of 235 ppm. Previously, no chemical shift change was detected under similar circumstances for a sample prepared from $Cr(CO)_6$ and Na-X zeolite.[9,16]

The sidebands in the spectrum (Figure 1b) for the orange sample (B) prepared from $Mo(CO)_6$ and Na-X by dry-mixing are quite different from those found in Figure 1a. In the static NMR investigation,[16] evidence for a broad powder pattern was found for the molybdenum subcarbonyl samples prepared by dry-mixing as well as for samples prepared by pentane impregnation. Assuming axial symmetry and a chemical shift anisotropy ($\delta_{33} - \delta_{11}$) of 400 ppm for this powder pattern, the relative MAS sideband intensities shown in the insert of Figure 1b were found. There are similarities between the calculated sideband intensities and the intensities of the sidebands corresponding to the 228 ppm isotropic resonance. The largest peak is the first downfield sideband and not the isotropic peak at 228 ppm. Clearly, sideband intensities of the isotropic peak at 239 ppm in Figure 1b fit neither of the calculated sets of sidebands. Perhaps both a broad powder pattern and a narrow powder pattern have isotropic peaks superimposed at 239 ppm. While the yellow sample (A) is mainly a single molybdenum subcarbonyl, the orange sample (B) is a mixture of this subcarbonyl and two less mobile subcarbonyls. It is possible that the only difference between the two subcarbonyls with isotropic peaks at 239 ppm is in their mobilities.

In contrast to the conclusion of the investigation by static NMR spectroscopy,[16] the presence of at least one of the molybdenum subcarbonyls with a broad powder pattern appears to give the dry-mixed sample (B) its orange color. The spectra in the earlier study were not of sufficient quality to compare the intensity of the broad component from the dry-mixed sample to the intensity from the pentane-impregnation sample.

Rapid mobility in a metal carbonyl with terminally bound CO groups is indicated whenever the ^{13}C chemical shift anisotropy is much less than 400 ppm. Therefore, the main isotropic resonances of zeolite-supported subcarbonyls listed in Table II all represent mobile subcarbonyl species. The sample prepared from $W(CO)_6$ and Na-X has an MAS spectrum (Figure 3a) with three isotropic resonances coming from one mobile subcarbonyl and two subcarbonyls that appear immobile. Chemical shift anisotropies of 200 ± 50 and 360 ± 50 ppm were estimated for the isotropic peaks at 233 and 218 ppm, respectively, by assuming axial symmetry and using Herzfeld and Berger graphs to analyze the sidebands.[24] The spectrum in Figure 2a for the molybdenum sample with Na-Y zeolite has a low signal-to-noise ratio, which makes the spectrum difficult to interpret. The isotropic peaks in this spectrum probably correspond to a narrow powder pattern and at least one broad pattern, as was the case for the spectrum in Figure 1b for the Na-X sample (B). Sidebands from the narrow powder pattern contribute more in Figure 2a than in Figure 1b because a higher field and a lower spinning rate were used to obtain Figure 2a.

The zeolite-supported tricarbonyls listed in Table II almost certainly are mononuclear complexes attached to the zeolite through the oxygen atoms of the zeolite framework. Recent EXAFS and IR analyses of the tricarbonyls on X and Y zeolites have shown that more complicated structures are unlikely.[6,12] The present NMR spectra give another perspective on the nature of the samples. The main tricarbonyls are in rapid motion, and their chemical shifts show little difference between species on the Na-X and Na-Y supports. Secondary species on the Na-X support do not move rapidly, and their presence can be controlled by the preparation technique. Molecular modeling studies now underway should provide more structural and motional details.

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Facile α/β Diastereomerism in Organocobalt Corrins. Evidence for Thermodynamic Control in the Synthesis of Alkylcobamides

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Reductive alkylation of aquacobalamin with certain alkyl halides is known to produce a mixture of diastereomeric β-alkylcobalamins (with the organic ligand in the "upper" axial ligand position) and α-alkylcobalamins (with the organic ligand in the "lower" axial ligand position) when the reducing agent is zinc/acetic acid. However, reduction with sodium borohydride followed by alkylation produces only β-alkylcobalamins. This difference has now been shown to be a pH effect, and the pH dependence of the relative proportions of α- and β-diastereomers produced upon reductive alkylation of aquacobalamin with CF_3CH_2I, CF_3I, and $NCCH_2Br$ has been studied. In each case, the fraction of the alkylcobalamin as the α-diastereomer increases with increasing acidity, following a typical titration curve. The apparent pK_a's obtained from these data (3.04 ± 0.03, 2.69 ± 0.02, and 2.25 ± 0.02 for R = CF_3CH_2, CF_3, and $NCCH_2$, respectively) are shown to be consistent with the hypothesis that the products are under equilibrium control and that the pH dependence is due to the base-on/base-off equilibrium of the product β-alkylcobalamin. The alternative of kinetically controlled products requires that the species being alkylated in zinc/acid reducing systems is cob(II)alamin, since cob(I)alamin is base-off at all pH's. The pK_a for the base-on/base-off reaction of cob(II)alamin has been determined spectrophotometrically to be 3.10 ± 0.01. However, interpretation of the apparent pK_a's for the pH dependence of the diastereomeric outcome of the reductive alkylation of aquacobalamin assuming kinetic control leads to relative reactivities of the base-off and base-on species of cob(II)alamin which are not consistent with the observed rates of product formation or with literature data on the reaction of cob(II)alamin with alkyl halides. Studies of the temperature dependence of the diastereomer ratio in the analogous alkylcobinamides show that the apparent equilibrium between diastereomers is entropically controlled.

Introduction

In recent publications[1,2] the facile formation of diastereomeric α- and β-alkylcobinamides[3] (RCbi's) and alkylcobalamins (RCbl's) (Figure 1) upon reductive alkylation of factor B[4] or H_2OCbl with various alkyl halides has been described. Interestingly, in the case of cobinamides, α- and β-RCbi's were formed in similar ratios regardless of whether factor B was reduced with sodium borohydride or with Zn/10% acetic acid, although the

(1) Brown, K. L.; Evans, D. R. *Inorg. Chem.* **1990**, *29*, 2559-2561.
(2) Brown, K. L.; Zou, X.; Salmon, L. *Inorg. Chem.* **1991**, *30*, 1949-1953.
(3) α is the "lower" and β the "upper" axial ligand position.
(4) Factor B is a mixture of the diastereomers of cyanoaquacobinamide,[5] α-(CN)-β-(H_2O)Cbi and α-(H_2O)-β-(CN)Cbi.
(5) Renz, P. *Methods Enzymol.* **1971**, *18*, 82-92.

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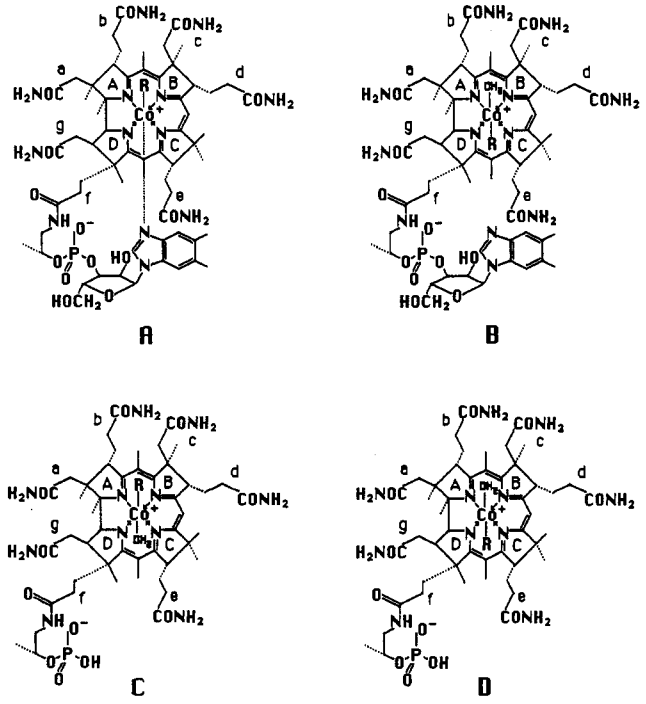


Figure 1. (A) Structure of a base-on β-alkylcobalamin (β-RCbl), β_{on} in Scheme I. In the base-off species the benzimidazole nucleotide is not coordinated to the cobalt atom and is either protonated ($\beta_{off}H^+$ in Scheme I) or unprotonated (β_{off} in Scheme I). In species β_T in Scheme I, the uncoordinated benzimidazole nucleotide is unprotonated and hydrogen-bonded to the g side chain amide. (B) Structure of an α-alkylcobalamin (α-RCbl), α in Scheme I. The benzimidazole nucleotide is protonated in species αH^+ in Scheme I. (C) Structure of a β-alkylcobinamide (β-RCbi). (D) Structure of an α-alkylcobinamide (α-RCbi).

ratio of diastereomers varied widely with the nature of the alkylating agent.[2] In contrast, reduction of H_2OCbl with $NaBH_4$ led only to β-RCbl's although reduction with Zn/10% acetic acid produced both α- and β-diastereomers, again with the ratio being highly dependent on the alkyl group.[2] As previously suspected,[2] this failure to obtain α-RCbl's with borohydride reduction of H_2OCbl has now been shown to be a pH effect (vide infra).

The existence of a significant pH dependence of the diastereomer ratio of RCbl's, but not RCbi's, has potentially important implications regarding the question of whether the products of these reductive alkylation reactions are under kinetic or thermodynamic control. Because of the thermodynamically favorable coordination of the pendant nucleotide to the α axial ligand position in β-RCbl's at neutral pH,[6,7] but the absence of such coordination in α-RCbl's, the β-RCbl's are the thermodynamically favored products at neutral pH. For example, when $R = CF_3CH_2$, the α-diastereomer of the cobinamide is favored by almost 7/1 over the β-diastereomer,[1] regardless of pH. In the case of cobinamides, pH dependence would not be expected from either kinetically or thermodynamically controlled products due to the lack of the pendant nucleotide. Since the formation constant for the base-on species of β-CF_3CH_2Cbl is 9.23×10^2 at neutral pH,[7] thermodynamic control of the outcome of reductive alkylation of H_2OCbl with CF_3CH_2I would be expected to yield less than 1% α-diastereomer.

Cob(I)alamin, most certainly the product when H_2OCbl is reduced with borohydride, is well-known from electrochemical studies[8,9] to be base-off at all pH's. Presumably, its α or β face can be alkylated with a facility approaching that of cob(I)inamide.[10] Thus, if cob(I)alamin is the species being alkylated at all pH's, the existence of a substantial pH dependence of the diastereomeric ratio of RCbl's would be inconsistent with kinetically controlled products. While hydridocobalamin (presumably the conjugate acid of cob(I)alamin, $pK = 1.0$[8,11] or 1.5[9]) has been claimed to be the product of reduction of cobalamin with zinc in glacial acetic acid,[12-14] cob(I)alamin is also known to be unstable in acid, forming cob(II)alamin and hydrogen[11,15-17] in a reaction known to be accelerated by protons.[15-18] Should cob(II)alamin be the species being alkylated in zinc/acid reducing systems, the interpretation of the pH dependence of the diastereomer ratio upon reductive alkylation of cobalamin becomes more complicated since cob(II)alamin does undergo a base-on/base-off reaction with a $pK_{base\text{-}off}$ value variously reported as 2.9[8,11] or 3.2.[9] Thus, at pH's above about 5.0, the α position of cob(II)alamin is blocked, and kinetic control of products would result in a substantial pH dependence of the diastereomer ratio due to the pH dependence of the position of the base-on/off equilibrium of cob(II)alamin.

This paper contains a detailed analysis of the pH dependence of the diastereomeric outcome of the reductive alkylation of H_2OCbl with CF_3CH_2I, $NCCH_2Br$, and CF_3I. The results of this analysis are consistent with a pH dependence due to the base-on/base-off equilibrium of the product β-RCbl rather than that of cob(II)alamin. This suggests that the diastereomeric α- and β-alkylcobamides are, indeed, under thermodynamic control.

Experimental Section

Factor B[4] was prepared as described previously,[5,6] and H_2OCbl was from Roussell. HPLC was performed with a 4.6 × 75 mm Beckman C_{18} Ultrasphere column using a 25 mM ammonium phosphate buffer, pH 3 (solvent A) and acetonitrile (solvent B),[19] and the gradient described previously,[2] or others, as needed. Reaction products were quantitated by using the averaged values of chromatogram integrations obtained by UV detection at 254 and 350 nm. Product yields were corrected for differing molar absorptivities of the α- and β-alkylcobamides as determined by quantitation via conversion to their dicyano derivatives ($\epsilon_{368} = 3.04 \times 10^4$ M^{-1} cm^{-1})[2,20] using a Cary 219 recording spectrophotometer. pH values were measured by using a Radiometer PHM 84 pH meter equipped with a Radiometer combined glass electrode.

Analytical-scale reductive alkylations were carried out as described previously, except that, for zinc reductions, the medium contained acetic acid at various concentrations, phosphoric acid at various concentrations, or acetic acid/acetate buffers, as necessary, to obtain the desired pH. Argon was bubbled through a glass vial containing 2.5 mL of the appropriate medium and 5 mg of H_2OCbl. Zinc wool, freshened with dilute HCl, was added to the solution, and reduction was permitted to occur for 30 min. Reaction mixtures were thermostatted at 25 °C or at other temperatures, as needed, by using a refrigerated water bath, or at 0 °C by using an ice/water slurry. Excess alkyalting agent was then introduced by gastight syringe (or by bubbling for CF_3I), and four to eight samples were taken as a function of time over a 10-min interval. pH's of the samples were measured immediately after sampling.

For reductive dealkylation experiments, a sample of the RCbl in pH 4.6 acetate buffer or 50% phosphoric acid in a glass vial was purged with argon for 1 h in an ice/water slurry. Zinc wool, freshened with dilute HCl, was added and samples were taken as a function of time. Con-

(6) Brown, K. L.; Hakimi, J. M.; Nuss, D. M.; Montejano, Y. D.; Jacobsen, D. W. *Inorg. Chem.* **1984**, *23*, 1463-1471.
(7) Brown, K. L.; Peck-Siler, S. *Inorg. Chem.* **1988**, *27*, 3548-3555.
(8) Lexa, D.; Savéant, J.-M. *J. Am. Chem. Soc.* **1976**, *98*, 2652-2658.
(9) Rubinson, K. A.; Parekh, H. V.; Itabashi, E.; Mark, H. B., Jr. *Inorg. Chem.* **1983**, *22*, 458-463.
(10) There is, of course, a possibility of some sterically diminished reactivity at the α face of cob(I)alamin due to the presence of the pendant, but uncoordinated, nucleotide.
(11) Lexa, D.; Savéant, J.-M. *J. Chem. Soc., Chem. Commun.* **1975**, 872-874.
(12) Schrauzer, G. N.; Holland, R. J. *J. Am. Chem. Soc.* **1971**, *93*, 4060-4062.
(13) Schrauzer, G. N.; Grate, J. H. *J. Am. Chem. Soc.* **1979**, *101*, 4601-4611.
(14) Chemaly, S. M.; Pratt, J. M. *J. Chem. Soc., Dalton Trans.* **1984**, 595-599.
(15) Tackett, S. L.; Collat, J. W.; Abbott, J. C. *Biochemistry* **1963**, *2*, 919-923.
(16) Das, P. K.; Hill, H. A. O.; Pratt, J. M.; Williams, R. J. P. *J. Chem. Soc. A* **1968**, 1261-1264.
(17) Das, P. K. *J. Chem. Soc., Dalton Trans.* **1974**, 2475-2479.
(18) Chao, T.-H.; Espenson, J. H. *J. Am. Chem. Soc.* **1978**, *100*, 129-133.
(19) Jacobsen, D. W.; Green, R.; Brown, K. L. *Methods Enzymol.* **1986**, *123*, 14-22.
(20) Barker, H. A.; Smyth, R. D.; Weissbach, H.; Toohey, J. I.; Ladd, J. N.; Volcani, B. E. *J. Biol. Chem.* **1960**, *235*, 480-488.

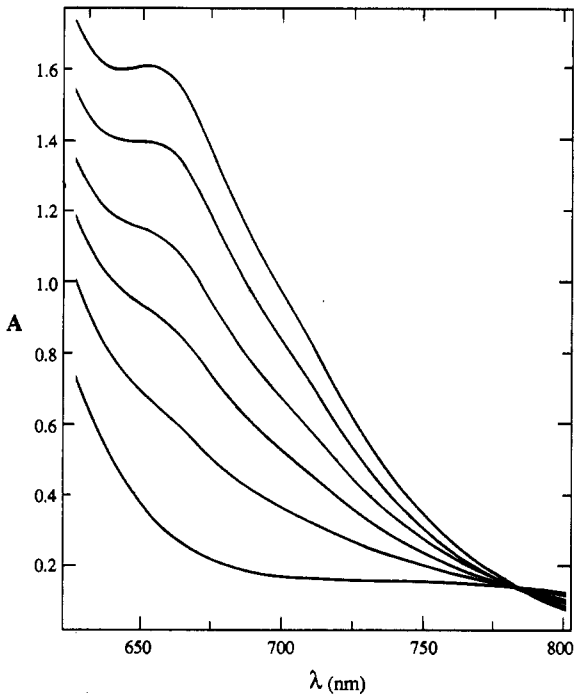


Figure 2. pH dependence of the long-wavelength region of the UV/visible spectrum of cob(II)alamin (2.23×10^{-3} M), obtained by anaerobic reduction with formate as described in the Experimental Section. All samples are at 25 °C, in 0.1 M phosphate, acetate, or chloroacetate buffers, and ionic strength was adjusted to 1.0 M with KCl. From top to bottom, the pH's were 5.92, 4.06, 3.41, 3.07, 2.68, and 1.09.

centrations of unreacted RCbl were determined by HPLC as described above.

The spectrophotometric titration of cob(II)alamin was carried out under anaerobic conditions in quartz cuvettes, using a Cary 219 recording spectrophotometer and formate as the reductant.[21] A solution containing H_2OCbl (2.33×10^{-3} M), with 0.1 M phosphate, chloroacetate, or acetate buffer (pH 1.0–6.0), and KCl (total ionic strength 1.0 M) was placed in a serum-stoppered cuvette and purged with argon for 1 h. Reduction was initiated by anaerobic injection (using a gastight syringe) of a solution of argon-purged formic acid (final concentration 1.53×10^{-2} M for samples above pH 2.0 or 0.153 M for samples at pH 2 or below)[21] which had been previously adjusted to the pH of the sample. Completion of reduction was monitored by the visible spectral change. The pH of each sample was measured before and after completion of the reduction. The $pK_{base\text{-}off}$ value was determined from a plot of eq 1, where A_{on} and A_{off} are the absorbances of the base-on and base-off species, respectively, and A_x is the absorbance at pH_x.

$$pH_x = pK_{base\text{-}off} + \log [(A_x - A_{off})/(A_{on} - A_x)] \quad (1)$$

Results and Discussion

Nature of the Reduced Cobamides and $pK_{base\text{-}off}$ of Cob(II)alamin. Spectrophotometric observation of anaerobic solutions of H_2OCbl or factor B reduced with excess $NaBH_4$ clearly reveals the formation of cob(I)alamin or cob(I)inamide with a prominent spectral band at 388 nm.[22,23] The spectra of both reduced species are essentially identical above 300 nm. However, when either H_2OCbl or factor B was reduced with excess zinc in 10% acetic acid (pH 2.3) or in acetic acid/acetate buffers at pH 3.7 and 4.9, the spectrum of the cobalt(II) species was obtained, with an α band at 469 nm and a γ band at 315 nm.[22,23] The spectrum obtained for cob(II)inamide was essentially identical with that generated by exhaustive anaerobic photolysis of CH_3Cbi. While the spectrum of cob(II)alamin showed considerable pH dependence in the molar absorptivities of the α and γ bands due to the base-on/base-off equilibrium, the most convenient wavelength for a spectrophotometric titration turned out to be 650 nm, where a weak transition in the base-on species ($\epsilon_{650} = 6.82 \times 10^2$ M^{-1} cm^{-1}) creates a shoulder which is absent in the spectrum of the base-off species ($\epsilon_{650} = 1.76 \times 10^2$ M^{-1} cm^{-1}). As shown in Figure 2, the spectra of the base-on and base-off species are isosbestic at 784 nm. H_2OCbl was anaerobically reduced with formate[21] as described in the Experimental Section, and absorbance measurements at 650 nm were used to determine a $pK_{base\text{-}off}$ value of 3.10 ± 0.01. This value is slightly closer to the value of 3.2 reported by Lexa and Savéant[8,11] than the value of 2.9 reported by Rubinson et al.[9] from the pH dependence of cyclic voltammetric measurements.

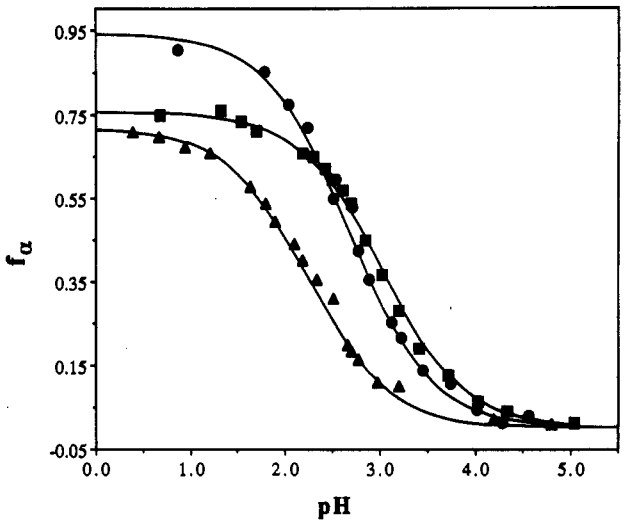


Figure 3. Plots of f_α (eq 2), the fraction of α-RCbl product from the reductive alkylation of H_2OCbl with RX, vs pH: (■) R = CF_3CH_2; (▲) R = $NCCH_2$; (●) R = CF_3. The solid lines were calculated from eq 3 by using the values of pK_a^{app} and f_α^{acid} in Table I.

Thus, while zinc/acid reducing systems may, indeed, transiently produce cobalt(I) cobamides, spectrophotometric observation of such solutions suggests that this reduction state does not persist under these conditions and that cobalt(II) cobamides are the major (if not the only) species present. Hence, it is unclear whether reductive alkylation of cobamides in zinc/acid can result from reaction of alkyl halides with cobalt(I) species or is solely due to reaction with cobalt(II) species.[24-31] As pointed out above, the observation of substantial pH dependence of the ratio of α- and β-diastereomers during the reductive alkylation of cobalamin in zinc/acid media strongly suggests the latter must be the case if the products are under kinetic control, since cob(I)alamin is base-off at all pH's.

pH Dependence of the Ratio of RCbl Diastereomers. As described previously,[1] time-resolved measurements of the ratio of diastereomers of CF_3CH_2Cbi formed during reductive alkylation of factor B with CF_3CH_2I show that the final ratio is established rapidly (<10–20 s, or at least as fast as the first sample can be taken) and remains constant throughout the alkylation period during which the total yield of RCbi's increases. The same has now been found to be true for the reductive alkylation of H_2OCbl with CF_3CH_2I. At a variety of pH's between 0.68 and 5.04, reaction mixtures at 25 °C were sampled as a function of time (generally 1–10 min after introduction of alkylating agent) and

(21) Linn, D. E., Jr.; Gould, E. S. *Inorg. Chem.* **1988**, *27*, 1625–1628.
(22) Rubinson, K. A.; Itabashi, E.; Mark, H. B. *Inorg. Chem.* **1982**, *21*, 3571–3573.
(23) Beaven, G. H.; Johnson, E. A. *Nature*, **1955**, *176*, 1264–1265.
(24) Blaser, H.; Halpern, J. *J. Am. Chem. Soc.* **1980**, *102*, 1684–1689.
(25) Cobalt(II) species in cobaloximes and in other cobalamin model chelates are well-known to react with alkyl halides to form alkylcobalt complexes.[26-31]
(26) Halpern, J.; Maher, J. P. *J. Am. Chem. Soc.* **1964**, *86*, 2311.
(27) Halpern, J.; Maher, J. P. *J. Am. Chem. Soc.* **1965**, *87*, 5361–5370.
(28) Schneider, P. W.; Phelan, P. F.; Halpern, J. *J. Am. Chem. Soc.* **1969**, *91*, 77–81.
(29) Chock, P. B.; Halpern, J. *J. Am. Chem. Soc.* **1969**, *91*, 582–588.
(30) Marzilli, L. G.; Marzilli, P. A.; Halpern, J. *J. Am. Chem. Soc.* **1971**, *93*, 1374–1378.
(31) Halpern, J.; Phelan, P. F. *J. Am. Chem. Soc.* **1972**, *94*, 1881–1886.

Table I. Equilibrium Constants Related to the pH Dependence of f_α under the Equilibrium Control Hypothesis (25 °C)

	R		
	CF_3CH_2	$NCCH_2$	CF_3
pK_a^{app} [a]	3.04 ± 0.03	2.25 ± 0.02	2.69 ± 0.02
f_α^{acid} [b]	0.756 ± 0.020	0.720 ± 0.020	0.941 ± 0.020
K_i' [c]	0.324 ± 0.012	0.398 ± 0.015	0.0623 ± 0.0019
$pK_{base\text{-}off}$ [d]	2.60[e]	1.81[f]	1.44[g]
K_{Co}^{Cbi} [g]	9.23 × 10^2	5.62 × 10^3	1.31 × 10^4
f_α^{Cbi} [h]	0.87	0.73	0.93
pK_a^{app}(calc)[i]	3.18	2.34	2.65

[a] From the observed pH dependence of f_α (eq 2) as determined via eq 4 (see Figure 3). [b] From extrapolation of linear plots of f_α vs $f_\alpha/[H^+]$ (eq 4). [c] Equation 11. Values calculated from f_α^{acid} by using eq 12. [d] Apparent pK_a of the protonated, base-off β-RCbl. [e] Reference 6. [f] Reference 7. [g] Equation 9; values from ref 7. [h] f_α^{Cbi} = [α-RCbi]/([α-RCbi] + [β-RCbi]). [i] Equation 14.

the fraction of α-CF_3CH_2Cbl product was determined by analytical HPLC. The rate of accumulation of products was significantly lower at low pH, but ratio of diastereomers was still time-independent. The average value of f_α, the fraction of RCbl product as the α-diastereomer (eq 2), is shown in Figure 3 as a

$$f_\alpha = [\alpha\text{-RCbl}]/([\alpha\text{-RCbl}] + [\beta\text{-RCbl}]) \quad (2)$$

function of pH. These data are seen to adequately fit a typical titration curve of the form of eq 3, where f_α^{acid} is the limiting value

$$f_\alpha = f_\alpha^{acid}[H^+]/([H^+] + K_a^{app}) + f_\alpha^{base}K_a^{app}/([H^+] + K_a^{app}) \quad (3)$$

of f_α in strong acid (i.e., the acid end point), f_α^{base} is the limiting value of f_α at neutral pH (i.e., the base end point), and K_a^{app} is the apparent acid dissociation constant governing the pH dependence. Because of the rapid consumption of zinc at very low pH and the slower accumulation of products, the value of f_α^{acid} was difficult to determine directly with sufficient precision. However, as the observed values of f_α at the upper end of the pH region examined were extremely small and no α-diastereomer is obtained when H_2OCbl is reductively alkylated at neutral pH with $NaBH_4$ as reducing agent, f_α^{base} in eq 3 may be set to zero. Consequently, f_α^{acid} and K_a^{app} were determined from linear least-squares fits of plots (not shown) of f_α vs $f_\alpha/[H^+]$ according to eq 4, derived from eq 3 with $f_\alpha^{base} = 0$. The resulting values,

$$f_\alpha = f_\alpha^{acid} - f_\alpha K_a^{app}/[H^+] \quad (4)$$

$f_\alpha^{acid} = 0.756 \pm 0.020$ and $pK_a^{app} = 3.04 \pm 0.03$ (Table I), were used in conjunction with eq 3 to calculate the solid line for the CF_3CH_2Cbl data in Figure 3. The value of f_α^{acid} for the CF_3CH_2Cbl's is slightly lower than the value previously reported for the CF_3CH_2Cbi's (0.874),[1] possibly reflecting a steric effect of the pendant, but uncoordinated, nucleotide on the preference of the organic ligand for the α axial ligand position. The value of pK_a^{app} is significantly higher than the apparent pK_a of the base-off species of β-CF_3CH_2Cbl ($pK_{base\text{-}off}$ = 2.60 at 25 °C).[6] However, as detailed below, this is expected if the products are under thermodynamic control.

Similar results were obtained when H_2OCbl was reductively alkylated with $NCCH_2Br$; i.e., f_α is time-independent but substantially pH-dependent. The data (Figure 3) were analyzed as described above for R = CF_3CH_2 and gave the values of $pK_a^{app} = 2.25 \pm 0.02$ and $f_\alpha^{acid} = 0.720 \pm 0.02$ (Table I). In this case, f_α^{acid} is much closer to the value of f_α previously reported for the diastereomeric $NCCH_2$Cbi's (0.73),[2] although pK_a^{app} remains significantly above $pK_{base\text{-}off}$ for β-$NCCH_2$Cbl (1.81).[32]

The situation with CF_3I as the alkylating agent was somewhat more complicated due to the reductive defluorination of CF_3-cobamides to give CF_2H-cobamides under the reaction conditions.[2,6] However, time-resolved measurements showed that as long as the total yield of CF_3Cbl's exceeded about 14% (of total cobalamins), the relative proportions of the two diastereomers remained constant with time. At short reaction times (generally 1–2 min) when the total yield of RCbl's was low, or at longer times (generally >6 min) when the ratio of CF_3Cbl's to CF_2HCbl's was low, integration of the CF_3Cbl peaks gave erratic results, particularly if the α/β ratio was far from 1.0. For instance, in a typical experiment at pH 3.4, samples were taken at 2, 3, 4, 6, 7, and 9 min. The total yields of CF_3Cbl's were 19%, 23%, 23%, 19%, 13%, and 9%, respectively, reflecting the increased amount of defluorination at longer times. During the period from 2 to 6 min the value of f_α for the CF_3Cbl's was 0.137 ± 0.009 (average of eight measurements during this time). However, while the yield of CF_2HCbl's increased steadily (6%, 17%, 28%, 44%, 62%, 74%), the values of f_α for the CF_2HCbl's for the samples in which the yield was suitably high (≥10%) to permit accurate determination decreased progressively (0.537, 0.515, 0.495, 0.464, 0.421). Thus, as was the case for R = CF_3CH_2 and $NCCH_2$, the values of f_α for R = CF_3 are time-independent (as long as the yield is sufficiently high to permit an accurate analysis) but those for the CF_2HCbl's, produced as a secondary product by reductive defluorination, are not. This suggests that if the diastereomeric products of the reductive alkylation of H_2OCbl with RX are, in general, under thermodynamic control, those of the secondary product CF_2HCbl's are not, at least under these conditions (i.e., in the absence of a CF_2HX alkylating agent). Evidence that possibly differing rates of reductive defluorination of α-CF_3Cbl, base-off β-CF_3Cbl, and base-on β-CF_3Cbl do not significantly influence the observed values of f_α for the CF_3Cbl's is presented below.

The pH dependence of f_α for R = CF_3 is shown in Figure 3. As with R = CF_3CH_2 and $NCCH_2$, eq 2 is obeyed and values of $pK_a^{app} = 2.69 \pm 0.02$ and $f_\alpha^{acid} = 0.941 \pm 0.02$ were obtained. The value of f_α^{acid} is very close to the value of f_α reported for the CF_3Cbi's (0.93),[2] while, again, pK_a^{app} exceeds $pK_{base\text{-}off}$ for β-CF_3Cbl (1.44)[6] significantly.

Reductive Dealkylation of RCbl's. As previously pointed out,[1] alkylcobamides undergo reductive dealkylation in zinc/acid reducing agents, presumably due to the well-known homolysis of the Co–C bond of reduced R–Co^{II} species as demonstrated in CH_3Cbl and CH_3Cbi by electrochemical techniques.[22,33-35] If the diastereomeric outcome of the reductive alkylation of cobamides with alkyl halides in such reducing systems is under thermodynamic control, it seems unlikely that the observed ratios of diastereomers could be significantly affected by dissimilar rates of reductive dealkylation of the diastereomers for the following reasons. The observation of substantial yields of alkylcobamides in such reaction mixtures (40–85%)[2] demands that the rates of reductive dealkylation not exceed those of reductive alkylation significantly.[36] Since the time-independent ratio of diastereomers is established rapidly (even at 0 °C for R = CF_3CH_2),[1] even when the total yield of alkylcobamides is low, the rate of equilibration of the diastereomers exceeds that of the alkylation reaction substantially. This in turn suggests that the ratio of diastereomers cannot be perturbed significantly by differential rates of dealkylation for thermodynamically controlled products.

However, if the products are under kinetic control, the absolute level of each diastereomeric product would be a sensitive function of its rate of formation and decay. It is consequently important to know if the rates of reductive dealkylation by zinc/acid reducing agents under these experimental conditions differ significantly

(32) Brown, K. L.; Hakimi, J. M. *J. Am. Chem. Soc.* **1986**, *108*, 496–503.
(33) Kim, M.-H.; Birke, R. L. *J. Electroanal. Chem. Interfacial Electrochem.* **1983**, *144*, 331–350.
(34) Lexa, D.; Savéant, J.-M. *J. Am. Chem. Soc.* **1978**, *100*, 3220–3222.
(35) Lexa, D.; Savéant, J.-M. *Acc. Chem. Res.* **1983**, *6*, 235–243.
(36) Reductive dealkylation of CH_3Cbl and CH_3Cbi in DMF/alcohol solvents is quite rapid (1200 and 2.7 s^{-1}, respectively, at −30 °C).[34] However, in aqueous media, Kim and Birke[33] obtained a rate constant of 0.37 s^{-1} for homolysis of base-off CH_3Cbl^+ at 25 °C. This difference has been attributed to a solvent effect,[33] evidently reflecting weak competition of solvent cage escape with rapid $CH_3^\bullet$ + cob(I)alamin recombination due to the scarcity of abstractable hydrogen atoms in aqueous media.

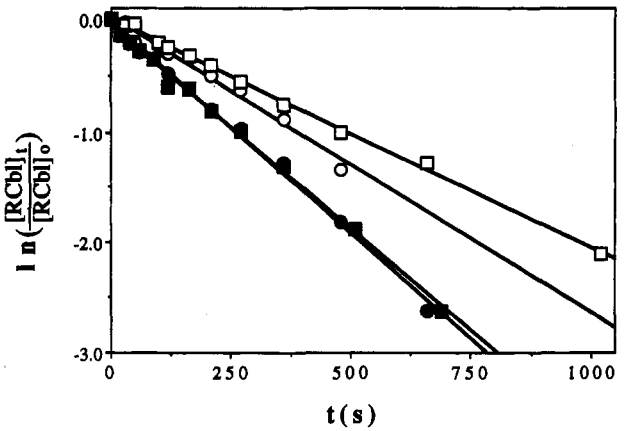


Figure 4. Representative plots of ln ($[RCba]_t/[RCba]_0$) vs time for the reductive dealkylation of CF_3Cbl's in zinc/acid media: (●) β-CF_3Cbl, pH 4.6, $k_{obs} = 3.8 \times 10^{-3}$ s^{-1}; (■) α-CF_3Cbl, $k_{obs} = 3.7 \times 10^{-3}$ s^{-1}; (○) β-CF_3Cbl, pH 0, $k_{obs} = 2.7 \times 10^{-3}$ s^{-1}; (□) α-CF_3Cbl, pH 0, $k_{obs} = 2.1 \times 10^{-3}$ s^{-1}.

Table II. Observed First-Order Rate Constants for the Reductive Dealkylation of Alkylcobalamins by Zinc in Acid Media

R	pH	k_{obs}, s^{-1} [a] β-RCbl	k_{obs}, s^{-1} [a] α-RCbl
CF_3	4.6[b]	3.8×10^{-3}	3.7×10^{-3}
	0[c]	2.7×10^{-3}	2.1×10^{-3}
CF_3CH_2	4.6[b]	5.6×10^{-3}	5.8×10^{-3}
	0[c]	2.8×10^{-3}	2.4×10^{-3}
$NCCH_2$	4.6[b]	1.3×10^{-2}	1.4×10^{-2}
	0[c]	9.2×10^{-3}	1.1×10^{-2}

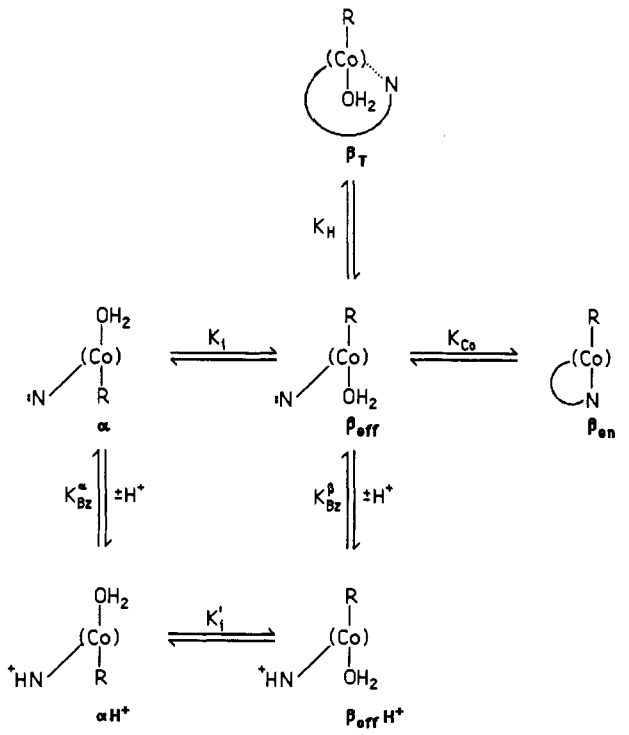
[a] Obtained from the slopes of plots of ln ($[RCbl]_t/[RCbl]_0$). These results most likely reflect the rate of reduction of the RCbl to $RCbl^{\bullet-}$ rather than dealkylation of the $RCbl^{\bullet-}$ species. [b] In acetic acid/acetate buffer. [c] In phosphoric acid.

among the base-on β-RCbl, the base-off β-RCbl, and the α-RCbl for any given R.

The reductive dealkylation of β- and α-CF_3CH_2Cbi was previously reported to be fairly rapid at 25 °C ($t_{1/2} \leq 1$ min).[1] In order to obtain more quantitative estimates of the relative lability of the various species of the RCbl's studied here, the β-RCbl's, and α-RCbl's were treated with zinc in phosphoric acid at pH ~0 or in acetic acid/acetate buffer at pH 4.6 at 0 °C. The amount of each alkylcobalamin remaining in solution as a function of time was determined by analytical HPLC. The disappearance of the alkylcobamides was found to be first-order, as shown in Figure 4, which contains representative plots of ln ($[RCbl]_t/[RCbl]_0$) vs time for R = CF_3, where $[RCbl]_0$ is the initial concentration of the alkylcobamide and $[RCbl]_t$ is the concentration at time t. The apparent first-order rate constants, which clearly reflect the rate of reduction of the RCbl species to the $RCbl^{\bullet-}$ radical anion rather than the rate of dealkylation of the radical anion, are listed in Table II. In the case of the CF_3-Cbl's, reductive dealkylation is complicated by reductive defluorination, but it is the rate of disappearance of the CF_3Cbl's which is important here and has been measured. At pH 4.6, where β-CF_3Cbl is base-on, the apparent rate constants for dealkylation of β- and α-CF_3Cbl were essentially identical (Figure 4, $t_{1/2} \sim 185$ s). At pH 0, the rate of dealkylation of both diastereomers was slightly lower ($t_{1/2} \sim 290$ s) but the rate constants for β-CF_3Cbl (largely base-off at this pH) and α-CF_3Cbl remained essentially the same. A similar pattern was found for R = CF_3CH_2 and $NCCH_2$ (Table II). Thus, if the diasteromers are under kinetic control, it is unlikely that their ratio is affected significantly by differential rates of dealkylation in these media.

pH Dependence Due to Equilibrium Control. If the diastereomeric outcome of the reductive alkylation of H_2OCbl with alkyl halides is under equilibrium control, the relevant equilibria are as shown in Scheme I. Equilibrium formation of the so-called "tuck-in" species (β_T in Scheme I) from the base-off but benz-

Scheme I



imidazole-deprotonated β-RCbl (β_{off} in Scheme I) has been included since both NMR[37] and thermodynamic[7] evidence for this species has been obtained. In the "tuck-in" species, the benzimidazole nitrogen is hydrogen-bonded to a side chain amide, now believed to be the g amide[38] (Figure 1). However, as pointed out below, the inclusion of this species has a negligible effect on the predicted pH dependence of f_α under the equilibrium control hypothesis. A similar "tuck-in" species for the benzimidazole-deprotonated α-RCbl (α in Scheme I) has been omitted since the pK_a for the protonated species (i.e., pK_{Bz}^{α} in Scheme I) was previously determined to be 5.54,[1] essentially identical with that for the cation of free α-ribazole (5.56)[6] and with the microscopic pK_a for benzimidazolium deprotonation of the zwitterion of α-ribazole 3′-phosphate (5.54).[37,39] Inclusion of such a species has a negligible effect on the outcome.

The predicted pH dependence of f_α

$$f_\alpha = ([\alpha] + [\alpha H^+])/([\alpha] + [\alpha H^+] + [\beta_{off}] + [\beta_{off}H^+] + [\beta_{on}] + [\beta_T]) \quad (5)$$

is derived by application of the law of mass action to Scheme I and results in the equation

$$f_\alpha = (K_{Bz}^{\alpha} + [H^+])/\{K_{Bz}^{\alpha}(1 + K_i + K_iK_{Co} + K_iK_H) + (1 + K_i')[H^+]\} \quad (6)$$

where

$$K_{Bz}^{\alpha} = [\alpha][H^+]/[\alpha H^+] \quad (7)$$

$$K_i = [\beta_{off}]/[\alpha] \quad (8)$$

$$K_{Co} = [\beta_{on}]/[\beta_{off}] \quad (9)$$

$$K_H = [\beta_T]/[\beta_{off}] \quad (10)$$

$$K_i' = [\beta_{off}H^+]/[\alpha H^+] \quad (11)$$

(37) Brown, K. L. *J. Am. Chem. Soc.* **1987**, *109*, 2277–2284.
(38) Brown, K. L.; Brooks, H. B.; Gupta, B. D.; Victor, M.; Marques, H. M.; Scooby, D. C.; Goux, W. J.; Timkovich, R. *Inorg. Chem.* **1991**, *30*, 3430–3438.
(39) The pK_a's of other α-RCbl's are currently under investigation.

This is the equation of a typical titration curve with acid and base end points given by eqs 12 and 13 and governed by an apparent

$$\lim_{[H^+]\to\infty} f_\alpha = f_\alpha^{acid} = 1/(1 + K_i') \quad (12)$$

$$\lim_{[H^+]\to 0} f_\alpha = f_\alpha^{base} = 1/(1 + K_i + K_iK_{Co} + K_iK_H) \quad (13)$$

K_a given by eq 14. The equation for the acid end point (eq 12)

$$K_a^{app} = K_{Bz}^{\alpha}(1 + K_i + K_iK_{Co} + K_iK_H)/(1 + K_i') \quad (14)$$

allows a determination of K_i' (Scheme I) from the experimental value of f_α^{acid} (Table I). Under the assumption that $K_i = K_i'$ (i.e., the thermodynamic preference of the alkyl group for the α axial ligand position is unaffected by the state of protonation of the pendant benzimidazole nucleotide[40]), previously determined values of K_{Co}[7] (Table I) permit calculation of the anticipated base end points from eq 13. Since eq 13 is dominated by K_{Co}, the limiting values of f_α predicted are quite small (0.0033, 0.000 46, and 0.0012 for R = CF_3CH_2, $NCCH_2$, and CF_3, respectively). This both agrees with the observation of very small values of f_α above pH 4.5 (Figure 3) and validates the assumption that the base end point f_α value is zero, used in deriving eq 4 from eq 3, above. The predicted K_a^{app} values governing the pH dependence of f_α for thermodynamic control can then be calculated from eq 14, by using only the assumptions that $K_i = K_i'$, that $pK_{Bz}^{\alpha} = 5.54$, and that $K_H = 4.1$, the value previously determined for CH_3Cbl.[7] Once again, the term by which K_{Bz}^{α} is multiplied in eq 14 is dominated by K_iK_{Co} (Table I) so that unanticipated variations in K_H with R would have a negligible effect on K_a^{app}.[41] The values calculated for pK_a^{app} from eq 14 (3.18, 2.34, and 2.65 for R = CF_3CH_2, $NCCH_2$, and CF_3, respectively) are collected in Table I and are in very good agreement with the values obtained from the observed dependence of f_α on pH (3.04, 2.25, and 2.69, respectively). Thus, the observed pH dependence of the diastereomeric outcome of the reductive alkylation of H_2OCbl is consistent with thermodynamic control of the products, at least for these alkyl groups.

The alternative of kinetic control of the diastereomeric products requires that the species being alkylated cannot be cob(I)alamin. While cob(II)alamin is known to react with alkyl halides by a two-step mechanism[24-31] in a process which is either first- or second-order in cob(II)alamin (depending on the nature of the halide[24]), Blaser and Halpern[24] have shown that the base-off species of cob(II)alamin is at least 100-fold less reactive than the base-on species. While this result is consistent with the effect of axial ligands on the rate of alkylation of bis(dimethylglyoximato)cobalt(II) complexes with alkyl halides,[31] it is consistent with the current results if kinetic control of the products is operative. Thus, while a significant pH dependence is observed for the rate of accumulation of RCbl products,[42] an appropriate treatment shows that, for kinetically controlled products, the observed pH dependence of f_α can only be explained if the relative reactivity of the base-on species of cob(II)alamin exceeds that of the base-off species by 2–7-fold, depending on the alkyl halide. Thus, kinetic control of the diastereomeric products does not appear to be consistent with the current results.[43]

Table III. Temperature Dependence of the Apparent Equilibrium between α- and β-Diastereomers of the RCbi's

		$K_i^{Cbi\,a}$		
		$NCCH_2Cbi$	CF_3CH_2Cbi	CF_3Cbi
T, °C	0	0.59 ± 0.05	0.22 ± 0.01	0.097 ± 0.005
	25	0.47 ± 0.02	0.18 ± 0.01	0.074 ± 0.003
	50	0.50 ± 0.02	0.21 ± 0.01	0.080 ± 0.008
	75	0.42 ± 0.01	0.17 ± 0.01	0.076 ± 0.005
$\Delta H°$,[b] kcal mol^{-1}		−0.73 ± 0.9	−0.42 ± 0.39	−0.48 ± 0.33
$\Delta S°$,[c] cal mol^{-1} K^{-1}		−3.8 ± 0.9	−4.7 ± 1.3	−6.5 ± 1.0
E_s[d]		−2.3	−2.4	−2.5
σ_I[e]		0.20	0.16	0.40

[a] K_i^{Cbi} = [β-RCbi]/[α-RCbi]. [b] From the slopes of plots of ln K_i vs $1/T$ (not shown). [c] From the intercepts of plots of ln K_i vs $1/T$ (not shown). [d] Taft steric substituent constant;[45,46] values from ref 47. [e] Inductive substituent constant.[48]

Thermodynamics of the α/β Diastereomerism. If it is correct that the diastereomeric alkylcobamide products are under thermodynamic control, then the thermodynamics of their interconversion are of considerable interest. In order to avoid the complication of pH effects, the ratios of the diastereomers of the RCbi's resulting from the reductive alkylation of factor B in zinc/10% acetic acid with $NCCH_2Br$, CF_3CH_2I, and CF_3I were determined as a function of temperature. For each experiment four to eight samples were taken during the reaction period (anywhere from 4 to 40 min, depending on the temperature) and the ratio of diastereomers were determined by HPLC as described in the Experimental Section. As before, the ratio was time-independent and the average values were used as determinations of K_i (Table III), defined analogously to K_i for the RCbl's (Scheme I); i.e., K_i = [β-RCbi]/[α-RCbi]. For these three alkyl groups, the α-diastereomer is favored by about 1.0–1.5 kcal (at 25 °C) but there is little change in K_i with temperature. The enthalpies and entropies of isomerization were determined from plots of ln K_i vs $1/T$ (not shown) and are listed in Table III. The enthalpy values are not statistically significant, suggesting that the equilibrium is controlled by entropy. While all of the relatively bulky and electron-withdrawing alkyl groups (Taft steric substituent constants, E_s,[45-47] and σ_I values[48] are listed in Table III) prefer the α axial ligand position, the smaller and slightly electron-donating CH_3 (E_s = −1.24,[47] σ_I = −0.01,[48] $K_i \sim 24$[2]) and CH_3CH_2 (E_s = −1.31,[47] σ_I = −0.01,[48] $K_i > 49$[2,49]) prefer the β position by 1.9 to at least 2.3 kcal. Since the α face of Cbi, with its downwardly projecting b, d, and e propionamide side chains and the even larger secondary amide f side chain (Figure 1), is clearly more sterically congested than the β face, with its three upwardly projecting acetamide side chains, it would seem reasonable to conclude that steric effects are not the controlling factor. Such a conclusion would seem to be further supported by the fact that in the base-off RCbl's, where the steric congestion at the α face is even greater due to the presence of the dimethylbenzimidazole nucleotide, the values of K_i are quite similar to those of the RCbi's (Tables I and III). However, electronic effects cannot be dominant since the equilibrium between the α- and β-diastereomers is es-

(40) This requires that $K_{Bz}^{\alpha} = K_{Bz}^{\beta}$, which is correct, at least for R = CF_3CH_2.[1]

(41) Inclusion of a "tuck-in" species for the α-RCbl in Scheme I, with an equilibrium constant of K_H' for its formation from species α, changes eq 14 for K_a^{app} to

$$K_a^{app} = K_{Bz}^{\alpha}(1 + K_i + K_iK_{Co} + K_iK_H + K_H')/(1 + K_i').$$

Since the value of this K_H' would be expected to be quite small compared to K_iK_{Co},[7] inclusion of this species has a negligible effect on K_a^{app}.

(42) For instance, when CF_3I is the alkylating agent, total yields of RCbl's (i.e., CF_3Cbl's + CF_2HCbl's) in excess of 80% are obtained in as little as 3 min at pH 4.0–4.5, while the total yield was only 30% after 10 min at pH 0.9. Similarly, for CF_3CH_2I, the maximum yield obtainable at pH 5.0 (55%) can be observed in 1 min at 25 °C, while at pH 0.7 the yield was only 11% after 5 min.

(43) An alternative possibility for the alkylation of cob(II)alamin by alkyl halides in zinc/acid reductants is that alkyl radicals formed by zinc reduction of the alkyl halide are captured by cob(II)alamin. However, the observation that $CH_3^\bullet$ reacts with base-on and base-off cob(II)alamin with identical rate constants[44] is inconsistent both with the observed dependence of the rate of accumulation of products on pH[42] and with the requirement that the base-on species of cob(II)alamin be 2–7-fold more reactive than the base-off species if the products are under kinetic control.

(44) Bakac, A.; Espenson, J. H. *Inorg. Chem.* **1989**, *28*, 4319–4322.
(45) Taft, R. W., Jr. *J. Am. Chem. Soc.* **1952**, *74*, 3120–3128.
(46) Taft, R. W., Jr. *J. Am. Chem. Soc.* **1953**, *75*, 4538–4539.
(47) Unger, S. H.; Hansch, C. *Prog. Phys. Org. Chem.* **1976**, *12*, 91–118.
(48) Charton, M. *Prog. Phys. Org. Chem.* **1981**, *13*, 119–251.
(49) α-CH_3CH_2Cbi has not been detected in reductive alkylations of factor B.[2] An upper limit of 2% α-diastereomer can be set, assuming this is the limit of detectability by HPLC.

sentially isoenthalpic; i.e., the bond dissociation energies of the Co–C bond in each pair of diastereomers are essentially identical. The argument against steric effects being the dominant factor assumes that the corrin is rigid and that, in all the alkylcobamides, the cobalt atom lies very nearly in the mean plane of the equatorial nitrogens. For such a situation, models clearly show that the α face is more sterically congested than the β face and, for bulky organic ligands, steric interactions do occur between the side chains and the axial organic group. Indeed, such interactions are believed to be the driving force behind the decomposition of thermally labile species such as β-benzyl-Cbl and β-neopentyl-Cbl.[50] However, the corrin is not rigid; it is quite flexible.[51] Flexing of the corrin with associated displacement of the metal atom from the mean equatorial nitrogen plane clearly relieves steric compression by the side chains on the face toward which the metal is displaced. Such flexing is thought to be responsible for the marked stabilization of the base-off species of β-benzyl- and β-neopentyl-Cbl relative to the base-on species (the so-called "base-on" effect).[50] Hence, the thermodynamics of the α/β diastereomerism might reflect a greater tendency for the corrin to flex "upward" with the cobalt displaced toward the α face in α-alkylcobamides than to flex "downward" with the cobalt displaced toward the β face in β-alkylcobamides. This possibility is currently under further study.

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Registry No. β-CF_3Cbl, 133318-72-6; α-CF_3Cbl, 133318-71-5; β-CF_3CH_2Cbl, 128050-97-5; α-CF_3CH_2Cbl, 128052-61-9; β-$NCCH_2Cbl$, 133318-69-1; α-$NCCH_2Cbl$, 133318-68-0; H_2OCbl, 20623-12-5; CF_3CH_2I, 353-83-3; $NCCH_2Br$, 590-17-0; CF_3I, 2314-97-8.

(50) Brown, K. L.; Brooks, H. B. *Inorg. Chem.* **1991**, *30*, 3420–3430.
(51) Glusker, J. In B_{12}; Dolphin, D., Ed.; Wiley: New York, 1982; Vol. 1, pp 23–106.

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Vanadium(IV,V) Salts as Homogeneous Catalysts for the Oxygen Oxidation of *N*-(Phosphonomethyl)iminodiacetic Acid to *N*-(Phosphonomethyl)glycine

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From screening studies we have found that several metal ions are capable of catalyzing the molecular oxygen oxidation of *N*-(phosphonomethyl)iminodiacetic acid (PMIDA) to *N*-(phosphonomethyl)glycine (PMG), the active agent in the herbicide Roundup. Of these metal ions, vanadium, manganese, and cobalt salts were the most active, with the relative order of activity under a given set of conditions being V > Mn > Co. The vanadium-catalyzed PMIDA oxidations proceed at much faster rates and under milder conditions than with the other metals, but the chemistry suffers from lower selectivities. Kinetic and mechanstic studies reveal that the reactions are first-order in the [PMIDA], $[V]_{tot.}$, and $[H^+]$. In addition, the rate exhibits O_2 saturation kinetics, while increasing O_2 pressure increases the selectivity to PMG. From spectrophotometric, deuterium isotope, and other mechanistic studies, key mechanistic features have been elucidated: (1) An OV^{IV}(PMIDA(3–)) complex is first oxidized to V(V). (2) V(V) oxidation of a carboxyl moiety yields an intermediate carbon-centered *N*-methylenePMG radical. (3) The trapping of this radical with O_2 results in the formation of *N*-formylPMG, which hydrolyzes to PMG. (4) H atom abstraction by the *N*-methylenePMG radical leads to the undesired byproduct *N*-methylPMG.

Introduction

Molecular oxygen is an attractive oxidant for carrying out industrial processes, not only owing to its relatively low cost and abundance but also from an environmental standpoint, as its reduction does not yield salt products. Consequently, improved catalysis technology for performing O_2-driven oxidations is of considerable commercial significance. Monsanto currently converts *N*-(phosphonomethyl)iminodiacetic acid (PMIDA) to *N*-(phosphonomethyl)glycine (PMG) using a heterogeneously catalyzed oxygen-driven process:

$$\underset{\text{PMIDA}}{H_2O_3PCH_2N(CH_2CO_2H)_2} \xrightarrow[H_2O,\,\Delta]{O_2,\ \text{"cat."}} \underset{\text{PMG}}{H_2O_3PCH_2\overset{H}{\overset{|}{N}}CH_2CO_2H}$$

In the absence of added acid or base, PMIDA and PMG are only sparingly soluble in water (the ideal oxidation solvent). Consequently, the isolation of PMG product first requires the filtration of the heterogeneous catalyst from a highly dilute PMG solution, followed by an energy-intensive product concentration step. An effective homogeneous catalyst for the oxidation of PMIDA would eliminate the need for the filtration of the heterogeneous catalyst. In principle, high payloads could be achieved, thus avoiding the costs associated with a dilute reaction step.

For these reasons we began studies to determine if homogeneous catalysts could promote this oxygen-driven conversion of PMIDA to PMG. From our early screening studies we found that simple salts of Mn,[1] Co,[2,3] and V were very active homogeneous catalysts for the oxidation of PMIDA. Of these metals vanadium was the most active, although the observed selectivities with V were consistently less than observed with the other metals, producing as high as 50% *N*-methylPMG. With the goal of enhancing the selectivity of the vanadium-catalyzed PMIDA oxidation, we initiated a study of the mechanistic aspects of this novel vanadium chemistry. Prior to our studies of this problem, the catalytic oxidative dealkylation of a tertiary amine to a secondary amine with molecular oxygen had been demonstrated in only two cases,[4,5] and these were with unfunctionalized trialkylamines.

Experimental Section

Materials. All inorganic salts were purchased from Alfa Inorganics and used as received. The vanadium source used in the catalytic studies was vanadyl sulfate hydrate (22.15% V), and it was used as supplied by Alfa Inorganics. The PMIDA substrate was synthesized according to the procedure of Moedritzer et al.[6] Analytical standards for organic products such as PMG and AMPA ((aminomethyl)phosphonic acid) were obtained from Aldrich.

Procedure. For kinetic analysis of reaction rates at any given temperature, the reactions were run in triplicate. For the kinetic studies, 0.100 M aqueous PMIDA solutions were utilized for obtaining reaction profiles. All kinetic runs were performed in a Hastaloy C Autoclave Engineer's 300-mL autoclave stirred at 1500 rpm modified to bring oxygen into the reactor beneath the stirrer vanes. The reactor system

(1) Riley, D. P.; Rivers, W. U.S. Patent 4965402, 1990.
(2) Riley, D. P.; Rivers, W. U.S. Patent 4898972, 1990.
(3) Riley, D. P.; Rivers, W.; Fields, D. *J. Am. Chem. Soc.*, in press.
(4) Riley, D. P. *J. Chem. Soc., Chem. Commun.* **1983**, 1530.
(5) Correa, P. E.; Riley, D. P. U.S. Patent 4565891, 1983.
(6) Moedritzer, K.; Trani, R. R. *J. Org. Chem.* **1966**, *31*, 1603.
(7) March, J. *Advanced Organic Chemistry*, 3rd ed.; J. Wiley & Sons: New York, 1988; p 788.

0020-1669/91/1330-4191$02.50/0