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Diastereomeric Control in the Formation of Carbon−Cobalt Bonds in Organocobalt Corrinoids: Reactions of Cobalt(II) Corrinoids with Organic Hydroperoxides[1]

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1,1-Dimethylpropyl hydroperoxide reacts with cobalt(II) cobinamide via a Fenton-like reaction to produce a mixture of the diastereomeric α- and *β*-ethylcobinamides ($CH_3CH_2Cbi^+$'s, in which the organic ligand is in the "lower" or "upper" axial ligand position, respectively), the composition of which depends on the ratio of starting materials. When the hydroperoxide reagent is in excess, <2% of the $CH_3CH_2Cbi^+$ product is the α diastereomer, a product distribution which agrees with previous observations of the equilibrium mixture. This distribution apparently arises because the previously demonstrated $CH_3CH_2^\bullet$-promoted isomerization of $CH_3CH_2Cbi^+$ diastereomers leads to equilibration. However, when cob(II)inamide is in excess over hydroperoxide, the $CH_3CH_2Cbi^+$ product contains 87% α diastereomer and 13% *β* diastereomer. Evidently, under these conditions, trapping of the $CH_3CH_2^\bullet$ radical is sufficiently rapid to prevent the radical-induced isomerization of diastereomers and a kinetically controlled product distribution results. This condition has been used to study the relative energetics of kinetically controlled α and *β* alkylation of cob(II)inamide by $CH_3CH_2^\bullet$. For cob(II)inamide itself, the α diastereomer is enthalpically stabilized relative to the *β* diastereomer in the transition state for carbon−cobalt bond formation, but an even larger entropic stabilization of the *β* diastereomer causes the latter to be the predominant product. The entropic preference for the *β* diastereomer is shown to be the result of the differential side chain configurations at the α and *β* faces of the cobalt corrinoids by experiments with side-chain-altered analogs. When the downwardly projecting *f* side chain is enlarged by esterification of the *N*-methylated nucleotide 1-α-D-ribofuranosyl-3,5,6-trimethylbenzimidazole 3′-phosphate, the proportion of the α diastereomer in the alkylated product drops to 74% and the effect is due solely to an increased entropic preference for the *β* diastereomer. Similarly, when the normally downwardly projecting *e* propionamide side chain is epimerized to the upward (*β*) face of the corrin, the proportion of the α diastereomer in the product is increased to 95% and the effect is entirely entropic again. Taken together with previous work, the results lead to a general picture of the energetics of alkyl radical + cobalt(II) corrinoid combination reactions and their microscopic reverse, the homolytic dissociation of carbon−cobalt bonds, a rare instance in which the subtleties of such diastereomeric control can be understood at a very fundamental level.

Introduction

Axial ligand diastereomerism in cobalt corrinoids lacking an appended axial nucleotide is a well-known phenomenon.[3−10] Although studies were originally confined to cyanocobalt corrinoids[3−5] and methylcobalt corrinoids,[6] recent work[8,9] has shown that mixtures of *β*-alkylcobalt corrinoids, in which the organic ligand is in the "upper" axial position, and α-alkylcobalt corrinoids, in which the organic ligand is in the "lower" axial ligand position (Figure 1), are to be expected whenever corrinoids lacking a coordinated, pendent lower axial ligand are reductively alkylated.[10] However, the product composition resulting from the oxidative addition of alkyl halides to reduced cobinamide, the base-off analog of cobalamin in which the axial nucleotide has been removed by phosphodiester hydrolysis, varies widely with the nature of the alkyl group, with as little as <2% of the alkylated product having the α configuration ($R = CH_3CH_2$) to as much as >90% of the alkylated product having the α configuration ($R = CF_3$, Table 1).[8a,b,11] In some cases ($R = CH_3$, CH_3CH_2), the product composition appears to be an equilibrium distribution of diastereomers,[12] although $R = CH_3$ is a special case, since α- and *β*-CH_3Cbi^+ have been shown to equilibrate via cobalt-to-cobalt methyl group transfer with cobinamide in any of its three available oxidation states.[12] However, in other cases ($R = CF_3CH_2$, $NCCH_2$), the oxidative

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(1) Standard IUPAC−IUB nomenclature[2] is used throughout. Abbreviations: CNCbl, cyanocobalamin (vitamin B_{12}); Cbi, cobinamide; 13-epiCbi, 13-epicobinamide; NpCbl, neopentylcobalamin; $Me_3BzmCba$, (3,5,6-trimethylbenzimidazolyl)cobamide; Me_3Bzm-3′-P, 1-α-D-ribofuranosyl-3,5,6-trimethylbenzimidazole 3′-phosphate. Factor B and its 13-epi and 3,5,6-trimethylbenzimidazolyl analogs are mixtures of the diastereomeric α-(CN)-*β*-(H_2O)-cobamide and α-(H_2O)-*β*-(CN)-cobamide.

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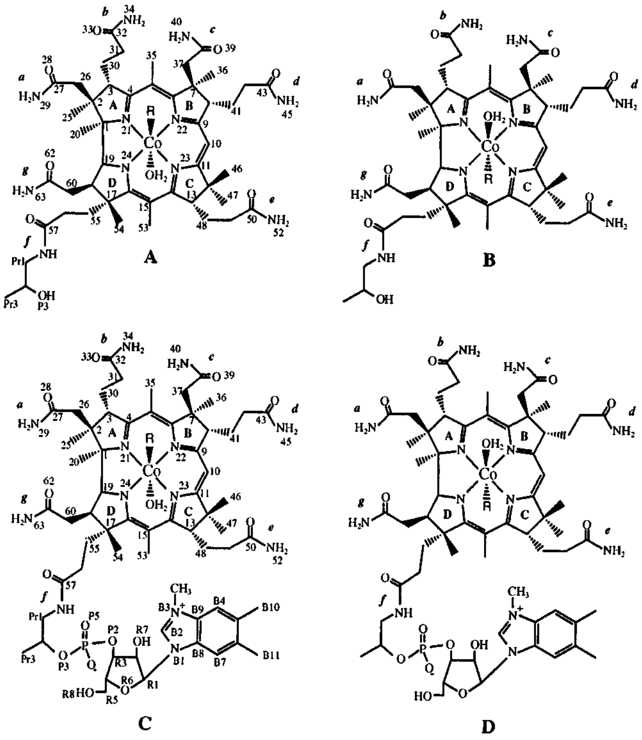


Figure 1. Structures of (A) a β-alkylcobinamide (β-RCbi$^+$), (B) an α-alkylcobinamide (α-RCbi$^+$), (C) a β-alkyl(3,5,6-trimethylbenzimidazolyl)cobamide (β-RMe$_3$BzmCba$^+$), and (D) an α-alkyl(3,5,6-trimethylbenzimidazolyl)cobamide (α-RMe$_3$BzmCba$^+$).

Table 1. Diastereomeric Outcome of the Oxidative Addition of Alkyl Halides to Reduced Cobinamide

R	% α-RCbi$^+$	% β-Rcbi$^+$	ref
CH_3CH_2	<2	>98	11
CH_3	4	96	8b
$EtOCH_2CH_2$	20	80	8b
$NCCH_2$	73	27	8b
CF_3CH_2	87	13	8a
CF_3	93	7	8b

addition product composition appears to be very far from equilibrium.[8a,b,12]

A recent study of the viscosity dependence of the kinetics of thermally-induced carbon−cobalt bond homolysis of α- and β-NCCH$_2$Cbi$^+$ [13] confirmed that such reactions are at least partly under diffusion control and proceed via the intermediacy of a solvent-caged organic radical, cob(II)inamide pair.[14] From the viscosity dependence of these thermolysis reactions, the fractional cage efficiencies could be calculated and an estimate was obtained of the ratio of the rate constant for in-cage recombination to form the α diastereomer to that for recombination to form the β diastereomer. Surprisingly, this ratio was larger than 1.0 ($k_c^{\alpha}/k_c^{\beta} = 2.6 \pm 0.6$). As the combination of an organic radical and cob(II)inamide is the prototypical reaction in which carbon−cobalt bonds are formed, this ratio of recombination rate constants predicts a kinetically controlled product distribution of 72% α-NCCH$_2$Cbi$^+$ and 28% β-NCCH$_2$Cbi$^+$. Interestingly, the observed product distribution from the oxidative addition of NCCH$_2$Br to reduced cobinamide is 73% α and 27% β.[8b] Evidently, the oxidative addition of NCCH$_2$Br to cob(II)inamide is under kinetic control. It thus appears that the oxidative addition of alkyl halides to reduced cobinamide is sometimes under thermodynamic control but sometimes under kinetic control, although the possible reasons for this dichotomy are not at all obvious.

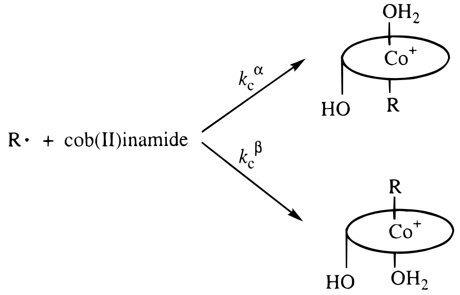
Recently,[15] we attempted to directly study the kinetic control of product diastereomerism in the combination of organic radicals with cob(II)inamide by use of the Fenton-like chemistry demonstrated by Espenson and Martin[16] (eqs 1−3). In this

$$\text{cob(II)inamide} + \text{RC(CH}_3)_2\text{OOH} \xrightarrow{\text{slow}} \text{HO(H}_2\text{O)Cbi}^+ + \text{RC(CH}_3)_2\text{O}^\bullet \quad (1)$$

$$\text{RC(CH}_3)_2\text{O}^\bullet \xrightarrow{\text{fast}} \text{R}^\bullet + \text{CH}_3\text{COCH}_3 \quad (2)$$

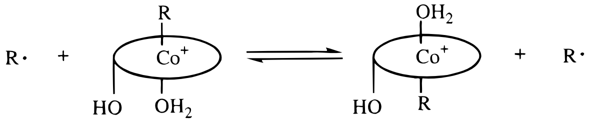
$$\text{R}^\bullet + \text{cob(II)inamide} \xrightarrow{\text{fast}} \text{RCbi}^+ \quad (3)$$

reaction, rate-determining abstraction of a hydroxyl radical from an organic hydroperoxide of the type RC(CH$_3$)$_2$OOH produces a hydroxocobalt(III) complex and the highly reactive RC(CH$_3$)$_2$O$^\bullet$ radical. The latter rapidly expels acetone to produce the R$^\bullet$ radical, which can subsequently combine with cob(II)inamide to form an alkylcobinamide. Since the latter reaction will partition between addition of the radical to the α or β axial ligand position (eq 4), the ratio of the products obtained from



(4)

these parallel bimolecular processes is equal to the ratio of the rate constants, k_c^{α}/k_c^{β}. Unfortunately, our attempts to study kinetic control in this manner were complicated by the observation that an excess of the radical, R$^\bullet$, induces the interconversion of α- and β-RCbi$^+$ (eq 5). Thus, when either an α-RCbi$^+$ or a



(5)

β-RCbi$^+$ was reacted with independently generated R$^\bullet$ (by reaction of RC(CH$_3$)$_2$OOH with Fe^{2+}(aq)), interconversion of the isomers occurred, providing a convenient way to evaluate equilibrium constants for diastereomerism under mild conditions but apparently preventing the use of reactions 1−3 for examination of kinetic product control.

We now wish to report that suitable adjustment of reaction conditions allows the reaction of cob(II)inamide with CH$_3$CH$_2$C(CH$_3$)$_2$OOH to produce either a kinetically controlled or an equilibrium-controlled distribution of CH$_3$CH$_2$Cbi$^+$ products. We have consequently used this method to study the temperature dependence of the kinetically controlled-product ratios and, hence, the differential enthalpies and entropies of activation for

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the reaction of $CH_3CH_2^{\bullet}$ with cob(II)inamide to form the diastereomeric α- and β-$CH_3CH_2Cbi^+$'s. In addition, we have carried out similar studies with cob(II)inamide analogs of altered-side-chain structure, including 13-epicob(II)inamide, the analog in which epimerization at C13 has caused the *e* side chain to adopt an "upwardly" pseudoaxial configuration (instead of the normal, pseudoaxially "downward" configuration),[17,18] and (3,5,6-trimethylbenzimidazolyl)cob(II)amide, the "base-off" analog of cob(II)alamin in which the bulky axial nucleotide is appended to the *f* side chain 2-propanolamine spacer group, but coordination of the axial base is prevented by methylation of the coordinating nitrogen. These studies permit an analysis of the effect of side-chain structure on the kinetics of $RCbi^+$ diastereomerism.

Experimental Section

Materials. CNCbl[1] was purchased from Roussell. 2-Methyl-2-butanol, trifluoroacetic acid, hydrogen peroxide, and triflic acid were from Aldrich. Factor B, a mixture of the diastereomeric cyanoaquocobinamides, was prepared from CNCbl by the triflic acid method.[19] CN-13-epiCbi^+ was obtained by acid-catalyzed epimerization and phosphodiester cleavage of CNCbl in trifluoroacetic acid.[20,21] β-$CH_3CH_2Cbi^+$ and β-CH_3CH_2-13-epiCbi^+ were synthesized by reductive alkylation with CH_3CH_2Br using Zn/10% acetic acid as reductant and purified by HPLC[22] as described elsewhere.[8c] α-$CH_3CH_2Cbi^+$ and α-CH_3CH_2-13-epiCbi^+ were obtained by anaerobic photolysis of β-$CH_3CH_2Cbi^+$ and β-CH_3CH_2-13-epiCbi^+, respectively, as reported previously.[11] Cyanoaquo-(3,5,6-trimethylbenzimidazolyl)cobamide ($CNMe_3BzmCba^+$) was prepared by a modification[8g] of the method of Friedrich and Bernhauer,[10] and α- and β-$CH_3CH_2Me_3BzmCba^+$ were prepared as described previously.[8g] $(H_2O)_2Cbi^{2+}$, $(H_2O)_2$-13-epiCbi^{2+}, and $(H_2O)_2Me_3BzmCba^{2+}$ were prepared by a previously reported method from the corresponding cyano aquo complexes.[24] $CH_3CH_2C(CH_3)_2OOH$ was synthesized from $CH_3CH_2C(CH_3)_2OH$ and hydrogen peroxide by a reported procedure.[15,25]

Methods. Analytical HPLC was performed with a 4.6 × 250 mm Beckman C8 Ultrasphere column as described previously.[22] UV−visible spectra were recorded on a Cary 219 recording spectrophotometer, and quantitative determination of cobalt corrinoids was carried out by conversion of complexes to their dicyano derivatives ($\epsilon_{368} = 3.04 \times 10^4\ M^{-1}\ cm^{-1}$ [26] for $(CN)_2Cbi$ and $(CN)_2Me_3BzmCbi$, $\epsilon_{366} = (2.14 \pm 0.02) \times 10^4\ M^{-1}\ cm^{-1}$ for $(CN)_2$-13-epiCbi[21]) by aerobic photolysis in excess cyanide. ^1H and ^{13}C NMR spectra were obtained on a GE QE 300 NMR spectrometer. Electrochemical reduction of the diaquocobalt corrinoids was conducted with a Bioanalytical Systems CV-27 voltammograph using a mercury pool electrode and a Ag/AgCl (satd), KCl (satd) reference electrode.

Reaction of $CH_3CH_2C(CH_3)_2OOH$ with Co(II) Corrinoids. These reactions were carried out under anaerobic conditions using the following procedure. $(H_2O)_2Cbi^{2+}$, or its 13-epi or 3,5,6-Me_3Bzm analog (1.0×10^{-4} M), was deaerated in 5 mL of aqueous acetic acid (1.0 M) by argon purging for 1 h in an electrochemical redox cell. Controlled-potential reduction to cob(II)inamide was conducted at −0.6 V to ensure the formation of the Co(II) species without the interference of the Co(I) species.[27] At the completion of reduction (as indicated by the cessation of current flow), the Co(II) solution was transferred by cannula to a purged empty vial. This vial and a purged aqueous solution of $CH_3CH_2C(CH_3)_2OOH$ were placed in a water bath whose temperature was controlled to within ±0.1 °C of the desired value. For reactions in which the Co(II) reagent was in excess, the peroxide solution was rapidly transferred to the Co(II) solution by cannula to initiate the reaction. For reactions where the peroxide reagent was in excess, the Co(II) solution was transferred to the peroxide solution by cannula. Multiple samples of the reaction mixture were taken and analyzed by HPLC. The ratio of diastereomers was determined by multiple HPLC chromatogram peak integrations after correcting for differing molar absorptivities of each isomer at the HPLC monitoring wavelengths of 254 and 350 nm as described previously.[15] Integrations at the two wavelengths were averaged to obtain final values. No time dependence was observed for the ratio of products at any temperature.

Alternatively, the cobalt corrinoid was reduced with zinc wool in 1.0 M acetic acid. The outcome of the alkylation reaction was unaffected by the method of reduction.

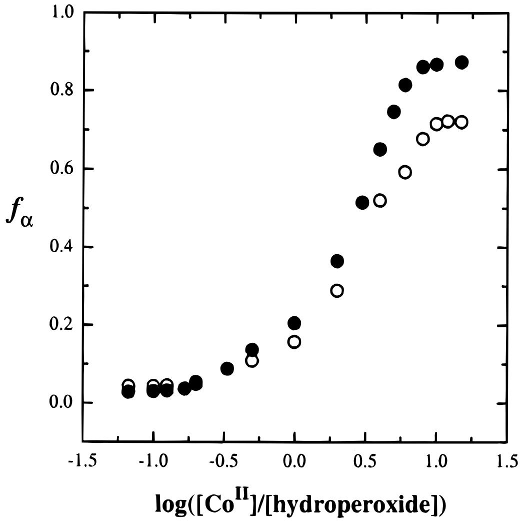

Figure 2. Plots of the dependence of f_α, the fraction of alkylcobalt corrinoid product as the α diastereomer, vs the logarithm of the ratio of cob(II)inamide to $CH_3CH_2C(CH_3)_2OOH$ (solid symbols) and the logarithm of the ratio of (3,5,6-trimethylbenzimidazolyl)cobamide to $CH_3CH_2C(CH_3)_2OOH$ (open symbols).

Results

Effect of Reagent Ratio on Product Distribution. Our original attempt[15] to use reactions of organic hydroperoxides with cob(II)inamide (eqs 1−3) to study the kinetically controlled distribution of $RCbi^+$ products resulting from the combination of $R^{\bullet}$ radicals with cob(II)inamide produced the observation that the ratio of diastereomers obtained depended on the ratio of cob(II)inamide to hydroperoxide employed. This unexpected result led to the suspicion and subsequent confirmation that organic radicals could cause the interconversion of the diastereomeric $RCbi^+$'s (eq 5).[15] We have now studied the effect of reagent ratio on $RCbi^+$ product distribution for the reaction of cob(II)inamide with $CH_3CH_2C(CH_3)_2OOH$. The results at 25 °C are shown in Figure 2, as a plot of f_α, the fraction of the $CH_3CH_2Cbi^+$ product as the α diastereomer, vs the logarithm of the ratio of cob(II)inamide to hydroperoxide, where this ratio has been varied by over 200-fold. These data show that when hydroperoxide is in at least 6-fold excess over cob(II)inamide (i.e., log([cob(II)inamide]/[hydroperoxide]) < −0.78), the product distribution becomes independent of the reagent ratio with

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Table 2. Rate Constant Ratios and Relative Enthalpies and Entropies of Activation for Diastereomer Formation from the Reaction of Organic Radicals with Excess Cobalt(II) Corrinoids

$CH_3CH_2Cbi^+$		$CH_3CH_2Me_3BzmCba^+$		CH_3CH_2-13-epiCbi$^+$	
T (°C)	k_c^{α}/k_c^{β}	T (°C)	k_c^{α}/k_c^{β}	T (°C)	k_c^{α}/k_c^{β}
10.0	7.65 ± 0.12	10.0	3.51 ± 0.15	9.8	20.8 ± 3.1
20.1	7.07 ± 0.27	20.2	2.84 ± 0.09	19.9	20.3 ± 1.7
25.0	6.68 ± 0.25				
30.0	6.36 ± 0.27	30.0	2.46 ± 0.06	29.9	17.9 ± 1.3
40.0	5.84 ± 0.28	40.1	2.35 ± 0.07	40.1	15.6 ± 2.8
50.1	5.15 ± 0.02	50.1	2.08 ± 0.07	50.0	15.3 ± 2.7

	$CH_3CH_2Cbi^+$	$CH_3CH_2Me_3BzmCba^+$	CH_3CH_2-13-epiCBi$^+$	$NCCH_2Cbi^{+\,a}$
$\Delta\Delta G^{\ddagger}_{c}{}^{b}$ (kcal mol^{-1})	−1.11 ± 0.09	−0.59 ± 0.30	−1.74 ± 0.28	−0.57 ± 0.13
$\Delta\Delta H^{\ddagger}_{c}{}^{c}$ (kcal mol^{-1})	−1.83 ± 0.07	−2.16 ± 0.21	−1.74 ± 0.20	−1.7 ± 0.4
$\Delta\Delta S^{\ddagger}_{c}{}^{d}$ (cal mol^{-1} K^{-1})	−2.40 ± 0.20	−5.25 ± 0.70	−0.01 ± 0.66	−3.7 ± 0.4

[a] Reference 13. [b] Calculated at 25 °C; $\Delta\Delta G^{\ddagger}_{c} = \Delta G^{\ddagger}_{c}{}^{(\alpha)} - \Delta G^{\ddagger}_{c}{}^{(\beta)}$. [c] $\Delta\Delta H^{\ddagger}_{c} = \Delta H^{\ddagger}_{c}{}^{(\alpha)} - \Delta H^{\ddagger}_{c}{}^{(\beta)}$. [d] $\Delta\Delta S^{\ddagger}_{c} = \Delta S^{\ddagger}_{c}{}^{(\alpha)} - \Delta S^{\ddagger}_{c}{}^{(\beta)}$.

$f_{\alpha} < 0.02$. Previous work[15] on the free-radical-promoted isomerization of $CH_3CH_2Cbi^+$'s showed that the equilibrium constant, $K_{eq} = [\alpha\text{-}CH_3CH_2Cbi^+]/[\beta\text{-}CH_3CH_2Cbi^+]$, is <0.02. We conclude that when hydroperoxide is in at least 6-fold excess over the Co(II) reagent, a sufficient steady state concentration of radicals is maintained to ensure diastereomer equilibration via eq 5, so that under these conditions, an equilibrium distribution of diastereomers is obtained.

In contrast, when the ratio of cob(II)inamide to $CH_3CH_2C(CH_3)_2OOH$ is increased above ~0.17, the proportion of α-$CH_3CH_2Cbi^+$ in the product increases until the Co(II) reagent is present in at least 8-fold excess, above which f_{α} becomes independent of the reagent ratio (Figure 2). From these results, it is difficult to avoid the conclusion that under these conditions of excess Co(II) reagent, trapping of the $CH_3CH_2^{\bullet}$ radical by cob(II)inamide (eq 3) has become sufficiently fast that the steady state concentration of radicals in the reaction mixture is too low to cause significant interconversion of the diastereomers via eq 5. Thus, under these conditions, the partitioning according to eq 4 is observed, and the product ratio, $[\alpha\text{-}CH_3CH_2Cbi^+]/[\beta\text{-}CH_3CH_2Cbi^+]$ is equivalent to the rate constant ratio, k_c^{α}/k_c^{β}. For cob(II)inamide, the average value of f_{α} for [Co(II)]/[hydroperoxide] ratios of 8 or larger was 0.867 ± 0.006, so that $k_c^{\alpha}/k_c^{\beta} = 6.52 \pm 0.06$, showing that there is a significant kinetic preference for the α diastereomer when $R^{\bullet} = CH_3CH_2^{\bullet}$ despite the fact that the equilibrium favors the β diastereomer by more than 50-fold. Thus, the situation for the ethyl radical is similar to, but even more extreme than, that for the $NCCH_2^{\bullet}$ radical, for which both the kinetic preference for the α diastereomer ($k_c^{\alpha}/k_c^{\beta} = 2.6 \pm 0.6$) and the equilibrium preference for the β diastereomer ($K_{eq} = 0.311$) were significantly smaller.

A similar study of the effect of reagent ratio on product distribution for the reaction of $CH_3CH_2C(CH_3)_2OOH$ with Me_3-Bzm-cob(II)inamide is also shown in Figure 2 (open symbols). The results are quite similar to those obtained with cob(II)inamide itself, except that the leveling off of f_{α} at high Co(II)/hydroperoxide ratios occurs at a somewhat lower limiting value of f_{α}. For this analog, the limiting value of f_{α} at high Co(II) reagent concentrations was 0.719 ± 0.004, so that k_c^{α}/k_c^{β} is 2.56 ± 0.02, showing that the kinetic preference of $CH_3CH_2^{\bullet}$ for the α axial ligand position is considerably reduced in Me_3Bzm-cob(II)inamide relative to cob(II)inamide itself.

Unfortunately, the position of the α/β equilibrium for the $CH_3CH_2Cbi^+$'s and their analogs, which favors the β diastereomer by at least 50-fold, made accurate determination of the equilibrium constants impossible. Thus, in the HPLC chromatograms, the integral of the peak for the α diastereomer was <2% of the total $RCbi^+$ product integral, so that reliable, reproducible quantitative determinations of the equilibrium ratios could not be obtained.

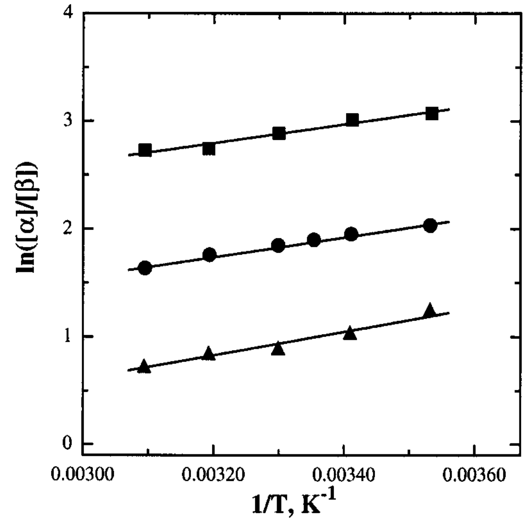

Figure 3. Eyring plots of $\ln([\alpha]/[\beta]) = \ln(k_c^{\alpha}/k_c^{\beta})$ vs $1/T$ for the reactions of $CH_3CH_2C(CH_3)_2OOH$ with excess cob(II)inamide (●; slope = 920 ± 33 K, intercept = −1.21 ± 0.10, $r^2 = 0.988$), 13-epicob-(II)inamide (■; slope = 875 ± 100 K, intercept = −0.005 ± 0.330, $r^2 = 0.963$), and Me_3Bzm-cob(II)inamide (▲; slope = 1,140 ± 130 K, intercept = −2.81 ± 0.43, $r^2 = 0.981$).

Kinetic Control of $CH_3CH_2Cbi^+$ Diastereomerism. It is evident from the data in Figure 2 and the discussion above that the product distribution observed upon reaction of $CH_3CH_2C(CH_3)_2OOH$ with excess cob(II)inamide is kinetically controlled and represents the partitioning of the products according to eq 4. Thus, studies of the product ratio under these conditions permit evaluation of the k_c^{α}/k_c^{β} ratio and, from its temperature dependence, the relative enthalpy of activation, $\Delta\Delta H_c^{\ddagger} = \Delta H_c^{\ddagger(\alpha)} - \Delta H_c^{\ddagger(\beta)}$, and the relative entropy of activation, $\Delta\Delta S_c^{\ddagger} = \Delta S_c^{\ddagger(\alpha)} - \Delta S_c^{\ddagger(\beta)}$. The results of these investigations of the reaction of $CH_3CH_2^{\bullet}$ with cob(II)inamide are given in Table 2 and shown in Figure 3 as an Eyring plot of $\ln(k_c^{\alpha}/k_c^{\beta})$ vs $1/T$. Values of the differential enthalpy and entropy of activation obtained from this plot are also given in Table 2 along with the data previously obtained for the $NCCH_2^{\bullet}$ radical. As was previously found to be the case for $NCCH_2^{\bullet}$,[13] the α diastereomer is the kinetically preferred product, although for $CH_3CH_2^{\bullet}$ it is preferred by about 7-fold at 20 °C as opposed to about 3-fold for $NCCH_2^{\bullet}$. For both radicals, the α diastereomer is enthalpically favored but is entropically disfavored as was also the case in the ground state for the $NCCH_2Cbi^+$'s, but the transition state entropic preference for the β diastereomer is much smaller than the ground state preference, leading to the observed kinetic preference for the α isomer. The differential enthalpies of activation are quite comparable for the two radicals, but the entropic preference for the β diastereomer is more pronounced for the $NCCH_2^{\bullet}$ radical, leading to the smaller proportion of α diastereomer in the kinetically controlled product for this radical.

This method was also used to study the effects of side-chain modification on the kinetic preference for the α diastereomer. Esterification of the bulky benzimidazole nucleotide to the *f* side chain to form the $Me_3BzmCba$ analog decreases the kinetic preference for the α diastereomer from about 7-fold to about 2.6-fold at 20 °C, confirming the idea that differential side-chain structure sterically controls access to the two corrin faces. From the temperature dependence of k_c^{α}/k_c^{β} for the $Me_3BzmCba$'s (Table 2), the differential enthalpies and entropies of activation for α and β face $CH_3CH_2^{\bullet}$ capture could again be determined (Figure 3). Again, the α diastereomer is enthalpically preferred by about 2 kcal mol^{-1}. However, the entropic preference for the β diastereomer is increased by more than 2-fold to 5.25 cal mol^{-1} K^{-1}.

Similar studies with 13-epicob(II)inamide in 20-fold excess over $CH_3CH_2C(CH_3)_2OOH$ provide the data for this structural analog given in Table 2 and Figure 3. Epimerization of the *e* side chain from the lower face to the upper face of the corrin increases the kinetic preference for the α diastereomer by nearly 3-fold to about 20/1. The α diastereomer is again enthalpically favored by about 2 kcal mol^{-1}, but the differential entropy of activation for α and β face $CH_3CH_2^{\bullet}$ capture is essentially zero. Thus, in this derivative, the entropic preference for the β diastereomer is removed and the α diastereomer comprises 95% of the product. The results for both of the side-chain-altered analogs of cob(II)inamide are consistent with the idea that the corrin ring side chains sterically control access to the upper and lower axial ligand positions and that this steric effect is expressed strictly as an alteration of the entropy of activation (vide infra).

Discussion

Utility of the Reactions of Cob(II)inamide with Organic Hydroperoxides. The surprising observation of the dependence of the stereochemical outcome of the reaction of $CH_3CH_2C(CH_3)_2OOH$ with cob(II)inamide on the ratio of reagents employed and the understanding of this observation developed above provide an outstanding tool for determination of kinetically controlled product ratios (at high Co(II)/hydroperoxide ratios) as well as the thermodynamics of diastereomer interconversion (at low Co(II)/hydroperoxide ratios). Under the latter conditions, the reaction is also a useful synthesis route, potentially providing the advantage of obtaining equilibrium-controlled products (which always favor the β diastereomer)[12,13,15] in those cases where oxidative addition of RX provides only an undesirable nonthermodynamic distribution of products. As a method for measuring diastereomerization equilibrium constants, it provides a number of advantages over thermal isomerization, as equilibration is rapidly achieved even at room temperature and below. In contrast, thermal equilibration requires elevated temperatures (at least 70 °C)[12,13] and long incubation times. The latter is particularly problematic since strictly anaerobic conditions are required to prevent alteration of the diastereomeric ratio by oxygen-trapped thermal decomposition, the α diastereomers being considerably more thermally reactive than the β diastereomers.[8f,13] Thus, purging reaction samples with even the purest of inert gas streams inevitably leads to some net decomposition due to trace oxygen over the long incubation times required for thermal equilibration, and accurate diastereomeric ratios can only be obtained in sealed-tube experiments. The only significant shortcoming of the hydroperoxide method is the difficulty we have encountered in synthesizing $RC(CH_3)_2OOH$'s with electron-withdrawing R groups. Thus, we have been unable to obtain the hydroperoxides in which $R = CF_3$ or $NCCH_2$.

Solvent Cage Effects. In the kinetically controlled limit (i.e., when the Co(II)/hydroperoxide ratio is high), the reaction of alkyl radicals with cob(II)inamide, the formal reverse of the reaction in which carbon−cobalt bonds are dissociated, is directly interrogated. The homolytic dissociation of carbon−cobalt bonds is known to occur by a process which is at least partially under diffusion control.[13,14,29−31] The principle of microscopic reversibility then requires that the combination of cobalt(II) reagents with alkyl radicals to form organocobalt complexes (eqs 3 and 4) must also be partly under diffusion control. Consequently, the rate constant ratios obtained from the observed product ratios in the kinetically controlled limit (Figure 2 and Table 2) are potentially complicated by solvent cage effects. Using the formalism of Koenig and Finke,[14a,b] eq 6 shows the applicable mechanism, proceeding via the solvent-caged [R$^{\bullet}$, cob(II)inamide] pair. Since k_1, the rate constant for carbon−cobalt bond dissociation, is many orders of magnitude smaller than k_c, the rate constant for in-cage radical combination,[14,32−34] the reaction is effectively irreversible in the direction written, and k_1 does not contribute significantly to the production of the caged radical pair. Application of the steady state approximation to the concentration of the caged pair leads to the rate equation (7) for the observed rate constant for carbon−cobalt bond formation. For organocobinamides in water,[35] the rate constant for diffusive separation of the caged pair, k_d, has been shown to be 10−20-fold larger than the rate constant for in-cage radical combination, k_c. Consequently, the simplification of eq 8 must be valid, and the ratio of the observed rate constants for formation of the two $RCbi^+$ diastereomers is given by eq 9. Since it is unlikely that the diffusion rate constants, k_{-1} and k_d, will differ for the caged pairs of the two relative orientations needed to produce α and β alkylation, eq 10 must be very nearly correct. Thus, the very small measured cage efficiencies for $RCbi^+$ carbon−cobalt bond dissociation

$$\text{cob(II)inamide} + R^{\bullet} \underset{k_d}{\overset{k_{-1}}{\rightleftharpoons}} \overline{[\text{cob(II)inamide}, R^{\bullet}]} \underset{k_1}{\overset{k_c}{\rightleftharpoons}} RCbi^{+} \tag{6}$$

$$k_{obs} = k_{-1}k_c/(k_c + k_d) \tag{7}$$

$$k_{obs} \approx k_{-1}k_c/k_d \tag{8}$$

$$k_{obs}{}^{\alpha}/k_{obs}{}^{\beta} = (k_{-1}{}^{\alpha}k_c{}^{\alpha}/k_d{}^{\alpha})/(k_{-1}{}^{\beta}k_c{}^{\beta}/k_d{}^{\beta}) \tag{9}$$

$$k_{obs}{}^{\alpha}/k_{obs}{}^{\beta} = k_c{}^{\alpha}/k_c{}^{\beta} \tag{10}$$

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(35) The cage effect for such complexes can be much larger in more associated solvents such as ethylene glycol.[14e,f]

in water means that cage effects do not significantly influence the observed product ratios and that the latter must represent a very good estimate of the ratio of the in-cage radical combination rate constants, k_c^{α}/k_c^{β}.

Kinetic Control of Diastereomerism and the Entropic Effect of Side Chains. The data in Table 2 show that the surprising result previously obtained for the $NCCH_2Cbi^+$'s,[13] that the α diastereomer is the kinetically preferred product despite the fact that it is significantly thermodynamically *dis*favored, is also true for the $CH_3CH_2Cbi^+$'s but is even more pronounced. Thus, for R = $NCCH_2$, the α diastereomer is kinetically favored by 2.6/1 despite the fact that the β diastereomer predominates by 3.2/1 at equilibrium. For R = CH_3CH_2, the α diastereomer is kinetically favored by 7/1 despite a thermodynamic preference for the β diastereomer of >50/1. In addition, the activation analysis for the $CH_3CH_2Cbi^+$'s (Table 2) shows that in the transition state for cob(II)inamide + $CH_3CH_2^{\bullet}$ combination, the α diastereomer is actually enthalpically favored, as was also the case for the $NCCH_2Cbi^+$'s. In both cases, however, the entropy of activation favors the β diastereomer but is insufficient to overcome the enthalpic preference for the α diastereomer. For the $CH_3CH_2Cbi^+$'s, the result is a 1.1 kcal mol^{-1} net kinetic stabilization of the α diastereomer, as opposed to the 0.6 kcal mol^{-1} net stabilization of α-$NCCH_2Cbi^+$.

The current results also permit an analysis of the effect of side-chain structure on the diastereomeric outcome of kinetically controlled $RCbi^+$ formation. Recent work has shown that the "upwardly" projecting acetamide side chains play a major role in determining the entropy of activation for carbon−cobalt bond homolysis, at least in the case of the bulky organic ligand in neopentylcobalamin.[21,36] Molecular mechanics calculations[36c] suggest that this effect is mediated by steric interactions of the acetamide side chains with the organic ligand, restricting the freedom of motion of these side chains in the ground state. As the carbon−cobalt bond is stretched during progress of the cleavage reaction, steric restriction of side-chain motion is reduced, increasing the net positional entropy of the complex. If this interpretation is correct, the principle of microscopic reversibility requires that side-chain thermal motions have the same effect on carbon−cobalt bond formation by cobalt(II) + radical combination. In addition, it has long been suspected that differential side-chain configuration, with three "upwardly" projecting acetamide side chains but four "downwardly" projecting side chains, including the *b*, *d*, and *e* propionamides and the even more elaborate *f* side chain, sterically controls the access to the "upper" (β) and "lower" (α) corrin ring faces, although there have been few hard data to substantiate this effect.

The data in Table 2 demonstrate conclusively that the corrin ring side chains significantly control the kinetic access of alkyl radicals to the α and β faces and that this steric effect is expressed entirely in the entropy of activation. Thus, the differential enthalpy of activation for α and β face $CH_3CH_2^{\bullet}$ capture favors the α diastereomer and is essentially invariant (average $\Delta\Delta H^{\ddagger}_c = -1.91 \pm 0.22$ kcal mol^{-1}) for cob(II)inamide and analogs in which the *e* propionamide is epimerized from the "lower" to the "upper" face (13-epicob(II)alamin) and in which the "downwardly" projecting *f* side chain is significantly increased in steric bulk by esterification of the *N*-methylated nucleotide, Me_3Bzm-3′-P (Me_3Bzm-cob(II)inamide). In each case, the diastereomeric outcome is controlled by the differential entropy of activation. For cob(II)inamide itself, an entropy difference of 2.4 cal mol^{-1} K^{-1} between the transition states for α and β face $CH_3CH_2^{\bullet}$ capture leads to a kinetic product distribution of 87% α and 13% β (at 20 °C). However, for Me_3Bzm-cob(II)inamide, the entropic preference for the β face is increased to 5.25 cal mol^{-1} K^{-1} and the kinetic product distribution becomes 74% α and 26% β. Thus, increasing the steric bulk of the "downwardly" projecting side chains favors β face alkylation and the effect is entirely entropic in nature. Similarly, in 13-epicob(II)alamin, the entropic preference for the β face is eliminated by the epimerization, and the kinetically controlled product distribution (now determined solely by the enthalpic preference for the α face) is 95% α and 5% β. Thus, removing a side chain from the α face and placing it on the β face by epimerization at C13 favors α face alkylation, and the effect is again entirely entropic.

General View of the Energetics of Diastereomeric Control. The data in Table 2 for the $CH_3CH_2Cbi^+$'s together with the previous data for the $NCCH_2Cbi^+$'s,[13] particularly in view of the apparent energetic similarities between the two systems despite the large difference in electron inductive effect, now permit the observation of some generalities about the energetics of carbon−cobalt bond dissociation and its microscopic reverse, the capture of alkyl radicals by cobalt(II) corrinoids. This is best done with the aid of the energy-reaction coordinate diagrams shown in Figure 4, which represent an amalgam of the two systems shown in the direction of carbon−cobalt bond cleavage. In the $RCbi^+$ ground state, the β diastereomer is the thermodynamically favored product, but the energetics are inverted in the transition state for bond cleavage (formation) so that the α diastereomer is favored, but less so than the β diastereomer is in the ground state (Figure 4A). In the solvent-caged pair, the energetics reinvert so that the β diastereomer is slightly favored, and this situation persists in the transition state for radical separation. The question mark above the energy levels for the caged pair in Figure 4 indicates that although the relative free energies of the diastereomeric caged pairs is calculable from the available data, the absolute free energies of these species relative to the other species diagrammed are unknown, since there are no independent values of k_c or k_d available for either diastereomer or either pair of $RCbi^+$'s.

The enthalpy-reaction coordinate diagram in Figure 4B shows that while the β diastereomer has the lower Gibbs free energy in the ground state, it is the α diastereomer that has the lower enthalpy. This enthalpic preference for the α diastereomer persists in the transition state for carbon−cobalt bond cleavage (formation) and directly implies that the transition state for α carbon−cobalt bond formation is "later" than that for β carbon−cobalt bond formation, with a shorter Co to C internuclear distance. In the caged radical pairs and their transition states for diffusional separation, the enthalpies are nearly the same for both diastereomers, as would be expected.

Figure 4C shows that the entropy component ($-T\Delta S$) of the energetics is responsible for the inversion of the relative free energies between the ground state and the transition state for carbon−cobalt bond dissociation (formation). Thus, in the ground state, the entropic preference for the β diastereomer is sufficiently large to overcome the enthalpic stabilization of the α diastereomer (Figure 4B) so that the β diastereomer is the thermodynamically more stable isomer. However, in the transition state, the entropic preference for the β diastereomer is significantly reduced and can no longer compensate for the enthalpic stabilization of the α diastereomer. Thus, the relative free energies invert, and the α diastereomer is preferred in the transition state. The entropic preference for the β diastereomer

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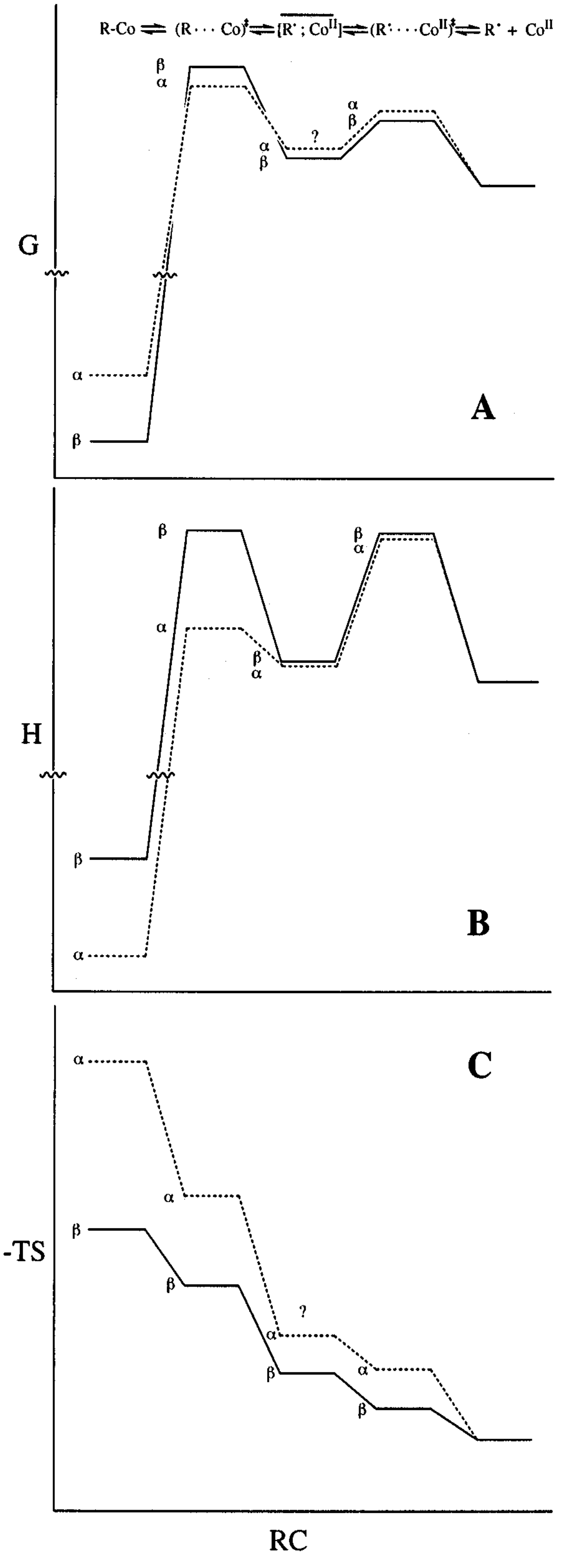

Figure 4. Energy-reaction coordinate diagrams for the carbon−cobalt bond dissociation reaction of an alkylcobinamide.

is further reduced in the caged pairs and in the transition state for their diffusive separation, as would be anticipated. The fact that the *β* diastereomer is entropically stabilized throughout the reaction and, most importantly, the fact that this entropic stabilization decreases steadily as the reaction progresses are consistent with the demonstrated influence of side-chain mobilities on cobalt corrinoid entropies. As the organic ligand moves further and further from the cobalt center, its steric influence on side-chain thermal mobility, and hence on complex entropy, steadily decreases.

This analysis represents a relatively rare instance in which fine diastereomeric control of a reaction can be understood at the very fundamental level of the relative energetics of individual elementary reaction steps. The most striking observation, that entropic effects cause an inversion of the relative free energies of the diastereomers between the ground and transition states, is the result of the differential configurations of side chains at the α and *β* faces of the corrinoid. While this distinctive feature of corrinoids may make this situation unique, other instances of sterically driven entropic effects derived from other structural motifs may well be more general in stereospecific and regiospecific control.

Control of Diastereomerism in Oxidative Addition. Finally, we return to the question posed in the Introduction: What controls the stereochemistry of the oxidative addition of alkyl halides to reduced cobinamides? Clearly, in some cases ($R = CH_3CH_2$), the products are under thermodynamic control, while in others ($R = NCCH_2$), the products are under kinetic control. As pointed out above, $R = CH_3$ is a special case, since cobalt-to-cobalt transfer of the CH_3 ligand occurs with all three available oxidation states of the metal,[12] leading to equilibration of the diastereomers regardless of the mechanism of carbon−cobalt bond formation and the means of its initial stereochemical control.

The mechanism of oxidative addition of alkyl halides to reduced cobalt species has long been debated, with claims of S_N2 nucleophilic displacements by cobalt(I) "supernucleophiles" (including observations of inversion) by Schrauzer[37] and others[38−43] and claims of other mechanisms (including observations of retention).[44−49] A recent, clever electrochemical study by Zhou et al.[50] showed that cobalt(I) reagents, including cob(I)alamin and cobalt(I) heptamethylcobyrinate, can react with alkyl halides by two-electron as well as one-electron mechanisms depending on the steric demands of the organic group and the nature of the leaving group. While two-electron reductants are normally used to prepare reduced cobalt corrinoids from air-stable cobalt(III) corrinoids, spectrophotometric observations of cobalt corrinoids reduced with zinc reductants show evidence of formation of only the cobalt(II) species at completion.[8c] Evidently this is due to the extraordinarily rapid one-electron transfer from cobalt(I) corrinoids to cobalt(III)

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corrinoids[51] following the relatively slow heterogeneous reduction and the inability of zinc to reduce cobalt(II) reagents. Consequently, for all of the synthetic results reported in Table 1, for which alkyl halides were added to cobinamide following completion of reduction by zinc, cob(II)inamide is the reacting cobalt species, and the mechanism is most likely the "atom transfer" reaction (eq 11 followed by eq 3) studied extensively

$$\text{cob(II)inamide} + \text{RX} \rightarrow \text{X-cob(III)inamide} + \text{R}^{\bullet} \quad (11)$$

by Halpern and co-workers for cobalt corrinoids and other cobalt reagents.[52] If this is correct, the data shown in Figure 2 suggest that the diastereomeric outcome of these reductive alkylations may depend on the steady state concentration of alkyl radical achieved during the synthesis. In those circumstances where radical formation is facile, sufficient radical may be present in the steady state to effect RCbi^+ isomerization via the radical-promoted reaction of eq 5, leading to an equilibrium distribution of products. Conversely, when the steady state concentration of radicals is low, rapid trapping by cob(II)inamide may effectively prevent radical-promoted isomerization, leading to a kinetic distribution of products. Interestingly, this hypothesis, which is currently under further study, and the data in Figure 2 suggest that intermediate cases, in which neither a thermodynamic nor a kinetic product distribution results, are also possible.

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