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Solvent Cage Effects in Organocobalt Corrinoid Chemistry: Thermal Homolysis of α- and *β*-(Cyanomethyl)cobinamides[1]

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The equilibrium constant for the thermal isomerization of the diastereomeric α- and *β*-(cyanomethyl)cobinamides (NCCH$_2$Cbi$^+$'s) has been measured over the temperature range 70−95 °C. Although the *β* diastereomer is the thermodynamically more stable isomer, it is favored by the entropy change, but *dis*favored by the enthalpy change. In the presence of $\geq 5 \times 10^{-3}$ M concentration of the radical trap 4-hydroxy-2,2,6,6,-tetramethylpiperidinyloxy (4-HTEMPO), thermolysis of either isomer leads to cob(II)inamide and the trapped NCCH$_2^\bullet$ radical (NCCH$_2$-4-HTEMPO) in high yield and no isomerization can be detected. The kinetics of the 4-HTEMPO-trapped thermal homolysis of α- and *β*-NCCH$_2$Cbi$^+$ have been studied in anaerobic glycerol/water mixtures of varying viscosity. The observed first-order rate constants for thermolysis show the expected inverse dependence on viscosity indicating that the process is at least partially diffusion controlled. From these data, the primary rate constant, k_1, for carbon−cobalt bond homolysis and the ratio of the rate constants for in-cage recombination and diffusional separation (k_c/k_d) can be extracted. The enthalpies of activation for Co−C bond homolysis are identical (29.0 ± 0.3 kcal mol^{-1}) while the entropy of activation is 2-fold higher for the α diastereomer. In water, the fractional cage efficiencies, F_c, are quite small (0.12 ± 0.01, α; 0.049 ± 0.008, *β*) and invariant for each complex in the temperature range 75−95 °C. Assuming that the rate constant for diffusional separation of the caged radical pairs is the same for both isomers, the ratio of the in-cage recombination rate constants, k_c^α/k_c^β, can be calculated to be 2.6 ± 0.6. This surprising kinetic preference for the α diastereomer results from enthalpic stabilization of the recombination transition state for the α diastereomer, since the *β* diastereomer is entropically favored.

Introduction

Solvent cage effects have long been recognized as being important in organic chemistry,[2−10] but the importance of such effects in the measurement of organometallic bond cleavage energetics was only recognized fairly recently.[9−21] Koenig and Finke[10,11] have provided the formalism needed to treat such cage effects in organometallic bond dissociation reactions exactly (eq 1). In the presence of a kinetically competent trap for one or

$$\mathrm{M{-}L} \underset{k_c}{\overset{k_1}{\rightleftharpoons}} [\overline{\mathrm{M^\bullet L^\bullet}}] \underset{k_{-1}}{\overset{k_d}{\rightleftharpoons}} \mathrm{M^\bullet} + \mathrm{L^\bullet} \xrightarrow{\text{trap}} \text{trapped product(s)} \tag{1}$$

both of the free radical products (which prevents reentry of the product radicals into the cage), application of the steady-state approximation[22] to the concentration of the caged pair leads to eq 2. If the fractional cage efficiency, F_c, is defined as the

$$k_{obs} = k_1 k_d/(k_d + k_c) \tag{2}$$

ratio of the rate constant for in-cage radical recombination, k_c, to the sum of the rate constants for all competing cage processes, then eqs 3 and 4 result. Equation 4 suggests that, in cases where

$$F_c = k_c/(k_c + k_d) \tag{3}$$

$$k_{obs} = (1 - F_c)k_1 \tag{4}$$

F_c is large (i.e., in-cage recombination is significantly faster than all other cage processes), the observed rate constant will differ substantially from k_1, the rate constant for the process of primary interest. Worse yet, comparison of values of k_{obs} (or of the observed enthalpy of activation, $\Delta H^\ddagger_{obs}$) for different M−L complexes may be meaningless if F_c varies significantly among them.

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(1) Abbreviations: CNCbl, cyanocobalamin (vitamin B$_{12}$); AdoCbl, 5′-deoxyadenosylcobalamin (coenzyme B$_{12}$); NCCH$_2$Cbl, (cyanomethyl)-cobalamin; H$_2$OCbl$^+$, aquocobalamin; AdoCbi$^+$, 5′-deoxyadenosylcobinamide; α-NCCH$_2$Cbi$^+$, α-(cyanomethyl)cobinamide; *β*-NCCH$_2$Cbi$^+$, *β*-(cyanomethyl)cobinamide; (H$_2$O)$_2$Cbi^{2+}, diaquocobinamide; α-NpCbi$^+$, α-neopentylcobinamide; *β*-NpCbi$^+$, *β*-neopentylcobinamide; 4-HTEMPO, 4-hydroxy-2,2,6,6-tetramethylpiperidinyloxy; NCCH$_2$-4-HTEMPO, *N*-(cyanomethoxy)-4-hydroxy-2,2,6,6-tetramethylpiperidine. Note that all organocobalt corrinoids referred to are assumed to have the organic ligand in the *β* axial position unless explicitly stated otherwise.

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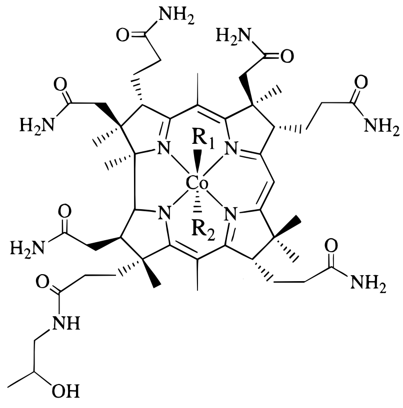
Values of F_c for M−L bond scissions have rarely been determined. Garr and Finke[18] have provided by far the most precise and reliable value of $0.94 \leq F_c \leq 1.00$ for homolysis of 5′-deoxyadenosylcobinamide (AdoCbi$^+$,[1] the axial nucleotide-free analog of coenzyme B_{12}) in ethylene glycol at 110 °C and an estimate of $0.4 \leq F_c \leq 1.0$ for AdoCbl under the same conditions. This suggests a very efficient cage, albeit in a highly associated solvent, and gives substantial credence to the fears expressed above regarding the possible influence of cage effects on observed rate constants for such reactions.

A value of about 0.7 for the fractional cage efficiency for Co−C bond photohomolysis of AdoCbl[1] itself in water (unfortunately at an unspecified temperature) can be calculated from the flash photolysis data of Endicott and Netzel,[24] suggesting that large cage efficiencies can occur in less highly associated solvents, as well. Unfortunately, the significance of this result is unclear, since the error limits for this calculated value of F_c overlap both zero and 1.0. Moreover, Finke[10,18] has cautioned against the assumption that photochemical and thermal cage efficiencies are identical, particularly when the spin state resulting from photolysis is unknown.[25]

A study of the viscosity dependence of the rate of photolysis of AdoCbl and AdoCbi$^+$ as well as the kinetics of thermolysis of AdoCbl in glycerol/water mixtures resulted in the values of 0.2 for F_c in water at 25 °C and $0.20 > F_c > 0.18$ in water in the temperature range 85−110 °C.[16] Unfortunately, as pointed out by Garr and Finke,[18] this study failed to account for an additional cage process, a hydrogen atom transfer reaction leading to the elimination product 4′,5′-didehydroadenosine. The importance of this process must be expected to increase with increasing solvent viscosity as the diffusion rate constant, k_d, becomes smaller and the cage becomes more robust. Since this additional cage process must affect the evaluation of the cage efficiency and the energetics of the recombination process, the reliability of these values for F_c is unclear. Obviously, additional reliable determinations of F_c, particularly in water, as well as evaluations of the relative energetics of the recombination and diffusion reactions are highly desirable.

Alkylcobinamides, and other alkylcobalt corrinoids lacking an intramolecular axial ligand, are well-known to occur as pairs of diastereomers in which the organic ligand is in the "upper" (or β) or "lower" (α) axial ligand position.[27−34] Oxidative addition of alkyl halides to reduced cobinamide produces diastereomeric products in which the α diastereomer represents anywhere from ≤4% to up to 98% of the product, depending on the alkyl group. These widely varying product ratios have never been satisfactorily explained, and although thermal equilibrium seems to favor the β diastereomers by >10:1,[35] virtually nothing is known regarding kinetically controlled product ratios in this system. Since such oxidative additions may well involve the coupling of cob(II)inamide to alkyl radicals,[36] the reverse reaction of carbon−cobalt bond homolysis, studies of the energetics of Co−C bond homolysis, in-cage radical recombination, and cage effects in RCbi$^+$'s are of considerable interest.



$R_1 = NCCH_2$ β-CNCH$_2$Cbi$^+$
$R_2 = H_2O$

$R_1 = H_2O$ α-NCCH$_2$Cbi$^+$
$R_2 = NCCH_2$

Figure 1. Structure of α- and β-NCCH$_2$Cbi$^+$.

We have consequently undertaken a study of the diastereomeric (cyanomethyl)cobinamides (α- and β-NCCH$_2$Cbi$^+$),[1] including the thermodynamics of diastereomer equilibration, the kinetics of trapped, anaerobic thermolysis of both diastereomers, and the dependence of thermolysis kinetics on viscosity using glycerol/water mixtures. The last provides direct evidence of caged intermediates and the diffusion-controlled nature of the reaction,[7,37] direct determination of the intrinsic rate constant (k_1 in eq 1) for Co−C bond homolysis, and evaluation of cage efficiencies and differential enthalpies and entropies of activation for cage escape vs in-cage recombination in water—rarely measured quantities.

The subject complexes for this study have been carefully chosen for several reasons. First, the lack of an axial nucleotide precludes the complications of the base-on/base-off equilibrium and its anticipated dependence on solvent composition.[12−15,18,19,38,39] Second, the lack of a β heteroatom in the alkyl ligand (such as the ribose ring oxygen in AdoCbl) prevents the thermal heterolytic elimination of Co^{III} to produce an olefinic product.[12−15,33c,40−43] Third, the absence of β hydrogens on the alkyl ligand precludes β-H elimination (via in-cage hydrogen atom transfer) leading to Co^I−H + olefin products.[18,43b,44−49]

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Finally, the $NCCH_2Cbi^+$'s represent a case in which the alkylation products from oxidative addition of $NCCH_2Br$ are predominately the α diastereomer (7:3),[33b] a product ratio which is apparently far from equilibrium.[35]

Experimental Section

Factor B (a mixture of the diastereomeric α-(CN)-*β*-(H_2O)Cbi^+ and α-(H_2O)-*β*-(CN)Cbi^+) was synthesized by the triflic acid method.[51] The diastereomeric α- and *β*-$NCCH_2Cbi^+$'s were synthesized and separated using the methods previously described,[33b,52] and $NCCH_2Cbl$ was prepared from CNCbl as previously described for its preparation from H_2OCbl^+.[33b] Diaquocobinamide ($(H_2O)_2Cbi^{2+}$) was prepared by reduction of factor B with zinc in 10% acetic acid under continuous argon purge for 1 h followed by reoxidation by cannula transfer into an aerobic solution of 0.1 M HCl. The preparation was desalted by chromatography on Amberlite XAD-2[53] and purified by semipreparative HPLC.[33c] Cob(II)inamide was obtained from $(H_2O)_2Cbi^{2+}$ by controlled-potential reduction at −0.8 V at a mercury pool electrode.

$NCCH_2$-4-HTEMPO was prepared as follows. $NCCH_2Cbl$ (1.5 g, 1.0 mmol) and 4-HTEMPO (0.1885 g, 1.0 mmol) were dissolved in 150 mL of water, and the solution was purged with argon overnight. While being stirred, the solution was photolyzed by irradiation with a 300 W tungsten lamp for 8 h. The solution was extracted three times with 150 mL of hexane, the combined extracts were dried over anhydrous Na_2SO_4, and the solvent was evaporated under vacuum to produce a white solid (56.6 mg, 27% yield). Final purification was effected by chromatography on silica gel (in $CHCl_3$) eluting with 10% acetone/$CHCl_3$ (v/v). Analytical GC showed a single peak at 10.7 min with >97% purity. ^1H NMR ($CDCl_3$): δ (TMS) 1.15 (6H, s), 1.24 (6H, s), 1.46 (2H, m), 1.80 (2H, m), 3.95 (1H, m), 4.52 (2H, s). GC-MS: *m/e* 212.3 (M^+), 197.4 ($M^+ - CH_3$), 172.3 ($M^+ - CH_2CN$).

UV−visible spectra and single-wavelength measurements were recorded on a Cary 219 recording spectrophotometer thermostated with a Neslab RTE-220 circulating water bath. Cobalt corrinoids were quantitated by conversion to their dicyano derivatives ($\epsilon_{368} = 3.04 \times 10^4$ M^{-1} cm^{-1})[54] by aerobic photolysis in excess cyanide. The relative viscosity (η_{rel}) of glycerol/water mixtures (50, 65, 70, and 75% glycerol, w/w) was determined by kinematic viscosity measurements using an Ostwald viscometer thermostated at 75, 80, 85, 90, or 95 °C. Analytical GC analysis of $NCCH_2$-4-HTEMPO was carried out on a Varian 3300 GC instrument equipped with a Restek 30 m DB5 column and an FID detector. The column temperature program was as follows: 1 min at 100 °C, increasing to 250 °C at a rate of 10 °C/min, followed by 1 min at 250 °C. The retention times were 10.7 min for $NCCH_2$-4-HTEMPO and 7.2 min for 4-HTEMPO.

Equilibrium constants for the isomerization of α- and *β*-$NCCH_2Cbi^+$ were determined by HPLC analysis of equilibrated mixtures by digital integration of chromatograms at 254 and 350 nm.[33b] Samples (20 *μ*L), containing either α- or *β*-$NCCH_2Cbi^+$ as the starting material, were prepared in glass tubes, made anaerobic by five freeze/pump/thaw cycles under an argon atmosphere, and were then sealed under vacuum. The samples were incubated for 20−40 h at the desired temperature (70−95 °C) to achieve equilibrium as determined by HPLC analysis of samples periodically removed and assayed.

Samples for spectrophotometric analysis of anaerobic, trapped thermolysis of the $NCCH_2Cbi^+$'s were prepared in the dark in Schlenk cuvettes in a glovebox under a nitrogen atmosphere using 4-HTEMPO[1] as a radical scavenger. Samples of the α- or *β*-$NCCH_2Cbi^+$ stock solution and sufficient phosphate buffer (pH 7.0) to make the final buffer concentration 0.1 M were placed in a round-bottomed flask and evaporated to dryness, transferred to the glovebox, and dissolved in a 3.00 mL of aqueous solution containing the desired amount of 4-HTEMPO which had been purged with argon for 2 h. The final concentration of the $NCCH_2Cbi^+$ was 2.4×10^{-5} M. Reference Schlenk cuvettes contained 3.0 mL of the aqueous 4-HTEMPO solution only.

The cob(II)alamin product resulting from α- or *β*-$NCCH_2Cbi^+$ thermolysis was quantitated spectrophotometrically in the presence of 20 mM 4-HTEMPO at 80 °C. Because of the relatively slow oxidation of cob(II)inamide by 4-HTEMPO,[39c,55] spectral kinetics were complicated. In the case of α-$NCCH_2Cbi^+$, thermolysis was about 7-fold faster than the subsequent oxidation. The reaction was followed at three wavelengths: 466 nm, at which the absorbance increased upon thermolysis but decreased upon oxidation of cob(II)inamide; 479 nm, which was an isosbestic point for the thermolysis reaction; and 500 nm, at which the absorbance decreased for both reactions. The resultant data were fitted to the appropriate double- or single-exponential functions to extract the absorbance of the intermediate cob(II)inamide, the concentration of which was then calculated from the molar absorptivities of cob(II)inamide at these three wavelengths. The latter were determined from the spectra of authentic cob(II)inamide ($\epsilon = 1.30 \times 10^4$, 1.18×10^4, and 8.07×10^3 M^{-1} cm^{-1} at 466, 479, and 500 nm, respectively). The yield of cob(II)inamide was 93.4 ± 3.6%.

For *β*-$NCCH_2Cbi^+$, which undergoes thermolysis significantly more slowly, the rates of the thermolysis and oxidation reactions were nearly equal, and so this technique could not be used. Instead, repetitive scanning during the late stages of the spectral changes located an apparent isosbestic point for the oxidation reaction between 560 and 570 nm, a long-wavelength region where the total absorbance was small and the spectral changes associated with oxidation were much smaller than those associated with thermolysis. The reaction was consequently monitored at 560 and 570 nm, and the data were fitted to a single-exponential equation using measured molar absorptivities for *β*-$NCCH_2Cbi^+$ (9.21×10^2 and 6.15×10^2 M^{-1} cm^{-1} at 560 and 570 nm, respectively) to extract the absorbance of the cob(II)inamide product of thermolysis. Using the measured molar absorptivities of cob(II)inamide (2.33×10^3 and 1.81×10^3 M^{-1} cm^{-1} at 560 and 570 nm, respectively), the yield was calculated to be 97.6 ± 0.4%.

The $NCCH_2$-4-HTEMPO product resulting from α- and *β*-$NCCH_2Cbi^+$ thermolysis in the presence of 4-HTEMPO was quantitated by analytical GC. In a 5 mL vial, 4-HTEMPO (0.5 mg, 3.0 mM final concentration) was added to 1.2 mL of a solution of α- or *β*-$NCCH_2Cbi^+$ ($\approx 6 \times 10^{-4}$ M) either in water or in 50% glycerol. The vial was capped with a serum stopper and purged with argon for 2 h. With argon flowing across the surface of the solution only, the vial was placed into a water bath at 85 °C for 16 h. The resulting solution was extracted with hexane (3 × 5 mL); the extracts were combined and dried over Na_2SO_4 and then evaporated to dryness on a rotary evaporator. The

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Table 1. Equilibrium Constants and Enthalpy and Entropy Changes for the Thermal Isomerism of α- and β-$NCCH_2Cbi^+$

temp, °C	K_{eq}[a,b]	ΔH, kcal mol^{-1}	ΔS, cal mol^{-1} K^{-1}
70.0	0.208 ± 0.007	−1.82 ± 0.05	−8.42 ± 0.14
75.0	0.200 ± 0.006		
80.0	0.192 ± 0.006		
85.0	0.185 ± 0.005		
90.0	0.181 ± 0.005		
95.0	0.173 ± 0.005		

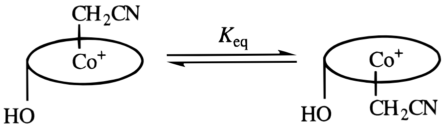
[a] K_{eq} = [α-$NCCH_2Cbi^+$]/[β-$NCCH_2Cbi^+$]. [b] At 25.0 °C, the calculated equilibrium constant is 0.311.

solid residue was dissolved in ethyl acetate for GC analysis. The molar amount of $NCCH_2$-4-HTEMPO formed was determined by integration of the GC peak at 10.7 min using a calibration curve obtained from standard samples made with authentic $NCCH_2$-4-HTEMPO. The identity of the product from the reaction mixtures was confirmed by co-injection with authentic $NCCH_2$-4-HTEMPO. No other organic products were detected in the hexane extracts (limit of detection ≈2%). The yields of $NCCH_2$-4-HTEMPO from α-$NCCH_2Cbi^+$ were 95.2 ± 7.0% in water and 91.7 ± 3.8% in 50% glycerol, and the yields from β-$NCCH_2Cbi^+$ were 92.4 ± 2.9% in water and 95.8 ± 4.2% in 50% glycerol.

Kinetics of the trapped thermolysis of α- and β-$NCCH_2Cbi^+$ were followed by HPLC. Samples were prepared by evaporating a mixture of a stock solution of α- or β-$NCCH_2Cbi^+$ (final concentration 3.7×10^{-4} M) and potassium iodide (final concentration 1.0×10^{-4} M, used as an internal integration standard) to dryness and then dissolving the residue in 1.12 mL of a glycerol/water mixture of the desired viscosity. The solution was transferred to a small vial containing solid 4-HTEMPO (final concentration 5.0×10^{-3} to 2.0×10^{-2} M), the vial was stoppered with a septum, and the solution was deoxygenated for 2 h by argon purge. With argon flowing only across the surface of the solution, the reaction vial was placed in a water bath at the desired temperature. Periodically, a sample taken with a gastight syringe that had been cooled to 0 °C was analyzed by HPLC.[33b] The chromatograms were monitored at 230 nm where $\epsilon = 9.13 \times 10^3$, 2.34×10^4, and 1.84×10^4 for KI, α-$NCCH_2Cbi^+$, and β-$NCCH_2Cbi^+$, respectively.

Results

Thermodynamics of the Diastereomeric Equilibrium of α- and β-$NCCH_2Cbi^+$. Values for the equilibrium constant for the isomerization of α- and β-$NCCH_2Cbi^+$ (eqs 5 and 6)



(5)

$$K_{eq} = [\alpha\text{-}NCCH_2Cbi^+]/[\beta\text{-}NCCH_2Cbi^+] \qquad (6)$$

were determined at six temperatures between 70 and 95 °C (Table 1). Measurement of the α/β isomerization equilibrium constants by this method requires complete exclusion of oxygen from the sample throughout the equilibration period at elevated temperature due to the fact that dissolved oxygen is an excellent scavenger of both reduced cobalt corrinoids and organic radicals.[39,56,57] Since the α diastereomer undergoes thermolysis considerably more rapidly than the β diastereomer (*vide infra*), and equilibrium is achieved rather slowly, any net decomposition due to oxygen contamination during incubation will necessarily cause an underestimation of K_{eq} (eq 6). Thus, attempts to measure equilibrium constants for the reaction of eq 5 in samples under continuous argon purge, even when the argon was passed through vanadous sulfate scrubbing towers,[58] invariably produced erroneously low values since even the tiny trace of residual oxygen in the gas stream became significant (compared to reagent concentration) after the long incubation times (20−40 h) needed to achieve equilibrium. This is undoubtedly why our previous estimate of K_{eq} (eq 6) at 70 °C gave a lower value than that reported here.

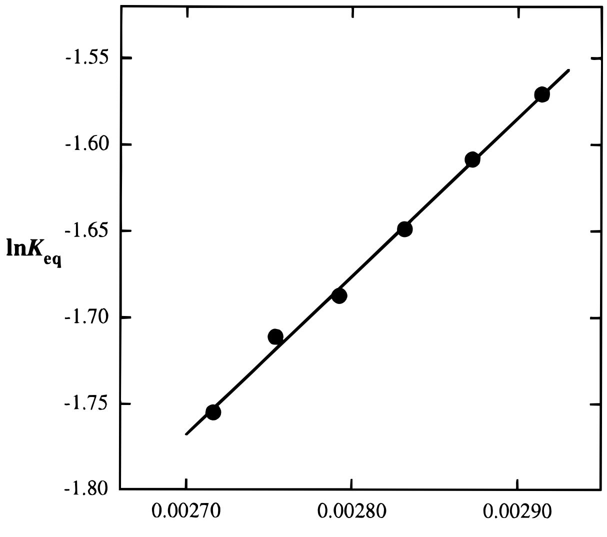


Figure 2. Plot of ln K_{eq} (eqs 5 and 6) vs 1/T, for the thermal interconversion of α- and β-$NCCH_2Cbi^+$. The straight line is a linear regression; slope = 917.9 ± 25.8 K^{-1}, intercept = −4.246 ± 0.073, r^2 = 0.997.

From the values of K_{eq} in Table 1, the enthalpy and entropy changes for the reaction of eq 5 were determined from a plot of ln K_{eq} vs $1/T$ (Figure 2) to be −1.82 ± 0.05 kcal mol^{-1} and −8.42 ± 0.14 cal mol^{-1} K^{-1}, respectively. These values can be used to calculate K_{eq} at 25 °C (0.311) which shows that at this temperature the equilibrium mixture is 76% β-$NCCH_2Cbi^+$ and 24% α-$NCCH_2Cbi^+$. This is in sharp contrast to the product distribution from oxidative addition of $NCCH_2Br$ to reduced cobinamide at this temperature (27% β-$NCCH_2Cbi^+$ and 73% α-$NCCH_2Cbi^+$),[33b] demonstrating that these oxadative addition products are clearly not under thermodynamic control. Moreover, while the β diastereomer is the more stable isomer (by 0.7 kcal mol^{-1} at 25 °C), this first determination of the thermodynamics of α/β diastereomerism shows that this is entirely an entropic effect—the α diastereomer is actually enthalpically favored by nearly 2 kcal mol^{-1}.

α-$NCCH_2Cbi^+$ Thermolysis. The products of the 4-HTEMPO-trapped thermolysis of α-$NCCH_2Cbi^+$, cob(II)alamin and $NCCH_2$-4-HTEMPO, were determined by UV−visible spectroscopy and gas chromatography, respectively (*vide supra*). The yield of cob(II)alamin at 80 °C in water was 93.4 ± 3.6%, and the yield of $NCCH_2$-4-HTEMPO was 95.2 ± 7.0% in water and 91.7 ± 3.8% in 50% glycerol. These important results demonstrate that, as anticipated, heterolytic cleavage to form cobinamide products in other oxidation states cannot occur here. Moreover, the high yield of $NCCH_2$-4-HTEMPO and its lack of dependence on solvent viscosity show that no competing cage processes (other than recombination, k_c in eq 1, and cage escape, k_d in eq 1) occur which might be enhanced in the stronger solvent cage at higher viscosities. Thus, simple Co−C bond homolysis is the only significant reaction which occurs at all viscosities.

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Table 2. Observed First-Order Rate Constants for the Thermolysis of α- and β-$NCCH_2Cbi^+$ in Water at Various Temperatures[a]

	10^4k_{obs}, s^{-1}	
temp, °C	α-$NCCH_2Cbi^+$	β-$NCCH_2Cbi^+$
75.0	0.619 ± 0.016	0.171 ± 0.004
80.0	1.17 ± 0.02	0.308 ± 0.003
85.0	2.05 ± 0.05	0.527 ± 0.010
90.0	3.66 ± 0.04	0.912 ± 0.015
95.0	6.58 ± 0.06	1.86 ± 0.03

[a] [4-HTEMPO] = 2.0×10^{-3} M.

Kinetic data for the 4-HTEMPO-trapped thermolysis of α-$NCCH_2Cbi^+$ followed simple first-order kinetics under all conditions examined. Observed rate constants, k_{obs}, were obtained by fitting these data to a single-exponential function. In addition, the observed rate constant was found to be independent of 4-HTEMPO concentration in the range 5×10^{-3} to 2×10^{-2} M ($k_{obs} = 3.42 \times 10^{-5}$ 3.38×10^{-5} and 3.50×10^{-5} s^{-1}, average = $3.43 \pm 0.06 \times 10^{-5}$ s^{-1}, at 5×10^{-3}, 1×10^{-2}, and 2×10^{-2} M 4-HTEMPO, respectively, at 70 °C). In the presence of 4-HTEMPO at $\geq 5.0 \times 10^{-3}$ M, no isomerization to the β diastereomer could be detected in HPLC chromatograms at any temperature or viscosity, confirming earlier conclusions[32,35] that thermal isomerization occurs via Co−C bond homolysis and that escape of the radicals from the solvent cage is required for isomerization.

Observed rate constants for α-$NCCH_2Cbi^+$ thermolysis were determined in water at five temperatures between 75.0 and 95.0 °C (Table 2). In addition, at each temperature, k_{obs} was also determined in four glycerol/water mixtures (50, 65, 70, and 75% glycerol, w/w) providing a variation of relative viscosity (η_{rel}) of 3.29−10.05 at 75 °C and 2.84−7.61 at 95 °C. At each temperature, k_{obs} decreased with increasing viscosity following a hyperbolic function, suggesting that the reaction is under at least partial diffusion control.

Assuming that the rate constant for diffusional separation of the caged pair (k_d in eq 1) is the only viscosity-dependent rate constant involved,[7] the dependence of k_{obs} (eq 2) on viscosity can be analyzed as follows. Since diffusion is inversely proportional to viscosity[7,59−62] (eq 7, where $k_d°$ and $\eta°$ refer to

$$k_d°\eta° = k_d\eta \tag{7}$$

the values without added viscogen), substitution for k_d in eq 2 provides eq 8 (where $\eta_{rel} = \eta/\eta°$), showing the expected

$$k_{obs} = k_1k_d°/(k_d° + k_c\eta_{rel}) \tag{8}$$

hyperbolic dependence of k_{obs} on η_{rel}. Plots of $1/k_{obs}$ vs η_{rel} (eq 9, the reciprocal of eq 8) are then expected to be linear with slope = $k_c/k_1k_d°$ and intercept = $1/k_1$. Such plots are shown

$$1/k_{obs} = 1/k_1 + (k_c/k_1k_d°)\eta_{rel} \tag{9}$$

in Figure 3 for α-$NCCH_2Cbi^+$ thermolysis, and the values of k_1 and $k_c/k_d°$ which can be calculated from their slopes and intercepts are collected in Table 3. These results show that the value of $k_c/k_d°$ for α-$NCCH_2Cbi^+$ is relatively small and apparently temperature independent over the temperature range 75−95 °C in water, the average value being 0.13 ± 0.02 (Table 4). This in turn leads to an average value of 0.12 ± 0.01 (Table 4) for the fractional cage efficiency, $F_c°$, in water. This value is substantially smaller than that found for $AdoCbi^+$ and AdoCbl thermolysis in ethylene glycol[18] but closer to the values found by Gerards et al. ($F_c \sim 0.2$) for AdoCbl photolysis at 25 °C in water.[16,63]

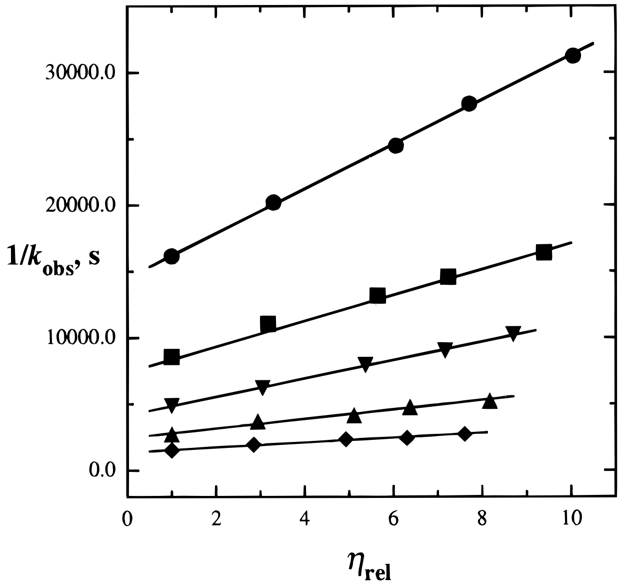

Figure 3. Plots of $1/k_{obs}$ vs η_{rel}, the relative viscosity (eq 9), for the trapped thermal homolysis of α-$NCCH_2Cbi^+$ in glycerol/water mixtures at (●) 75, (■) 80, (▼) 85, (▲) 90, and (◆) 95 °C.

Once values of k_1 (eq 1) have been isolated from these data, the activation parameters associated with Co−C bond homolysis and free of any complications due to cage effects can be obtained from an Eyring plot (Figure 4). The resulting values for α-$NCCH_2Cbi^+$ are $\Delta H_1^\ddagger = 29.0 \pm 0.3$ kcal mol^{-1} and $\Delta S_1^\ddagger = 5.4 \pm 0.8$ cal mol^{-1} K^{-1} (Table 4).

***β*-$NCCH_2Cbi^+$ Thermolysis.** Yields of the primary products of 4-HTEMPO-trapped thermolysis of β-$NCCH_2Cbi^+$ were determined as described above. The yield of cob(II)inamide at 80 °C in water was 97.6 ± 0.4%, and the yields of $NCCH_2$-4-HTEMPO were 92.4 ± 2.9% in water and 95.8 ± 4.2% in 50% glycerol. These results again demonstrate that β-$NCCH_2Cbi^+$ thermolysis is strictly a homolytic process uncomplicated by other cage processes leading to other products and confounding the evaluation of cage efficiencies.

Observed rate constants were again measured in water at five temperatures between 75 and 95 °C (Table 2), but because of the slowness of the thermolysis reaction ($t_{1/2}$ = 11.3 h at 75 °C) and in light of the lack of temperature dependence of $k_c/k_d°$ for α-$NCCH_2Cbi^+$ (Table 3), k_{obs} for β-$NCCH_2Cbi^+$ was studied as a function of solvent viscosity at only two temperatures (80.0 and 95.0 °C). At both temperatures, plots (not shown) of $1/k_{obs}$ vs η_{rel} (eq 9) were linear and the values of k_1 and $k_c/k_d°$ obtained from their slopes and intercepts are given in Table 3. The weighted averages of the values of $k_c/k_d°$ and $F_c°$ were 0.051 ± 0.009 and 0.049 ± 0.008, respectively. Thus, the cage efficiency for β-$NCCH_2Cbi^+$ is about half that for the α diastereomer.

Using this average value of $F_c°$ for β-$NCCH_2Cbi^+$ and the observed rate constants for thermolysis at 75.0, 85.0, and 90.0 °C, values of k_1 for Co−C bond homolysis in β-$NCCH_2Cbi^+$ could be calculated from eq 4, and these are also listed in Table 3. Along with the k_1 values at 80.0 and 95.0 °C obtained from the viscosity dependence of k_{obs} at these temperatures, these

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(63) Note, however, the uncertainties regarding possible other products in the study described in ref 16, as discussed in the Introduction and in footnote 12 of ref 18.

Table 3. Values of k_1, $k_c/k_d°$, and $F_c°$ for Thermolysis of α- and *β*-$NCCH_2Cbi^+$ [a]

temp, °C	α-$NCCH_2Cbi^+$ 10^4k_1, s^{-1} [b]	α-$NCCH_2Cbi^+$ $k_c/k_d°$ [c]	α-$NCCH_2Cbi^+$ $F_c°$ [d]	*β*-$NCCH_2Cbi^+$ 10^4k_1, s^{-1} [b]	*β*-$NCCH_2Cbi^+$ $k_c/k_d°$ [c]	*β*-$NCCH_2Cbi^+$ $F_c°$ [d]
75.0	0.688 ± 0.027	0.115 ± 0.006	0.103 ± 0.007	0.180 ± 0.004[e]		
80.0	1.28 ± 0.02	0.119 ± 0.003	0.106 ± 0.004	0.325 ± 0.003	0.047 ± 0.003	0.045 ± 0.004
85.0	2.40 ± 0.06	0.166 ± 0.007	0.142 ± 0.008	0.554 ± 0.012[e]		
90.0	4.17 ± 0.06	0.148 ± 0.004	0.129 ± 0.005	0.959 ± 0.018[e]		
95.0	7.31 ± 0.08	0.137 ± 0.004	0.121 ± 0.005	1.93 ± 0.04	0.063 ± 0.005	0.059 ± 0.006

[a] k_1, k_c, $k_d°$, and F_c are defined in eqs 1, 3, and 7. [b] From the intercepts of plots of $1/k_{obs}$ vs η_{rel} (eq 9) as in Figure 3, except as noted. [c] From the slopes and intercepts of plots of $1/k_{obs}$ vs η_{rel} (eq 9) as in Figure 3. [d] In water, without added viscogen, calculated from $F_c° = (k_c/k_d°)/[(k_c/k_d°) + 1]$. [e] Calculated from k_{obs} and eq 4 using $F_c° = 0.049 \pm 0.008$.

Table 4. Summary of Cage Parameters and Activation Parameters for α- and *β*-$NCCH_2Cbi^+$ Thermolysis in Water at 75−95 °C

parameter	α-$NCCH_2Cbi^+$	*β*-$NCCH_2Cbi^+$
$k_c/k_d°$	0.13 ± 0.02	0.051 ± 0.009
$F_c°$	0.12 ± 0.01	0.049 ± 0.008
$\Delta H_1^‡$, kcal mol^{-1}	29.0 ± 0.3	29.0 ± 0.2
$\Delta S_1^‡$, cal mol^{-1} K^{-1}	5.4 ± 0.8	2.7 ± 0.6
$\Delta H^‡_{obs}$, kcal mol^{-1}	29.2 ± 0.2	29.0 ± 0.3
$\Delta S^‡_{obs}$, cal mol^{-1} K^{-1}	5.8 ± 0.7	2.9 ± 0.8

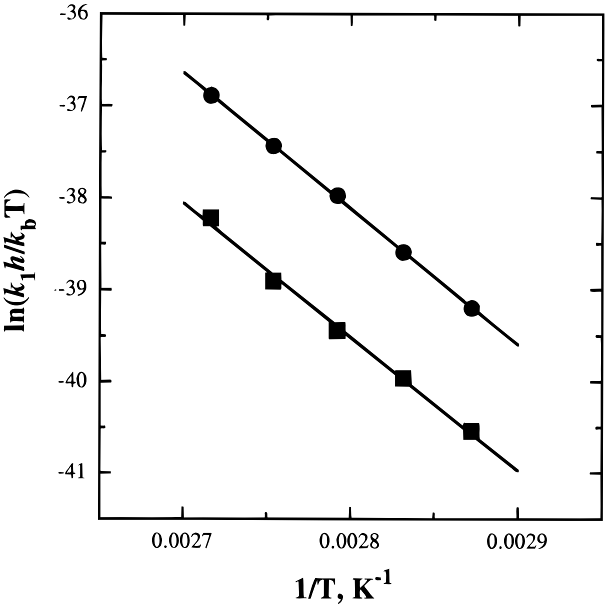

Figure 4. Eyring plots for the specific rate constant, k_1 (eq 1), for Co−C bond homolysis of α-$NCCH_2Cbi^+$ (●) and *β*-$NCCH_2Cbi^+$ (■).

values permitted determination of the activation parameters for k_1 from an Eyring plot (Figure 4). The values obtained were $\Delta H_1^‡ = 29.0 \pm 0.2$ kcal mol^{-1} and $\Delta S_1^‡ = 2.7 \pm 0.6$ cal mol^{-1} K^{-1} (Table 4). Thus, the enthalpies of activation for Co−C bond homolysis are identical for the two diastereomers, but the (positive) entropy of activation for the α diastereomer is twice as large as that for the *β* diastereomer.

Discussion

Quantitative analysis of the products of the 4-HTEMPO-trapped thermolysis of α- and *β*-$NCCH_2Cbi^+$ shows that the products cob(II)inamide and $NCCH_2$-4-HTEMPO are formed essentially stoichiometrically. Moreover, the persistence of the essentially quantitative yield of $NCCH_2$-4-HTEMPO even in solutions of increased relative viscosity indicates the lack of any competing cage processes which would be accentuated in the more robust solvent cages formed at such viscosities. Thus, the $NCCH_2Cbi^+$'s represent an ideal system of pure Co−C bond homolysis in which to evaluate cage effects in the absence of complications seen in such studies of the 5′-deoxyadenosylcobalt corrinoids.[16,18]

The significant effect of solvent viscosity on the observed rate of thermolysis (Figure 3) firmly demonstrates the importance of diffusion in the overall process and indicates that the reaction is at least partially diffusion controlled. However, the relatively small effect of viscosity (e.g., at 75 °C, k_{obs} for α-$NCCH_2Cbi^+$ is decreased only about 2-fold when the viscosity is increased 10-fold) indicates that the solvent cage effects are small in water. Indeed, the quantitative analysis of the viscosity effect described above results in values of F_c of 0.12 and 0.049 for the α and *β* diastereomers, respectively, far smaller than the value determined for $AdoCbi^+$ by Garr and Finke in ethylene glycol at only slightly higher temperatures and significantly below the range of values estimated for AdoCbl under these same conditions.[18] This is as anticipated,[13,15,19,38] since the viscosity of ethylene glycol is substantially higher (by 8.5-fold at 80 °C[64]) than that of H_2O. However, there is no experimentally significant effect of temperature on F_c[10,11] (Table 3) despite the fact that the viscosity of water decreases by 21% over the temperature range studied.[64,65] This suggests that the enthalpies of activation for diffusion (k_d) and in-cage radical recombination (k_c) are quite similar (*vide infra*).

It is tempting to conclude that similarly small values of F_c will be the rule for other alkylcobalt corrinoids in water. However, such a conclusion must be drawn with caution. First, the rate of diffusive separation of the caged radical pair must be expected to be significantly affected by the size and shape of the organic radical, $R^•$.[66] Second, the in-cage recombination rate constant, k_c, could vary significantly for different $R^•$. However, given the high rate constants for this reaction (Table 3), substituent effects of this kind are expected to be small. Importantly, measurement of the apparent rate constants for reaction of cobalt(II) macrocycles with organic radicals confirms this.[67−69] Thus, although such rate constants vary from about 10^7 to 10^9 M^{-1} s^{-1} for various cobalt(II) complexes, for a given cobalt(II) complex the variation with $R^•$ is only about 2-fold.[69b] For cob(II)alamin itself, the rate constants for reactions with $CH_3^•$, $CH_3CH_2^•$, $CH_3CH_2CH_2^•$, $CH_3OCH_2^•$, and $ClCH_2^•$ are

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(64) *CRC Handbook of Chemistry and Physics*, 55th ed.; Chemical Rubber Co.: West Palm Beach, FL, 1974; pp F49 and F52.

(65) A similarly small apparent dependence of F_c on temperature results from Gerard et al.[16] (however, see ref 63).

(66) The observed diffusive separation of a caged cobalt(II) corrinoid and an organic radical must be expected to be dominated by the rate of diffusion of the organic radical, since most of the mass of the starting material lies in the cobalt corrinoid moiety. For the current examples, the ratio of the mass of cob(II)inamide to $NCCH_2^•$ is 38.8:1, so that some 86% of the net motion of diffusive separation can be expected to be due to $NCCH_2^•$ motion.

(67) (a) Roche, T. S.; Endicott, J. F. *J. Am. Chem. Soc.* **1972**, *94*, 8622. (b) Roche, T. S.; Endicott, J. F. *Inorg. Chem.* **1974**, *13*, 1575. (c) Endicott, J. F.; Ferraudi, G. *J. Am. Chem. Soc.* **1977**, *99*, 243. (d) Endicott, J. F.; Lilie, J.; Kuszaj, J. M.; Ramaswamy, B. S.; Schmonsees, W. G.; Simic, M. G.; Glick, M. D.; Rillema, D. P. *J. Am. Chem. Soc.* **1977**, *99*, 429.

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essentially identical, and the rate constant for $BrCH_2^{\bullet}$ is only about 2-fold higher. Thus, it may be reasonable to assume that cage efficiencies for other alkylcobalt corrinoids in water may be similarly small.

The small values of F_c for α- and β-$NCCH_2Cbi^+$ mean that the intervention of the solvent-caged pair between the starting complex and the final products has only a very small effect on the measured rate constants (compare the values of k_{obs} in Table 2 to those of k_1 in Table 3). Similarly, values of $\Delta H_{obs}^{\ddagger}$ and $\Delta S_{obs}^{\ddagger}$ (Table 4, obtained from Eyring plots of k_{obs}, not shown) are very close to the correct values for Co−C bond homolysis, $\Delta H_1^{\ddagger}$ and $\Delta S_1^{\ddagger}$ (Table 4). This shows that, in this case at least, the cage effect could in fact be safely ignored in an analysis of the activation parameters for Co−C bond homolysis.

The availability of reliably deconvoluted values of $\Delta H_{obs}^{\ddagger}$ and $\Delta H_1^{\ddagger}$ and of $\Delta S_{obs}^{\ddagger}$ and $\Delta S_1^{\ddagger}$ now permits a rare[10] estimation of the differential activation parameters for radical recombination and diffusive cage separation. Koenig and Finke[10,11] have shown that the observed activation parameters are related to those for the homolysis step (k_1) as shown in eqs 10 and 11.

$$\Delta H_{obs}^{\ddagger} = \Delta H_1^{\ddagger} + F_c(\Delta H_d^{\ddagger} - \Delta H_c^{\ddagger}) \qquad (10)$$

$$\Delta S_{obs}^{\ddagger} = \Delta S_1^{\ddagger} + F_c(\Delta S_d^{\ddagger} - \Delta S_c^{\ddagger}) \qquad (11)$$

From the data in Table 4, the values of $\Delta H_d^{\ddagger} - \Delta H_c^{\ddagger}$ (hereafter, $\Delta(\Delta H^{\ddagger})_{d-c}$[10]) can be *estimated* to be 1.7 and 0 kcal mol^{-1} for α- and β-$NCCH_2Cbi^+$, respectively. These estimates confirm the conclusion, above, that the enthalpy of activation for diffusive separation and in-cage recombination are quite similar, so that any temperature dependence of F_c is expected to be small. In addition, the very small values of $\Delta(\Delta H^{\ddagger})_{d-c}$ imply that even in the presence of a significantly more robust cage, the net influence of the cage effect on the observed enthalpy of activation is likely to be quite small. Finally, the enthalpy of activation for diffusive separation, $\Delta H_d^{\ddagger}$, is often estimated to be equivalent to the enthalpy of activation for viscous flow, ΔH_η.[10−15,19] For water in the temperature range 75−95 °C, the value of ΔH_η is 2.35 kcal mol^{-1},[70] which leads to values of $\Delta H_c^{\ddagger}$ of 0.7 and 2.4 kcal mol^{-1} for α- and β-$NCCH_2Cbi^+$, respectively. As expected,[10,21] these values are quite small. Importantly, however (*vide infra*), the enthalpy of activation for in-cage recombination is larger for the β diastereomer than for the α diastereomer.

A similar analysis of the entropies of activation in Table 4 provides estimates of 3.4 and 4.5 cal mol^{-1} K^{-1} for $\Delta S_d^{\ddagger} - \Delta S_c^{\ddagger}$ for α- and β-$NCCH_2Cbi^+$, respectively. Both values are positive as anticipated[10,21] from the fact that $\Delta S_d^{\ddagger}$ is the entropy of activation for separation of a caged pair (and should be positive) while $\Delta S_c^{\ddagger}$ is the entropy of activation for recombination (and should be negative). Perhaps surprisingly, these values are of the same order as the measured activation entropies for thermolysis (i.e., $\Delta S_1^{\ddagger}$ and $\Delta S_{obs}^{\ddagger}$) and so could make a significant contribution to $\Delta S_{obs}^{\ddagger}$ in cases where the fractional cage efficiency is much higher.

The data in Table 1 represent the first investigation of the thermodynamics of α/β diastereomerism in alkylcobalt corrinoids. As indicated by earlier work at a single temperature,[35] the β diastereomer is the thermodynamically favored isomer. However, the temperature dependence of the equilibrium constant reveals that this thermodynamic preference for the β diastereomer is entirely entropic—the α diastereomer is actually enthalpically favored by nearly 2 kcal mol^{-1}. This directly implies that, in the ground state, the α diastereomer has the shorter Co−C bond.

The thermodynamic preference for the β diastereomer is in agreement with the normal corrinoid paradigm that the α face of cobalt corrinoids, carrying the axially "downward" *b*, *d*, *e*, and *f* propionamide side chains, is more sterically hindered than the β face, which is bracketed by the smaller and less numerous "upwardly" axial *a* and *c* acetamides and the equatorial *g* acetamide. The current data imply that the putative steric preference for the β face is purely an entropic phenomenon. This conclusion is in complete agreement with our recent work on the effect of corrinoid side chain thermal motions on the entropy of activation for Co−C bond homolysis in β-RCbl's.[21,39c,d] Here, ground state interference of side chain rotational mobility by steric interactions with the organic ligand leads to a decreased ground state entropy, an effect which is partially releaved in the homolysis transition state as the Co−C bond is stretched. Thus, an increase in the number of "upwardly" projecting side chains (by side chain epimerization) is accompanied by an increase in the entropy of activation.[21,39c] Similarly, modifications of the "upwardly" projecting *c* acetamide which increase its steric bulk and hence its steric interactions with the organic ligand also lead to increases in the entropy of activation for Co−C bond. Seen in this light, the entropic preference for the β face in the ground state can be anticipated to be due to a more severe lowering of the ground state entropy in the α diastereomer due to steric interactions of the organic ligand with the *b*, *d*, *e*, and *f* side chains than in the β diastereomer, where steric interactions of the organic ligand interfere with the motions of only the *a*, *c*, and *g* side chains.

In the presence of ≥5 × 10^{-3} M 4-HTEMPO, as discussed above, Co−C bond homolysis is the only observed reaction—no isomerization of either diastereomer could be observed. Since, at these modest concentrations of radical trap, trapping can only be occurring outside the solvent cage,[18] these observations confirm that isomerization of α- and β-$RCbi^+$'s requires escape from the solvent cage and subsequent cage-reformation. Thus, no rotation of the cob(II)inamide moiety within the solvent cage can occur without solvent separation of the radical pair.[32,35]

The activation parameters for this trapped Co−C bond homolysis in α- and β-$NCCH_2Cbi^+$ also hold a number of surprises. The enthalpies of activation for Co−C bond homolysis are identical for the two diastereomers, so that all of the labilization of the α diastereomer is due to a larger (positive) entropy of activation. Again, the increased entropy of activation for the α diastereomer can be attributed to the increased number and length of the α-face side chains and the entropic impact of their interactions with the α-face organic ligand. The identical enthalpies of activation observed here imply that differential steric interactions between at least the relatively small $-CH_2CN$ organic ligand and the side chains in the two diastereomers do *not* lead to distortion and weakening of the α-Co−C bond in the ground state and stand in sharp contrast to the case of α- and β-neopentylcobinamides ($NpCbi^+$'s[1]) where the observed enthalpy of activation for the α diastereomer is some 9 kcal mol^{-1} lower than that for the β diastereomer.[33f,39a] If the cage efficiencies for α- and β-$NpCbi^+$ are small so that $\Delta H^{\ddagger}_{obs} \approx \Delta H_1^{\ddagger}$, this suggests that, for the bulky Np ligand, steric interactions with the side chains on the α-face are sufficiently severe to give rise to distortion of the α-Co−C bond and to consequent enthalpic destabilization relative to the β-Co−C bond. Presumably, the smaller $NCCH_2$ ligand undergoes smaller steric interactions with the side chains and experiences no ground state Co−C bond distortion in the α position relative

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(70) Obtained from a plot of ln η^{64} vs 1/*T*, as described in ref 15.[71]

(71) Glasstone, S.; Laidler, K. J.; Eyring, H. *Theory of Rate Processes*; McGraw-Hill: New York, 1941.

to the β position. Unfortunately, the ground state enthalpy change accompanying α/β diastereomerism in the NpCbi$^+$'s is unknown.

The entropy of activation for Co−C bond homolysis in β-NCCH$_2$Cbi$^+$ is some 8 cal mol^{-1} K^{-1} lower than the observed entropy of activation for β-NpCbi$^+$ thermolysis. Again, assuming that the cage efficiency for β-NpCbi$^+$ is suitably small to make the comparison in the two systems, this is the expected trend since the bulkier Np ligand would be expected to exert a larger steric restriction on *a*, *c*, and *g* side chain mobility than the NCCH$_2$ ligand. Surprisingly, the opposite effect is seen in the α diastereomers, α-NpCbi$^+$ having the smaller entropy of activation. As discussed elsewhere,[33f] this unintuitive effect may be due to a substantial upward flexing of the corrin ring in α-NpCbi$^+$ in response to the steric interactions among the *b*, *d*, *e*, and *f* side chains, thus partially relieving the restrictions to side chain mobility.[72] Such upward flexing of the corrin ring is well-known to occur in cobalamins, at least in the solid state,[73−77] while downward flexing of the corrin ring is unknown.

The current data can also be used to investigate the energetics of the formation of Co−C bonds by cob(II)inamide−R$^\bullet$ coupling, the formal reverse of eq 1 and the prototypical reaction in which Co−C bonds are formed. As pointed out above, thermal equilibrium clearly favors formation of the β diastereomers in RCbi$^+$'s (Table 1 and ref 35). However, oxidative addition of RX to reduced cobinamides produces diastereomeric products of widely varying ratios depending on R, with the α diastereomer sometimes predominating by >20:1.[33b] From the values of k_c/k_d° for the CNCH$_2$Cbi$^+$'s (Table 4), a value of 2.6 ± 0.6 can be calculated for the ratio of the in-cage recombination rate constant for α-NCCH$_2$Cbi$^+$ to that for β-NCCH$_2$Cbi$^+$ (k_c^α/k_c^β), *assuming* that the rate constants for diffusive separation of the two caged radical pairs are the same. This *kinetic* preference for the α diastereomer is surprising and totally unintuitive but was nonetheless recently confirmed in the diastereomeric ethylcobinamides using a completely different technique.[78]

The apparent basis for this kinetic discrimination for the α diastereomer can be addressed using the current results. The entropic preference for the β diastereomer in the ground state of the NCCH$_2$Cbi$^+$'s (Table 1) must be expected to be reduced in the transition state, and even further reduced (or absent) in the ground states for the caged radical pairs. The reduction in the transition state entropic preference for the β diastereomer can be documented by calculation of the relative transition state entropies for the two diastereomers ($S_\alpha^\ddagger - S_\beta^\ddagger$) from the values of ΔS (Table 1) and $\Delta S_{1(\alpha)}{}^\ddagger$ and $\Delta S_{1(\beta)}{}^\ddagger$ (Table 4). The value obtained, −5.6 ± 1.0 cal mol^{-1} K^{-1}, is 2.8 ± 1.0 eu less negative than the NCCH$_2$Cbi$^+$ ground state entropy difference (−8.4 ± 0.1 cal mol^{-1} K^{-1}). Thus, the transition state for β-Co−C bond formation by radical combination is clearly entropically stabilized relative to that for α-Co−C bond formation. This means that the α transition state must be *enthalpically stabilized* relative to that for the β diastereomer (since $k_c^\alpha/k_c^\beta > 1$), a conclusion supported by our current estimates of $\Delta H_c^\ddagger$ for the α (0.7 kcal mol^{-1}) and β diastereomers (2.4 kcal mol^{-1}; *vide supra*). This in turn directly implies that the transition state for α-Co−C bond formation is "later" than that for β-Co−C bond formation and that the Co−C internuclear distance is shorter in the α transition state than in the β transition state.

Interestingly, the calculated value of k_c^α/k_c^β (2.6 ± 0.6) implies that the product distribution for kinetically controlled Co−C bond formation in the NCCH$_2$Cbi$^+$'s would be 72% α:28% β. This is distinctly different from the equilibrium distribution of products at 25 °C (24% α:76% β, from K_{eq} = 0.311, Table 1) but essentially identical to the observed product distribution resulting from oxidative addition of NCCH$_2$Br to cobinamide at room temperature (73% α:27% β).[33b] This suggests, in this case at least, that the oxidative addition products are under kinetic control, although for other RX, product distributions at or near equilibrium seem to be obtained.[33b,35] The energetics of Co−C bond formation by radical combination and the question of product distribution control in the oxidative addition of RX to reduced cobinamides are currently under further investigation and will be the subject of a future report.[78]

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(72) Such upward folding of the corrin ring in the α-NpCbi$^+$ ground state must still leave significant steric interactions between the Np ligand and the "downwardly" projecting side chains leading to a decrease in ground state entropy. However, if such flexing is reduced as steric pressure is reduced approaching the ground state, the increased steric interaction in the transition state might lead to a very low entropy of activation.

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