime)	3.40
Methyl-Co-(cyclohexyl isocyanide)bis(dimethylglyoxime)	1.30
Methyl-Co-(pyridine)bis(glyoxime)	1.20
Methyl-Co-(pyridine)bis(cyclohexanedione dioxime)	0.20

[a] Specific activity is defined as millimicromoles of CH_4 formed per milligram of protein per minute. Each reaction contained 3.5 μmol of methylcobaloxime derivative, 1.0 μmol of B_{12r}, 10 μmol of ATP, and 100 μmol of TES buffer, pH 7.0. Gas phase H_2, incubation temperature 40°.

specific activity values for the methane enzyme for several different methylcobaloxime substrates. The rates of methane evolution evidently depend on the nature of the in-plane ligands as well as the axial base

(1) Hydrogen-utilizing organism from the culture known as *Methanobacillus omelanskii;* M. P. Bryant, B. C. McBride, and R. S. Wolfe, *J. Bacteriol.*, **95**, 1118 (1968).
(2) Methylcobalamin is methyl-Co-5,6-dimethylbenzimidazolylcobamide.
(3) Vitamin B_{12r} is Co^{II}-5,6-dimethylbenzimidazolylcobamide.
(4) Factor III is Co^{III}-5-hydroxybenzimidazolylcobamide: J. M. Wood and R. S. Wolfe, *Biochemistry*, **5**, 3598 (1966).
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(7) Preparation and properties of the cobalt methyl derivatives of chelates II–V will be described in a forthcoming publication: G. N. Schrauzer, J. W. Sibert, and R. J. Windgassen, *J. Am. Chem. Soc.*, in press. The cationic complexes II and III were supplied as the perchlorates.
(8) The cobalt methyl complexes II, IV, and V were reported independently by G. Costa and his coworkers. See, *e.g.*, *Tetrahedron Letters*, 1783 (1967); *J. Organometal. Chem.* (Amsterdam), **6**, 181 (1966); 7, 493 (1967).
(9) The cobalt methyl derivative V showed very weak activity (~0.5), while IV and the perchlorates of II and III were completely inactive.