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Organic Free Radical-Promoted Isomerization of α- and β-Alkylcobinamides[1]

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Anaerobic reaction of α- or β-alkylcobinamides (α- or β-RCbi$^+$'s) with the corresponding alkyl free radical, R$^\bullet$ (where R = CH_3, CH_3CH_2, or $CH_3CH_2OCH_2CH_2$), generated by the Fenton reaction using Fe^{2+} and an alkyl hydroperoxide, $RC(CH_3)_2OOH$, causes isomerization and leads to mixtures of α- and β-RCbi$^+$'s. The reaction does not occur, however, under aerobic conditions or under anaerobic conditions in the presence of an excess of the free radical scavenger H-Tempo. In addition, α-$CH_3CH_2Cbi^+$ reacts with 50 molar equiv of *tert*-butyl hydroperoxide and Fe^{2+} to give a mixture of alkylcobinamides that contains 6% α-CH_3Cbi^+ and 94% β-CH_3Cbi^+, showing that multiple transalkylations occur. A Co^{II}-induced isomerization and the S_H2 mechanism are ruled out on the basis of the known reactivity of RCbi$^+$ and product analysis. A mechanism is proposed which involves a direct oxidative free radical displacement by an R$^\bullet$ to the metal of RCbi$^+$ via a dialkylcobalt(IV) corrinoid species. Since the reaction leads to equilibration of the two diastereomers under mild conditions, it can be used to study the equilibria between diastereomeric RCbi$^+$'s. Thus, the equilibrium for the diastereomeric ethyl-13-epicobinamides, in which the *e* propionamide side chain of the corrin ring has been epimerized from the α to the β face of the corrinoid, lies significantly more toward the α diastereomer than that for the normal ethylcobinamides. This represents the most direct experimental evidence obtained to date that the corrin ring side chains control the relative steric accessibility of the two faces of the cobalt corrinoids.

Introduction

It is now well-known that alkylation of cobalt corrinoids using Zn/acid reductants or controlled-potential reduction with a variety of alkyl halides leads to mixtures of α- and β-alkylcobalt corrinoids.[1−9] For the alkylcobinamides (RCbi$^+$'s, Figure 1), the proportion of the two diastereomers obtained has been found to vary widely depending on the nature of R (Table 1). Thus, while little or no α-$CH_3CH_2Cbi^+$ is obtained upon alkylation of factor B[1] with CH_3CH_2Br,[8b] oxidative addition of $NCCH_2Br$ or CF_3CH_2I to the reduced corrinoids yields 73% or 87% of the α-RCbi$^+$, respectively, and α:β ratios >10:1 can also occur (Table 1).

Table 1. Comparison of the Diastereomeric Compositions of the RCbi$^+$'s Obtained from Reductive Alkylation and from Thermally-Induced Isomerization

	f_α[a]	
RCbi$^+$	reductive alkylation[b]	thermally-induced isomerization[c]
$CH_3CH_2Cbi^+$	<0.02[d]	0.03
CH_3Cbi^+	0.04	0.07
$EtOCH_2CH_2Cbi^+$	0.20	0.04
$NCCH_2Cbi^+$	0.73	0.07
$CF_3CH_2Cbi^+$	0.87	0.05
CF_3Cbi^+	0.93	*e*
CF_2HCbi^+	0.98	<0.25[f]

[a] Fraction of the RCbi$^+$ product as the α diastereomer. [b] Reductive alkylation of factor B in Zn/acid with RX.[8b] [c] Final product composition upon heating an anaerobic aqueous solution, pH 7.0, at 70 °C, except as noted.[11] [d] Undetectable. [e] Undergoes decomposition only; no isomerization can be detected. [f] At 135 °C. Decomposition prevented following the reaction to completion.

The most striking result of these observations is that a number of bulky organic ligands prefer the α axial ligand position to the β position under these conditions. This is surprising because it is generally assumed that the α face of corrinoids is more sterically congested due to the "downward" projecting *b*, *d*, and *e* propionamide and the *f* secondary amide (nucleotide loop) side chains. In contrast, the β face is bracketed only by the three "upward" projecting *a*, *c*, and *g* acetamides (Figure 1). Thus, questions of whether the presumptions about the steric consequences of α and β face structure are correct have become paramount. It is known that the RCbi$^+$ products are in a steady state under synthetic conditions due to reductive dealkylation;[8b,d,10] however, the ratio of diastereomers is *not* affected by differential rates of decomposition, as the rates of reductive destruction of pairs of α and β diastereomers by various reductants are the same.[10]

In order to determine if the products of oxidative additions of alkyl halides to reduced cobalt corrinoids are under equilibrium or kinetic control, accurate assessment of the thermody-

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(1) Standard IUPAC−IUB nomenclature[2] is used throughout. Factor B is a mixture of α-(CN)-β-(H_2O)-cobinamide and α-(H_2O)-β-(CN)-cobinamide. CN-13-epi-Cbi$^+$ is a mixture of α-(CN)-β-(H_2O)-13-epicobinamide and α-(H_2O)-β-(CN)-13-epicobinamide. Abbreviations: Cbi, cobinamide; Cbl, cobalamin; α-RCbi$^+$, α-alkylcobinamide; β-RCbi$^+$, β-alkylcobinamide. H-Tempo, (4-hydroxy-2,2,6,6-tetramethylpiperidinyl)oxy; R-13-epiCbi$^+$, alkyl-13-epicobinamide.

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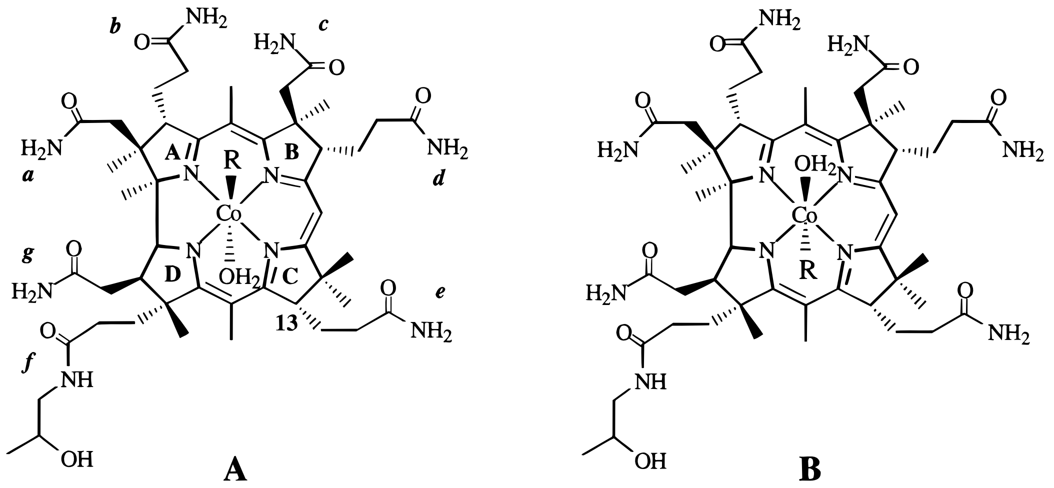

Figure 1. Structures of a β-alkylcobinamide (β-RCbi$^+$) and an α-alkylcobinamide (α-RCbi$^+$). For the R-13-epiCbi$^+$'s, the *e* side chain (at carbon-13 as labeled) is inverted to point "upward" instead of "downward".

namics of α/β diastereomerism is needed. While α- and β-RCbi$^+$'s are known to equilibrate at elevated temperatures via Co−C bond homolysis,[11] accurate determination of equilibrium constants under these conditions is difficult since strict anaerobic conditions are necessary to prevent decomposition. Thus, in previous attempts to estimate such equilibrium constants,[11] it was very difficult to avoid some RCbi$^+$ decomposition despite efforts to exclude air from the system.

In an attempt to obtain kinetically controlled α/β-diastereomeric RCbi$^+$ products, we recently tried to measure the product ratios resulting from the reaction of cob(II)inamide with alkyl hydroperoxides[12] (eqs 1−3, M^{2+} = cob(II)inamide), since the

$$M^{2+} + RC(CH_3)_2OOH \xrightarrow{\text{slow}} HO{-}M^{3+} + RC(CH_3)_2O^{\bullet} \tag{1}$$

$$RC(CH_3)_2O^{\bullet} \xrightarrow{\text{fast}} R^{\bullet} + CH_3COCH_3 \tag{2}$$

$$R^{\bullet} + Co^{II} \xrightarrow{\text{fast}} RCo \tag{3}$$

coupling of alkyl radicals with cob(II)inamide (eq 3) represents a prototypical reaction in which the Co−C bonds are formed. To our surprise, we discovered that the product in eq 3, alkylcobinamide, reacts with the homologous alkyl radical $R^{\bullet}$ to undergo isomerization, thus, ironically, providing a method for studying diastereomer equilibration under mild conditions. We now report our observations of free radical-promoted isomerization of RCbi$^+$'s and demonstrate the utility of this method for the determination of equilibrium constants for interconversion of RCbi$^+$'s.

Experimental Section

Materials. CNCbl[1] was purchased from Roussell. *tert*-Butyl hydroperoxide, 2-methyl-2-butanol, iodomethane, bromoethane, (4-hydroxy-2,2,6,6-tetramethylpiperidinyl)oxy (H-Tempo[1]), trifluoroacetic acid, hydrogen peroxide, ethyl ethoxyacetate, and 2-bromoethyl ethyl ether were from Aldrich. Factor B, a mixture of the diastereomeric cyano(aquo)cobinamides,[1] was prepared from CNCbl by the triflic acid method.[13] CN-13-epi-Cbi$^+$ was obtained by acid-catalyzed epimerization of CNCbl in trifluoroacetic acid.[14,15] α- and β-ethoxyethylcobinamides ($EtOCH_2CH_2Cbi^+$'s), β-RCbi$^+$'s, and β-R-13-epiCbi$^+$'s[1] (R = CH_3 and CH_3CH_2) were synthesized by reductive alkylation using 10% acetic acid/Zn and RX and separated by HPLC[16] as described elsewhere.[8b] α-RCbi$^+$'s (R = CH_3 and CH_3CH_2) and α-R-13-epiCbi$^+$'s (R = CH_3CH_2) were obtained by anaerobic photolysis of the corresponding β-RCbi$^+$ and β-R-13-epiCbi$^+$ as reported previously.[17]

$CH_3CH_2C(CH_3)_2OOH$ (**1**) was synthesized by a reported procedure[18] using $CH_3CH_2C(CH_3)_2OH$ and hydrogen peroxide. NMR, δ (TMS, acetone-d_6, ppm): CH_3CH_2, 0.86 (t); CH_3CH_2O, 1.55 (q); $C(CH_3)_2$, 1.13 (s); OO*H*, 9.88 (s).

$EtOCH_2CH_2C(CH_3)_2OH$ (**2**) was prepared by a standard Grignard reaction. In an inert atmosphere and with an ice/water bath, iodomethane was dissolved in anhydrous ether with Mg turnings. After the Grignard reagent formation was complete, $EtOCH_2CH_2CO_2Et$ (0.3 equiv) was added dropwise. The solution was allowed to stir for 1 h. Unreacted Mg was filtered off, and the reaction mixture was poured into ice/water. After the organic layer was isolated and dried, the ether was removed by vacuum evaporation. The product was purified by silica gel chromatography. NMR, δ (TMS, acetone-d_6, ppm): CH_3CH_2, 1.11 (t); CH_3CH_2O, 3.44 (q); OCH_2CH_2, 3.57 (t); OCH_2CH_2, 1.71 (t); $C(CH_3)_2$, 1.17 (s); O*H*, 2.97 (s).

$EtOCH_2CH_2C(CH_3)_2OOH$ (**3**) was obtained by the reaction of **2** with hydrogen peroxide.[18] NMR, δ (TMS, acetone-d_6, ppm): CH_3CH_2, 1.14 (t); CH_3CH_2O, 3.45 (q); OCH_2CH_2, 3.51 (t); CH_2CH_2, 1.83 (t); $(CH_3)_2$, 1.18 (s); OO*H*, 10.11 (s).

Organic free radicals were generated by the well-known reaction of alkyl hydroperoxide with a divalent metal salt as shown in eqs 1 and 2 (M^{2+} = Fe^{2+}).[12,19−22]

Free Radical-Promoted Isomerization. These reactions were carried out under anaerobic conditions using the following general procedure. An aqueous solution of α- or β- RCbi$^+$ with $FeSO_4$ and an aqueous solution of alkyl hydroperoxide were deaerated separately by argon purge for 1 h. The RCbi$^+$ solution was transferred by a cannula to the alkyl hydroperoxide solution to initiate the reaction. Samples of the reaction mixture were taken periodically and analyzed by HPLC.[16] The ratio of the diastereomers was determined by multiple HPLC chromatogram peak integrations and was corrected for differing molar absorptivity of each isomer at the HPLC monitoring wavelength of 254 nm (R = CH_3CH_2, $\epsilon_\alpha = 13\,700$, $\epsilon_\beta = 12\,300$; R = CH_3, $\epsilon_\alpha = 23\,800$, $\epsilon_\beta = 27\,000$; R = $EtOCH_3CH_2$, $\epsilon_\alpha = 11\,900$, $\epsilon_\beta = 14\,100$). The HPLC detection limit was estimated to be ~2%.

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Table 2. Reaction Conditions and Product Compositions of α- or β-RCbi$^+$ with $R'^{\bullet}$ and with Alkyl Hydroperoxide

RCbi$^+$	[RCbi$^+$], mM	R′	[R′C(CH$_3$)$_2$O$_2$H], mM	[Fe^{2+}], mM	f_α[a]
α-$CH_3CH_2Cbi^+$	0.1	CH_3CH_2	1	1	≤0.02[b]
	0.1	CH_3CH_2	0.2	0.2	≤0.02[c]
	0.1	CH_3CH_2	5	1	0.94[d]
	0.1			1	1.00[e]
	0.1	CH_3CH_2	1	0	≤0.02[f]
	0.1	CH_3CH_2	0.2	0	≤0.02[g]
	0.1	CH_3CH_2	0.02	0	1.00[h]
	0.1	CH_3	10	0	≤0.02[i,j]
	0.1	CH_3	5	1	*b, i, k*
	0.1	CH_3	0.02	0.02	*i, l*
β-$CH_3CH_2Cbi^+$	0.1	CH_3CH_2	0.5	0.5	≤0.02[b]
	0.1	CH_3	1	1	*b, i, m*
α-CH_3Cbi^+	0.1	CH_3	1	1	0.07[b]
	0.2	CH_3	0.04	0.2	0.06[n]
	0.1	CH_3	0.001	0.001	0.07[o]
	0.1	CH_3	0.5	0.5	1.00[p]
	0.1	CH_3CH_2	10	0	0.09[i,q]
β-CH_3Cbi^+	0.1	CH_3	1	1	0.06[b]
	0.1	CH_3CH_2	1	1	*b, i, r*
α-$EtOCH_2CH_2Cbi^+$	0.1	$EtOCH_2CH_2$	1	1	0.05[b]
β-$EtOCH_2CH_2Cbi^+$	0.1	$EtOCH_2CH_2$	1	1	0.05[b]

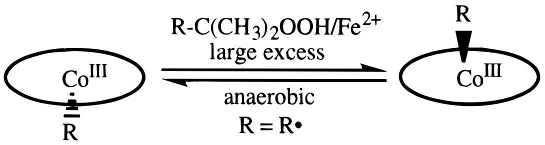
[a] Fraction of RCbi$^+$ product as the α diastereomer based on RCbi$^+$'s. [b] Completed as soon as the reactants were mixed (<1 min). [c] Completed in 10 min. [d] With 10 mM H-Tempo. Followed for 12 h. [e] Control experiment. No alkyl hydroperoxide was used. [f] $t_{1/2} \approx {}^1/_2$ h. [g] $t_{1/2} \approx 5$ h. [h] Followed for >5 h. [i] Crossover experiment. See text. [j] Completed in ~2.5 h. The final reaction mixture contained ≤2% β-CH_3Cbi^+ and 95% β-$CH_3CH_2Cbi^+$. [k] The products were α-CH_3Cbi^+ (6%) and β-CH_3Cbi^+ (94%). [l] With less than 1 molar equiv of $CH_3C(CH_3)_2OOH$, the products were 7% α-CH_3Cbi^+, 10% β-CH_3Cbi^+, and 80% β-$CH_3CH_2Cbi^+$. Completed in 5 min. [m] The products were 6% α-CH_3Cbi^+, 88% β-CH_3Cbi^+, and 6% β-$CH_3CH_2Cbi^+$. [n] Completed within 5 min. [o] Completed within ~36 h. [p] Under aerobic conditions. Reaction followed for 5 h. [q] The final reaction mixture contained ≤2% β-$CH_3CH_2Cbi^+$. Completed in ~2 h. [r] The final reaction mixture contained 85% β-$CH_3CH_2Cbi^+$.

For equilibrium constant measurements, the reactions between R-13-epiCbi$^+$ (or RCbi$^+$) and alkyl hydroperoxide/Fe^{2+} were carried out at 20 °C. The HPLC chromatograms were monitored at both 254 and 350 nm. Integrations from the two wavelengths were corrected for the extinction coefficients and averaged to obtain the final values.

Results

Reactions of RCbi$^+$ with R$^\bullet$. While a number of means can be used to generate organic free radicals, photolytic and thermal methods[19] are not suitable here since the complexes being examined are labile under these conditions. We have thus resorted to the classical Fenton-type reagents using alkyl hydroperoxides and a divalent metal ion (Fe^{2+}) as the source of organic free radicals, R$^\bullet$ (eqs 1 and 2). Although metal-induced alkyl hydroperoxide decomposition follows somewhat complicated mechanisms,[20] it does, however, provide a reliable source for organic free radicals.[12,20−22] Several metal cations with low reductive potentials are known to participate in such reactions, including Co^{2+}, Cr^{2+}, Cu^{2+}, and Fe^{2+}.[12,21,22] Fe^{2+} was used in this study since its reaction with alkyl hydroperoxide is fast,[23] and the oxidized Fe^{3+} will not react with R$^\bullet$ to form stable alkylmetal complexes, in contrast to Co^{2+}, Cr^{2+}, and Cu^{2+}.[12,22]

The reaction conditions and the results of radical-promoted isomerization of RCbi$^+$ are summarized in Table 2. With a ratio of 10:1 (1:0.1 mM) for alkyl hydroperoxide/Fe^{2+} to RCbi$^+$, the reaction was completed as soon as the reactants were mixed. This was evident since no time dependence of the α- and β-RCbi$^+$ product ratio could be detected. In a typical reaction, for example, the products of anaerobic reaction of α-CH_3CH_2-Cbi$^+$ with 10 molar equiv of 1,1-dimethylpropyl hydroperoxide, $CH_3CH_2C(CH_3)_2OOH$, and 10 equiv of ferrous sulfate were found to be a mixture of diastereomers which contained ≤2% α-$CH_3CH_2Cbi^+$ and 98% β-$CH_3CH_2Cbi^+$ (eq 4) with negligible net decomposition. Similar results (Table 2) were obtained when either α- or β-CH_3Cbi^+ was treated with *tert*-butyl hydroperoxide in the presence of ferrous sulfate. In this case, the product distribution was 6−7% α- and 93% β-CH_3Cbi^+ (Table 2 entries 13−15 and 18). In control experiments, no isomerization was observed using any of the α- or β-RCbi$^+$'s with only FeSO$_4$ or with relatively low concentrations of alkyl hydroperoxide alone (≤0.02 mM; vide infra; Table 2, entry 7). In addition, under aerobic conditions, where O$_2$ serves as a good radical trap,[24,25] or in anaerobic solution with 10 mM H-Tempo[26] as a free radical scavenger, no interconversion of RCbi$^+$ diastereomers was observed (Table 2, entries 3 and 16), demonstrating that at least one step of the isomerization reaction involves a free radical.



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Crossover Reactions. In order to confirm that an organic free radical derived from the alkyl hydroperoxide is indeed involved in the isomerization reaction, we performed the following "crossover" reactions. In one experiment, α-ethylcobinamide, α-$CH_3CH_2Cbi^+$ (R = CH_3CH_2), was allowed to react with a 50-fold excess of *tert*-butyl hydroperoxide, $CH_3C(CH_3)_2OOH$ (R′ = CH_3), and Fe^{2+} (eq 5; Table 2, entry 9). The final reaction mixture under these conditions contained 6% α-CH_3Cbi^+ and 94% β-CH_3Cbi^+, and no $CH_3CH_2Cbi^+$'s

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(23) (a) A comparative study using metal cations with alkyl hydroperoxides, monitored by the formation of acetone (eq 2), showed that Fe^{2+} is the most efficient in generating acetone (and thus R$^\bullet$) among Cu^{2+}, Fe^{2+}, and Co^{2+}. (b) The acetone product was monitored by HPLC analysis of the Schiff's base formed between acetone and 2,4-dinitrophenylhydrazine.

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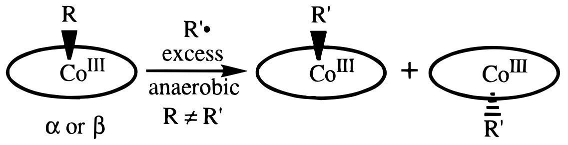
(25) This reaction was carried out as described in the text for anaerobic reactions, except that the argon-purging step was omitted.

(26) At this concentration, H-Tempo can only trap free, but not caged, radicals.[27]

(27) Garr, C. D.; Finke, R. G *J. Am. Chem. Soc.* **1992**, *114*, 10440.

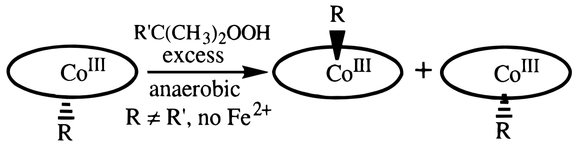


(5)

could be detected. When the ratio of α-$CH_3CH_2Cbi^+$ and $CH_3C(CH_3)_2OOH/Fe^{2+}$ was 1:02, i.e., when less than a stoichiometric amount of alkyl hydroperoxide was used, the products were 7% α-CH_3Cbi^+, 10% *β*-CH_3Cbi^+, and 80% *β*-$CH_3CH_2Cbi^+$ (Table 2, entry 10). These results clearly show that, in the presence of excess alkyl hydroperoxide/Fe^{2+}, transalkylation occurs in such crossover reactions since the original alkyl group in the starting $RCbi^+$ is replaced by the R′ from the alkyl hydroperoxide.

Isomerization with Hydroperoxide Alone. The $RCbi^+$'s were found to be quite stable in low concentrations of alkyl hydroperoxide alone (≤0.02 mM; Table 2, entry 7), but high concentrations of alkyl hydroperoxide induced a slow isomerization. Thus, in the presence of 0.2 mM $CH_3CH_2C(CH_3)_2$-OOH, α-$CH_3CH_2Cbi^+$ rearranged to a mixture of α- and *β*-$CH_3CH_2Cbi^+$'s (∼2:98) with a half-time of several hours without detectable dealkylation (Table 2, entry 6). Increasing the concentration of hydroperoxide 5-fold to 1.0 mM did not change the product composition but did speed up the reaction ($t_{1/2} \sim 30$ min; Table 2, entry 5). These experiments qualitatively indicate that, without Fe^{2+}, the rate of conversion from α- to *β*-$CH_3CH_2Cbi^+$ under these conditions appears to be dependent on the concentration of alkyl hydroperoxide. Even hydrogen peroxide promoted the rearrangement from α- to *β*-$CH_3CH_2Cbi^+$ (data not shown), albeit at a much slower rate and with some dealkylation. Thus, the reactions promoted by alkyl hydroperoxide alone (or by hydrogen peroxide) were noticeably slower than those by alkyl hydroperoxide and Fe^{2+}. At the same peroxide concentration, the former reaction is at least 100 times slower than the latter.

Isomerization promoted by alkyl hydroperoxide alone was, however, found to occur *without* crossover products in heterologous experiments. Thus, when α-$CH_3CH_2Cbi^+$ (0.1 mM, R = CH_3CH_2) was allowed to react with excess $CH_3C(CH_3)_2$-OOH (R′ = CH_3, 10 mM) anaerobically *without* Fe^{2+} in a crossover experiment, *β*-$CH_3CH_2Cbi^+$ was the only significant product (Table 2, entry 8) found in the final reaction mixture. Similarly, CH_3Cbi^+'s (R = CH_3) were the only major products starting from α-CH_3Cbi^+ (R = CH_3) and $CH_3CH_2C(CH_3)_2OOH$ (R′ = CH_3CH_2) at a ratio of 1:100 (eq 6; Table 2, entry 17).



(6)

These results demonstrate that, without Fe^{2+}, peroxide-promoted isomerization of $RCbi^+$'s does not involve the $R'^\bullet$ radical derived from the hydroperoxide since the reagent R′ is not found in the $RCbi^+$ products. Thus, in contrast to the results when Fe^{2+} is used, no crossover occurs for these reactions.

Equilibration of Diastereomers by Reaction with R•. For R = CH_3 and CH_3CH_2, the product ratios obtained from synthesis and from thermal equilibration (Table 1) are not significantly different and so it is impossible to distinguish whether the product composition from reaction with the homologous radical represents a nonequilibrium steady state (as in synthesis)[8b] or a thermal equilibrium.[11] In order to answer this question, $EtOCH_2CH_2C(CH_3)_2OOH$ was synthesized and used to carry out the isomerization. For the $EtOCH_2CH_2Cbi^+$'s, the fractions as the α isomer in the product (f_α) by synthesis and by thermal equilibration are 0.20 and 0.04, respectively, making it possible to make such a distinction. When either α- or *β*-$EtOCH_2CH_2Cbi^+$ was reacted with excess $EtOCH_2$-$CH_2C(CH_3)_2OOH$ and Fe^{2+}, f_α was found to be 0.05, starting from either direction of eq 4 (Table 2, entries 20 and 21). This value agrees well with the results of thermal equilibration[11] but is quite different from the results of reductive alkylation (Table 1), demonstrating that free radical-promoted isomerization of $RCbi^+$ leads to equilibration of the diastereomers in the presence of a large excess of the homologous radical.

It is obvious that this convenient method can be used to measure equilibrium constants for α/*β* diastereomerism under mild conditions. It was consequently used to address the question of whether or not there is a difference in steric congestion of the two corrinoid faces due to differential side chain structures. This can be done by use of corrinoid epimers, in which epimerization at a corrin ring carbon inverts the position of the attached side chain. Thus, for the 13-epicorrinoids, the *e* propionamide side chain at C-13 (Figure 1), normally in a pseudoaxially downward position, adopts a pseudoaxially upward position,[28,29] altering the distribution of side chains bracketing the α and *β* faces. At 20 °C, the measured equilibrium constant ($K = [\alpha\text{-}RCbi^+]/[\beta\text{-}RCbi^+]$) for the two $CH_3CH_2Cbi^+$ diastereomers was 0.02 ± 0.02, but for CH_3CH_2-13-epiCbi^+, the equilibrium constant was increased to 0.39 ± 0.02. This suggests that side chain steric structure does, indeed, influence the accessibility of the two faces of the corrin ring and hence the steric outcome of diastereomeric equilibrium of $RCbi^+$'s.

Discussion

Reaction of Cob(II)inamide with Alkyl Hydroperoxides/Fe^{2+}. When we started this project, our initial plan was to measure the kinetically-controlled product ratios for formation of the diastereomeric $RCbi^+$'s via radical combination of cob(II)inamide (Co^{II}) with $R^\bullet$ (eqs 1−3), in order to shed light on the factors that control the synthetic product ratios. It quickly became apparent to us, however, that the ratio of the two diastereomers formed in this reaction was concentration dependent when various amounts of alkyl hydroperoxide were used, and the reaction seemed to go to equilibrium with excess alkyl hydroperoxide. This was surprising, since in the absence of further reaction of the product $RCbi^+$'s, the ratio of the two diastereomers resulting from the reaction of eqs 1−3 should be constant and depend only on the differential rates of radical combination to form the two isomers. This observation prompted us to examine the possible reactions between the $RCbi^+$ products and the organic free radical.

The reaction of $RCbi^+$'s with the homologous radical, $R^\bullet$ (generated by reaction of an alkyl hydroperoxide and $FeSO_4$), caused isomerization and produced the same final ratios of α- and *β*-$RCbi^+$'s starting from either diastereomer for all the R groups studied (eq 4). For R = CH_3, the ratio was ∼15:1, and for R = CH_3CH_2, it was ∼50:1, both favoring the *β* diastereomer. The isomerization was inhibited, however, when H-Tempo was added to the reaction under anaerobic conditions, and it would not proceed under aerobic conditions where O_2 serves as a good radical trap. These observations demonstrate that at least one step of the isomerization involves a free radical

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intermediate. When the reaction was carried out with excess heterologous organic free radical ($R \neq R'$) in the "crossover" experiments (eq 5), the products were found to be a mixture of $R'Cbi^+$'s, showing that $R'^\bullet$, derived from the reagent alkyl hydroperoxide, participates in the radical reaction and replaces the original R group in $RCbi^+$. Since $R'Cbi^+$'s are the only products when a large excess of $R'^\bullet$ is used, but a smaller portion of the products with limiting $R'^\bullet$ (Table 2), the product composition in these crossover reactions seems to depend on the ratio of the heteroalkyl groups present in the system, including R′ from the reagent peroxide and R from $RCbi^+$.

For $R = CH_3CH_2OCH_2CH_2$, the fraction of products as the α isomer, f_α, by radical reaction was found to be 0.05 (Table 2), starting from either the α- or β-$RCbi^+$. This is almost identical to the ratio previously obtained by thermal equilibration (0.04)[11] but significantly different from that obtained by reductive alkylation[8b] of cobinamide with ethoxyethyl bromide (0.20; Table 1), showing that the organic free radical-promoted isomerization reaction leads to diastereomer equilibration.

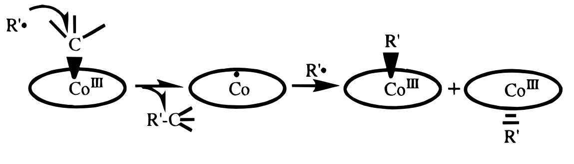
It is intriguing to note, however, that alkyl hydroperoxides alone (*without* the radical chain initiator, Fe^{2+}) also promote the isomerization of $RCbi^+$, although at a much slower rate than the reaction with Fe^{2+} (Table 2). A close examination of the results of the crossover reactions with and without Fe^{2+} reveals that the difference between the two reactions goes far beyond the difference in reaction rates. For reactions using both alkyl hydroperoxide and Fe^{2+}, the organic free radical, $R^\bullet$, is generated from the peroxide and found in the products. In contrast, for the reactions promoted by alkyl hydroperoxide alone, the products contain little or none of the alkyl group from the peroxide. This is not surprising, however, since alkyl hydroperoxides are fairly stable in the absence of divalent metal ions, and no acetone formation (and hence no $R^\bullet$ formation) could be detected when these reagents were permitted to stand at room temperature for 24 h.[23b]

In order to find out whether any free radical at all is involved in the reaction promoted by peroxide alone, trapping experiments were also used to see if efficient radical traps would inhibit isomerization. Somewhat unexpectedly, no isomerization of $RCbi^+$'s could be detected using only alkyl hydroperoxide under aerobic conditions or in the presence of H-Tempo under anaerobic conditions, showing that the alkyl hydroperoxide-promoted reaction also involves free radicals. One possibility is that a small amount of alkyl hydroperoxide can thermally decompose even under these mild conditions to give a minute amount of $R^\bullet$ which could, if formed, initiate the isomerization of $RCbi^+$. Alternatively, oxidation of a trace amount of $RCbi^+$ by the alkyl hydroperoxide (or hydrogen peroxide) to a higher oxidation state and subsequent homolytic cleavage of the Co−C bond of this oxidized complex can also generate $R^\bullet$. This is consistent with the observation that the rates of isomerization of $RCbi^+$'s, with or without Fe^{2+}, are peroxide (and thus $R^\bullet$) concentration dependent. For reactions promoted by peroxide alone, slow isomerization (Table 2) is the expected consequence if only a tiny amount of $R^\bullet$ is generated.[30] Direct addition of thermally decomposed products of R′OOH, $R'OO^\bullet$, to $RCbi^+$ to form $RCbi^+{-}OOR'$ followed by its decomposition could also account for the slow isomerization.

Measurements of Equilibrium Constants by Reaction of $RCbi^+$'s and R-13-epiCbi$^+$ with $R^\bullet$. Since the reaction of $RCbi^+$ with $R^\bullet$ leads to equilibration of the α and β diastereomers, it can be used to determine equilibrium constants for the diastereoisomerization under mild conditions. This method has now been used to test the assumption that the α face of cobalt corrinoids is more sterically congested than the β face due to the configurations of the corrin ring side chains, an assumption often postulated but never proven. Thus, we found the equilibrium constant, $K = [\alpha\text{-}RCbi^+]/[\beta\text{-}RCbi^+]$, for $CH_3CH_2Cbi^+$'s to be 0.02, but upon epimerization of the *e* propionamide side chain from its normal "downward" to an "upward" pseudoaxial position in the CH_3CH_2-13-epiCbi$^+$'s, the equilibrium is significantly shifted toward the α isomer ($K = 0.39$). The observed difference in equilibrium constants for the two epimers is not likely to be due to differences in electronic effects since the inner spheres of CNCbl and CN-13-epiCbl have been shown to be essentially identical.[29] This result is the most direct experimental evidence confirming the notion that differential steric congestion of the corrin faces is largely determined by the configurations of the side chains. It should be noted that the β face in R-13-epiCbi$^+$ is still preferred by the ethyl ligand by a factor of ~2:1. Such a preference is possibly due to the large size of the *f* side chain at the α face (Figure 1).

Mechanism of the Radical-Promoted Isomerization of $RCbi^+$'s. In general, $RCbi^+$'s are quite stable thermally and undergo only slow Co−C cleavage (and hence isomerization) at ~70 °C or above.[11,31−33] Under the reaction conditions used here (room temperature), there must be a negligible amount of homolytic C−Co bond cleavage to form cob(II)inamide species, which could, if formed, react with the alkyl hydroperoxide/Fe^{2+} according to eqs 1−3. It is thus highly unlikely that thermally-generated Co^{II} is involved as a reaction intermediate (via an S_H1 mechanism) in the radical-promoted isomerization.

Equilibration of two isomers involving a carbon free radical intermediate has been common for organic compounds.[34,35] Radical-promoted isomerization of organometallic compounds, on the other hand, usually involves attack on the α carbon of the organic ligand to form a metal-centered radical via an S_H2 mechanism[36−38] or occurs by a group transfer mechanism.[11,39−41] The S_H2 reactions have been extensively studied in the alkylcobaloxime system as well as for other metal complexes.[36,37] While an isomerization mechanism based on an S_H2 reaction (eq 7) can explain some of the results discussed above, it requires, in theory, at least 2 equiv of $R'^\bullet$ to complete the reaction to the right and an even larger excess of $R'^\bullet$ to achieve



(7)

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[30] The rate of the isomerization reaction with hydrogen peroxide is even slower than that with alkyl hydroperoxide alone, and some dealkylation of $RCbi^+$ always occurs. In this case, either $HO^\bullet$ radicals derived from hydrogen peroxide or $R^\bullet$ radicals from Co−C cleavage of peroxide-oxidized $RCbi^+$'s must be involved.

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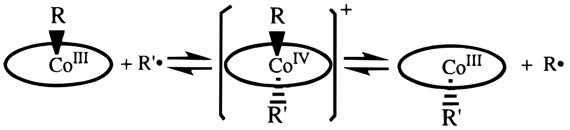
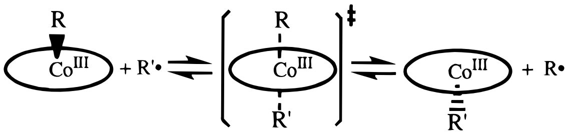
equilibration of the two isomers. Some dealkylation product should also be observed with limiting $R'^{\bullet}$ due to the formation of the alkane. These requirements are not consistent with our observations that when $CH_3C(CH_3)_2OOH$ was used to effect isomerization of CH_3Cbi^+ or $CH_3CH_2Cbi^+$, as little as 0.2 (or even 0.01; Table 2, entries 14 and 15) molar equiv of $CH_3C(CH_3)_2OOH/Fe^{2+}$ was needed to achieve a complete isomerization and that there was no net destruction of $RCbi^+$'s (Table 2).[42] Furthermore, the S_H2 mechanism dictates that the incoming radical reacts with the alkyl group of $RCbi^+$ to form an $R'-R$ alkane (eq 7), and thus it is not possible for the original R group to appear in the isomerized products. This is also not consistent with our results that when less than a stoichiometric amount of heteroalkyl hydroperoxide/Fe^{2+} was used in the crossover experiments, the original R group from $RCbi^+$'s was found in the rearranged products, showing that the reaction also involves the organic group from $RCbi^+$'s under these conditions (Table 2). On the basis of these results, we concluded that it is very unlikely that the S_H2 mechanism with radical attack on the α carbon of the organic ligand in $RCbi^+$ is involved in the isomerization of $RCbi^+$'s.

Radical-promoted rearrangement of $RCbi^+$'s could also result from direct, reversible oxidative addition of $R'^{\bullet}$ to form a dialkylcobalt(IV) species (eq 8). Subsequent release of $R^{\bullet}$ or $R'^{\bullet}$ would lead either to isomerization in the case of homologous radicals or transalkylation in the case of crossover reactions involving heterologous radicals. Such a reversible radical chain reaction will necessarily lead to an equilibration of alkyl corrinoid isomers, provided excess free radical is present or the chain length is large enough for multiple turnovers.



(8)

Oxidative addition of $R^{\bullet}$ to organometallic and organic compounds to form transient, and in some cases stable, species has been postulated for radical displacement reactions in a number of systems.[43−47] Dialkylcobalt(IV) species have also been suggested as transient radical intermediates in the oxidative cleavage of the dimethylcobaloxime complex,[48,49] although they are as yet unknown in the corrin system. However, stable organocobalt(IV) complexes were recently isolated and characterized in the 1,2-bis(2-pyridinecarboxamido)benzene ligand system.[50] Such species would be expected to be more labile in the corrinoid system than in the cobaloximes or other simpler systems due to greater steric congestion in the former and would also be expected to be more labile than dialkylcoblat(III) complexes.[48−51] If the lifetime of such a Co^{IV} species were sufficiently short, the reaction would, in fact, be an S_H2-like homolytic displacement reaction by an $R^{\bullet}$ on the metal center (but not the α carbon) in $RCbi^+$ to form the diastereomer of opposite configuration (in the case of the homologous radical reaction, $R = R'$, eq 9). Mechanisms such as eq 8, with a discrete dialkylcobalt(IV) intermediate, or eq 9, a concerted displacement, achieve equilibrium via multiple displacements and subside when termination reactions (such as $R^{\bullet}$ combination) consume the organic free radical. Such mechanisms gain some support from the observation that the reaction of β-CH_3CH_2-Cbi^+ ($R = CH_3CH_2$) with 0.5 equiv of *tert*-butyl hydroperoxide ($R' = CH_3$) and Fe^{2+} at ∼0 °C initially produced about ∼40% α-CH_3Cbi^+, possibly due to a single trans substitution.



(9)

In conclusion, we have found that organic free radicals promote the interconversion of the two diastereomers of alkylcobinamides. Since the reaction with homologous radicals leads to equilibration of the two isomers under mild conditions, this convenient method has been used to measure the equilibrium constants for the α/β diastereomerism. Thus, the effects of epimerization of the *e* propionamide side chain in CH_3CH_2-Cbi^+ on the diastereomer equilibrium have been determined by comparing the equilibrium constant for the CH_3CH_2-13-epiCbi^+'s with that of the normal $CH_3CH_2Cbi^+$'s. For the C-13 epimer, in which the *e* side chain is inverted from a pseudoaxially downward to a pseudoaxially upward position, the α/β equilibrium constant is ∼20 times larger than that for CH_3CH_2-Cbi^+'s, showing that the accessibility of the two faces of the corrinoid is largely controlled by the side chain configurations.

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(42) The reaction of $CH_3CH_2Cbi^+$ with a catalytic amount of ethyl radical, $CH_3CH_2^{\bullet}$, does not seem to go to equilibrium, possibly due to a shorter radical chain length for the ethyl radical than that for the methyl radical. However, the reaction does proceed to more than 50% completion when only a 0.1 molar equiv of alkyl hydroperoxide/Fe^{2+} per $RCbi^+$ is used, which clearly violates the mechanism of eq 7. There is a possibility, although unlikely, that the isomerization of CH_3Cbi^+ occurs by a group transfer mechanism[11,39−41] if a trace amount of Co^{II} is present in such a system.

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