Side Chain Entropy and the Activation of Organocobalamins for Carbon−Cobalt Bond Homolysis: Synthesis, Characterization, and Thermolysis of the Neopentyl Derivative of a Unique Cobalamin Analog Lacking a *c* Side Chain

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Hydrodeamination of the *c*-amino derivative, **5**, of cyanocobalamin (CNCbl) with hydroxylamine-*O*-sulfonic acid in aqueous base leads to an extensively rearranged product instead of the *c* side chain truncated derivative, **1**, expected from simple deamination. The rearranged product (CNCbl-8-butanamide) crystallizes in the orthorhombic system, space group $P2_12_12_1$ with unit cell dimensions $a = 16.041(11)$, $b = 21.94(2)$, and $c = 25.43(2)$ Å. It is devoid of substituents at corrin ring C(7) but quarternized at C(8) with an "upwardly" pseudoaxial methyl group and a *d* side chain expanded by one methylene group to a butanamide. The corrin ring of this rearranged derivative is significantly flatter (corrin ring fold angle 9.9°) than CNCbl itself (fold angle 18.0°). Conversion of CNCbl-8-butanamide to its neopentyl derivative (NpCbl-8-butanamide), a NpCbl analog which lacks a *c* acetamide side chain, permits a quantitative assessment of the influence of thermal motions of the *c* side chain on the entropy of activation for carbon−cobalt bond thermal homolysis in NpCbl. NpCbl-8-butanamide is shown to thermolyze homolytically to give products derived from the Np• radical quantitatively. The kinetics of the thermolysis of NpCbl-8-butanamide were studied in aerobic aqueous solution at temperatures between 15 and 45 °C. After correction of the observed first-order rate constants for the presence of the essentially unreactive base-off species using an established NMR method, an Eyring plot yields the activation parameters $\Delta H^{\ddagger}_{on} = 26.7 \pm 0.1$ kcal mol^{-1} and $\Delta S^{\ddagger}_{on} = 13.2 \pm 0.2$ cal mol^{-1} K^{-1}. While the enthalpy of activation is slightly reduced (6%) from that of NpCbl, the entropy of activation is reduced by 6.1 ± 0.6 cal mol^{-1} K^{-1}, or 32 ± 3%. The *c* side chain thus contributes about one-third of the total entropic activation of NpCbl for carbon−cobalt bond homolysis, and the entropy of activation for this reaction is probably dominated by changes in the thermal motions of the "upwardly" pseudoaxial *a* and *c* acetamide side chains as the reaction progresses.

Introduction

Enzymes dependent on coenzyme B_{12} (5′-deoxyadenosylcobalamin, AdoCbl[1] Figure 1), are well-known to induce a highly efficient cleavage of the carbon−cobalt bond of this organometallic coenzyme,[2−5] with rate enhancements as high as 10^{12} (or more)[6,7] relative to the nonenzymatic thermolysis of AdoCbl. This tremendous enhancement of carbon−cobalt bond homolysis[9] has engendered studies of the thermal homolysis of a number of simpler alkylcobalamins in order to understand structural and chemical bases for the labilization of the carbon cobalt bond.[11−17] A considerable amount of this effort has focused on neopentylcobalamin (NpCbl[1]), considered by some

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(1) Abbreviations: AdoCbl, 5′-deoxyadenosylcobalamin (coenzyme B_{12}); NpCbl, neopentylcobalamin; CNCbl-*c*-lactone, cyanocobalamin-*c*-lactone; CNCbl-*c*-COO^-, cyanocobalamin-*c*-monocarboxylate; H-TEMPO, (4-hydroxy-2,2,6,6-tetramethylpiperidinyl)oxy; Np-H-TEMPO, *N*-(2,2-dimethylpropanoxy)-4-hydroxy-2,2,6,6-teteramethylpiperidine; H_2OCbl^+, aquacobalamin.

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(7) Recent NMR and molecular mechanics studies of AdoCbl[8] suggest that extrapolation of the high-temperature thermolysis data for AdoCbl[6a,b] to ordinary temperatures may understate the catalytic efficiency of AdoCbl-dependent enzymes, albeit probably by a relatively small amount compared to the 10^6-10^{12} factors under discussion.
(8) Brown, K. L.; Marques, H. M. *Polyhedron* **1996**, *15*, 2187.
(9) In at least one case (the ribonucleotide reductase from *Lactobacillus leichmanii*), enzymatic "activation" of AdoCbl is known to yield cob(II)alamin, adenosine, and a thiyl radical derived from an active-site cysteine residue.[10] However, it is not known whether this results from a concerted reaction between AdoCbl and the active-site cysteine or a subsequent hydrogen atom transfer from the cysteine residue to a 5′-deoxyadenosyl radical formed in a discrete prior homolysis step.
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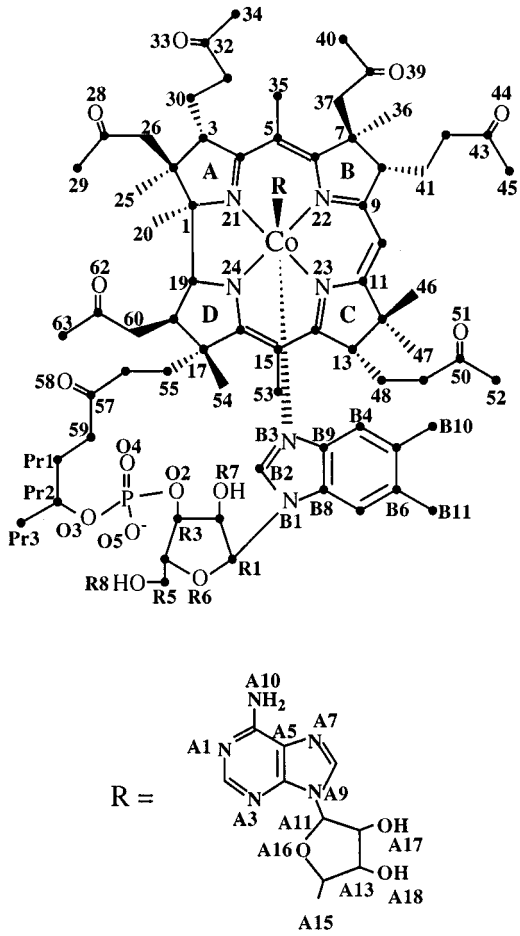

Figure 1. Structure and numbering scheme of 5′-deoxyadenosylcobalamin (coenzyme B_{12}).

to be the "best" model for AdoCbl.[16c] This complex is of interest because it appears to be nearly 6 orders of magnitude more thermally labile toward carbon−cobalt bond homolysis than AdoCbl itself.[18] Interestingly, studies of the activation parameters for such homolysis reactions show that while the labilization of NpCbl is due in part to a decrease in the enthalpy of activation, there is also a substantial increase in the entropy of activation, which is, in fact, the dominent component at least for ethylene glycol.[19]

The positive, and often substantial,[6,16,17] entropies of activation for these carbon−cobalt bond homolyses are of considerable interest.[24] Although the extent of bond breaking in the transition state for these reactions is unknown, they are expected to proceed via "late" transition states since the equilibrium constant for formation of the radical products is quite small.[25] However, the incipient separation of the organic radical fragment from the cobalt complex is not expected to give rise to a substantial increase in positional entropy. Moreover, since there is no charge separation in the transition state, it seems unlikely that a major reorganization of solvent will accompany reaction progress and contribute substantially to the entropy of activation. Consequently, values of $\Delta S^{\ddagger}$ as high as 33 cal mol^{-1} K^{-1} for such reactions[16c] would seem to require other sources of motional freedom to accompany formation of the transition state.

As has been pointed out elsewhere,[26] the corrin ring side chains represent the only parts of the cobalamin structure with sufficient motional freedom to contribute substantially to the internal positional entropy of these complexes. Recent work in our laboratory[17b,d,e] strongly suggests that the motional freedom of the "upwardly" projecting acetamide side chains (Figure 1) contributes significantly to the entropy of activation of carbon−cobalt bond homolysis in solution. This is due to the fact that, in the ground state, bulky organic ligands such as Np sterically restrict the freedom of rotational motion of the *a*, *g*, and *c* acetamide side chains. Partial relief of this rotational confinement as the carbon−cobalt bond is stretched in the transition state, then, leads to increased positional entropy due to increased side chain motion and contributes to the entropic driving force for reaction.

Evidence for such an effect has been obtained by studies of the activation parameters for carbon−cobalt bond homolysis of the Np derivatives of Cbl analogs, NpCbl-*c*-COX, in which the steric bulk of the substituent on the *c* side chain carbonyl was systematically varied, including the *c*-monocarboxylate, the *c*-*N*-methylamide, the *c*-*N*,*N*-dimethylamide, and the *c*-*N*-isopropylamide, a series in which the van der Waals volume of X varies by 270%.[17e] Molecular mechanics calculations found that the steric strain upon rotation of the *c* side chain increased monotonically with the steric bulk of this side chain but that the carbon−cobalt bond length and Co−C−C and Co−C−H bond angles were unaffected by such rotation or by the size of the side chain substituent. In addition, stretching the carbon−cobalt bond to simulate the approach to the transition state was found to significantly lower the steric strain associated with *c* side chain rotation in NpCbl. Kinetic measurements showed that the enthalpy of activation was essentially unchanged across the series of NpCbl analogs but that the entropy of activation increased (from about 16 to about 25 cal mol^{-1} K^{-1}) with increasing size of the *c*-COX moiety. These results were interpreted to mean that the increased steric strain due to *c* side chain rotation accompanying the increase in steric bulk of this side chain resulted in a progressive decrease in ground state entropy due to increasing motional restriction of the side chain.

While these results represent good evidence that acetamide side chain motional freedom can contribute significantly to the entropy of activation for carbon−cobalt bond homolysis, they do not permit an estimate of the importance of an individual side chain to the entropic activation of homolysis. To this end, we have attempted the synthesis of a Cbl analog, **1**, in which the *c* side chain is truncated to a methyl group. To our surprise,

(18) This comparison, at 25 °C, may underestimate the increased reactivity of NpCbl as it requires extrapolation of the kinetic data for AdoCbl from much higher temperatures.[7]

(19) In ethylene glycol,[20,21] in which the most precise comparisons are available, a 8.0 kcal reduction in free energy of activation (at 25 °C)[18] is due to a 2.3 kcal reduction in the enthalpy of activation but a 19 cal mol^{-1} K^{-1} increase in entropy of activation (or 5.7 kcal at 25 °C). Thus, 70% of the labilization of Co−C bond homolysis in NpCbl is due to entropic factors.

(20) Hay, B. P.; Finke, R. G. *Polyhedron* **1988**, *7*, 1469.

(21) There is a large and surprising difference in the entropy of activation for NpCbl thermolysis in water[17d] and in ethylene glycol,[16c] given the fact that there is no separation of charge in the transition state so that differential solvent reorganization at the fissile bond as the transition state is approached seems unlikely. The discrepancy could be due to differences in intramolecular hydrogen bonding among the corrin ring side chains in the different solvents (vide infra).[22,2]

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(25) (a) Wayland, B. B.; Gridnev, A. A.; Ittel, S. D.; Fryd, M. *Inorg. Chem.* **1994**, *33*, 3830. (b) Woska, D. C.; Xie, Z. D.; Gridnov, A. A.; Ittel, S. D.; Fryd, M.; Wayland, B. B. *J. Am. Chem. Soc.* **1996**, *118*, 9102.

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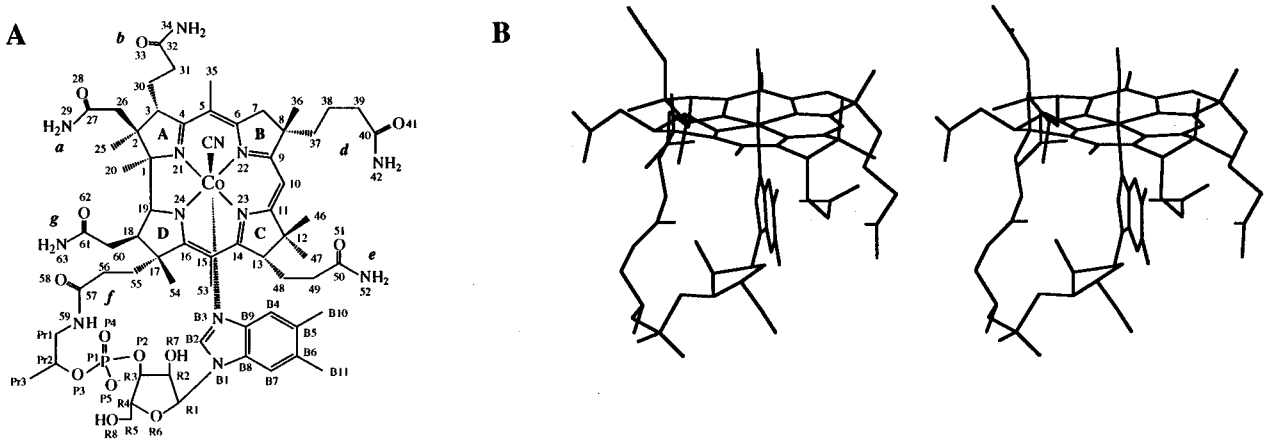
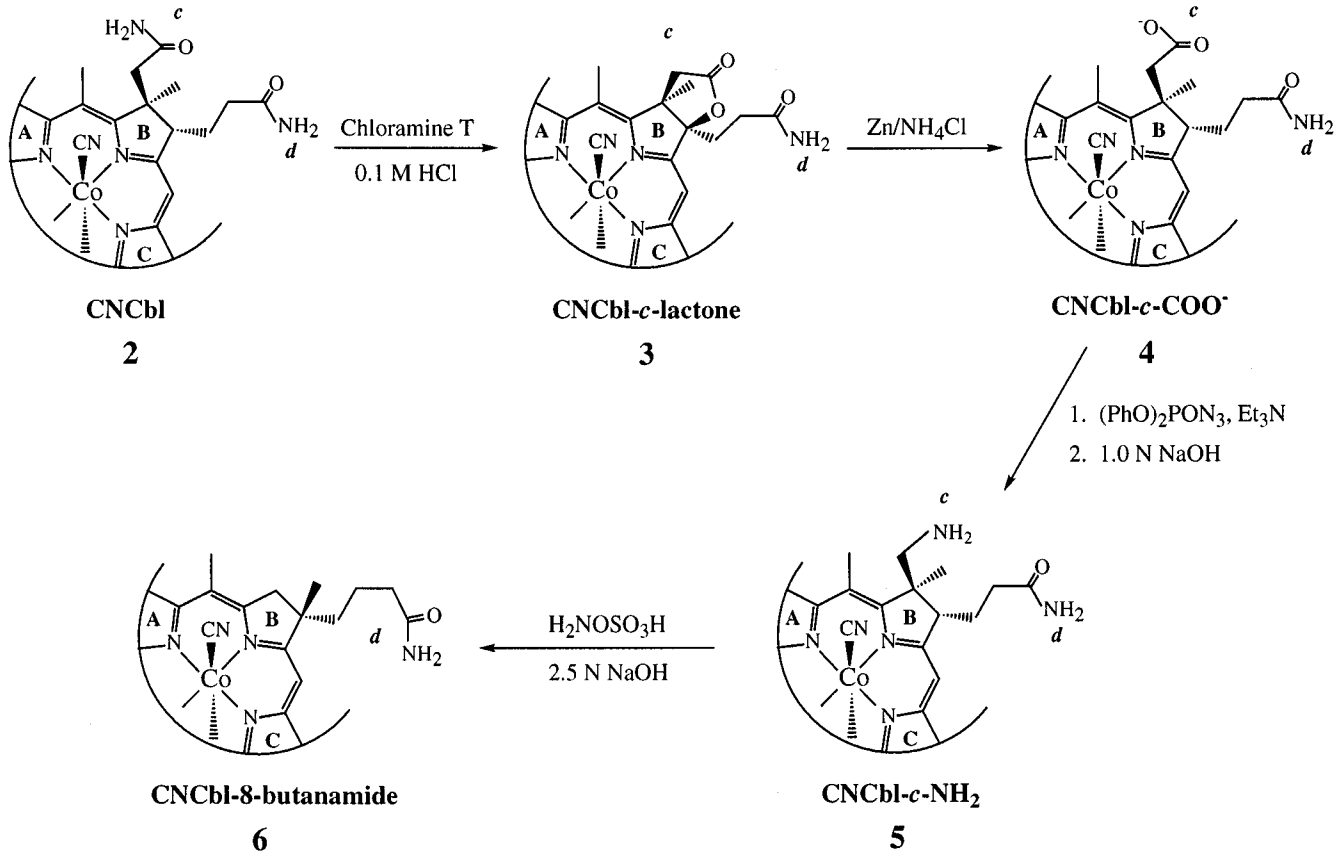
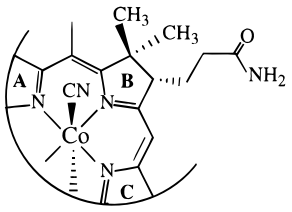


Figure 2. Structural representation (A) and stereo line drawing (B) of CNCbl-8-butanamide, **6**.

Scheme 1



the deamination of the recently reported[27] CNCbl-*c*-NH_2 complex, **5** (Scheme 1), gave instead a novel analog in which



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the C(7) corrin ring carbon is devoid of substituents due to an apparent rearrangement of the B pyrrole and its substituents. The synthesis, characterization, and kinetics of homolysis of the Np derivative of this interesting Cbl analog are the subject of this report.

Experimental Section

Materials. 1-Bromo-2,2-dimethylpropane (neopentyl bromide), chloramine-T hydrate, H-TEMPO,[1] trifluoromethanesulfonic acid, diphenylphosphoryl azide, triethylamine, and hydroxylamine-*O*-sulfonic acid were obtained from Aldrich. CNCbl was from Roussell.

The 8-butanamide derivative of CNCbl, **6** (Figure 2), was obtained from CNCbl as shown in Scheme 1, via CNCbl-*c*-lactone,[28] CNCbl-*c*-COO^-,[17e] and CNCbl-*c*-NH_2[27] as follows. CNCbl-*c*-NH_2 (**5**, 100 mg, 74.5 μmol) was dissolved in 10 mL of 2.5 M NaOH solution at 0 °C.

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To this solution was added 0.5 g of hydroxylamine-*O*-sulfonic acid, and the reaction mixture was stirred at 0 °C for 90 min. The solution was adjusted to pH 5 with 1.0 M HCl and the mixture desalted on a column of Amberlite XAD-2. The product was purified by semi-preparative HPLC[29] (yield 35 mg, 26.7 μmol, 35%). FAB MS (*m*/*z*): calculated for M + H^+, 1313.4; found, 1313.2. The ^{1}H and ^{13}C NMR spectra were unambiguously assigned using 2D homonuclear and heteronuclear NMR methods (correlation table and assignments available as Supporting Information). The ^{1}H, ^{15}N HMQC spectrum (Supporting Information) was assigned by analogy to that of CNCbl.[22a] The cobinamide derivative (lacking the axial nucleotide) of CNCbl-8-butanamide was obtained via the triflic acid hydrolysis method.[30]

The neopentyl derivative of CNCbl-8-butanamide, NpCbl-8-butanamide, was obtained as follows. CNCbl-8-butanamide (50 mg, 38.1 μmol) was dissolved in 30 mL of 10% (w/v) NH_4Cl solution, and the solutions was purged with argon for 2 h, after which it was transferred by cannula to a deaerated flask containing excess zinc wool that had been freshened briefly with 1.0 M HCl, and the reduction to the Co^{II} species was allowed to proceed for 2 h. The solution was then transferred by cannula to a deareated flask containing 60 mg of neopentyl(aquo)cobaloxime[31] in 30 mL of 50% (v/v) CH_3OH/0.01 M HCl solution, and the mixture was photolyzed with a 200 W tungsten lamp for 45 min. The resulting solution was evaporated to a small volume under vacuum and separated by semipreparative HPLC (yield 26 mg, 50%). The cobinamide derivative, Np-Cbi-8-butanamide$^+$, was obtained in 50% yield by reductive alkylation of CNCbi-8-butanamide$^+$ with neopentyl bromide as previously described for other NpCbi$^+$ derivatives.[17e]

Methods. Red crystals of CNCbl-8-butanamide, **6**, were grown by vapor phase diffusion of acetone into an aqueous solution. A specimen, 0.8 × 0.4 × 0.4 mm, was wedged into a 0.5 mm capillary in contact with acetone, and the tube was sealed with paraffin. The crystal was orthorhombic, space group $P2_12_12_1$. A total of 7310 data, of which 6401 were independent, were collected in shells to $\theta = 22.48°$ with a Siemans R3m/V diffractometer (Mo Kα radiation, $\lambda = 0.710\,73$ Å). The structure was solved by direct methods (SHELXS-90[32]) using the data to 1.1 Å resolution. Most non-H atoms were found in the electron density map, and the balance, in several successive difference Fourier maps. An acetone solvate and ordered and disordered water oxygen positions were also located. Positions of the atoms of the complex, the acetone, and nine ordered water oxygens were refined with anisotropic vibrational parameters. Hydrogens were placed in calculated positions (except for waters) and allowed to ride on their attached atoms with fixed isotropic vibrational factors equivalent to 120% of the U_{eq} values of the attached atoms. The absolute configuration was established by refinement of Flack's parameter[33] to −0.02(4). The model converged through least-squares calculations based on F^2 to $R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o| = 0.0554$ (on F for $I > 2\sigma(I)$), $R_{2w} = \{\Sigma[w(F_o^2 - F_c^2)^2]/\Sigma[w(F_o^2)^2]\}^{1/2} = 0.1207$ (on F^2 for all 7310 data).

All work with organocobalt corrinoids was carried out in the dark, with the aid of flashlights. Measurements of pH were made with a Radiometer PHM 84 pH meter and a Radiometer type C combined glass electrode. UV−visible spectra and single-wavelength measurements were obtained on a Cary 219 recording spectrophotometer equipped with a five-cell thermostated sample turret, and temperature was maintained with a Neslab RTE-220 circulating water bath. Corrinoids were quantified by conversion to their dicyano derivatives using $\epsilon_{368} = 3.04 \times 10^4$ M^{-1}.[34] Temperature was measured with a YSI 702A thermistor probe and a Cole Parmer 93-100 thermistor device, calibrated as described previously.[17d]

Samples for aerobic spectrophotometric kinetic measurements (3.0 mL) were prepared in 1.000 cm path length cuvettes and contained NpCbl-8-butanamide, (1.0−2.5) × 10^{-5} M, 0.1 M phosphate buffer, pH 7.5, and KCl to maintain the ionic strength at 1.0 M. NpCbl-8-butanamide stock solutions were stored at −20 °C as the base-off form (pH 3.0) to prevent decomposition. Reactions were initiated and temperature was maintained and measured as described previously, in order to minimize errors associated with temperature inaccuracies.[17d] Four independent kinetic measurements were made at each temperature, observed first-order rate constants, k_{obs}, were obtained by nonlinear least-squares fitting to an exponential function, and the weighted average of k_{obs} at each temperature (calculated as described previously[17d]) was used to determine the activation parameters from Eyring plots.

Samples for kinetic measurements of NpCbl-8-butanamide anaerobic thermolysis in the presence of the radical trap, H-TEMPO, were prepared in a Vacuum Atmospheres glovebox under an atmosphere of argon with O_2 < 2 ppm. Samples containing 1.27 × 10^{-5} M NpCbl-8-butanamide, 1.0 × 10^{-3} M H-TEMPO, 0.1 M phosphate buffer (pH 7.5), and KCl (ionic strength 1.0 M) were sealed in Schlenk cuvettes (path length 1.000 cm), and the reaction was monitored at 358 and 322 nm at 30.0 °C. Thermolysis reaction products were quantitated as the H-TEMPO trapped Np-H-TEMPO (anaerobic thermolysis) or the Schiff's base of pivalaldehyde and aniline (*N*-(2,2-dimethylpropylidene)benzeneamine, aerobic thermolysis) by GC analysis as described previously.[17c,35]

Anaerobic NMR samples of NpCbl-8-butanamide and NpCbi-8-butanamide$^+$ (ca. 20 mM) in "100% D_2O", pD = 8.2 (0.1 M phosphate buffer), ionic strength 1.0 M (KCl), were prepared as described previously.[17d] ^{1}H NMR spectra of these samples were obtained on a GE QE-300 NMR spectrometer with temperature equilibration and measurement as described elsewhere.[17c,d] Homonuclear and heteronuclear NMR spectra (COSY, HOHAHA, ROESY, HMQC, and HMBC) were obtained as described previously[28b] on a Bruker AMX 600 NMR spectrometer.

Results

Synthesis and Characterization of CNCbl-8-butanamide, 6. In order to attempt to evaluate the contribution of *c* side chain motional freedom to the entropy of activation of carbon−cobalt bond cleavage reactions, the *c* side chain-truncated derivative of CNCbl, **1**, became a synthetic target. Because of the ready availability of CNCbl-*c*-COO^-, **4**,[17e] a number of attempts were made to obtain **1** from **4** by decarboxylation including routes via *N*-(acyloxy)phthalimides,[36] benzophenone oxime esters,[37] and thiohydroxamic esters.[38] None of these methods were successful in producing **1**. However, since the amine, **5**, can be obtained from CNCbl-*c*-COO^- via a modified Curtius reaction[39] in reasonable yield,[27] an attempt was made to hydrodeaminate **5** under modified Kollonitsch conditions.[40] Treatment of **5** with hydroxylamine-*O*-sulfonic acid in 2.5 M NaOH afforded in reasonable yield a cobalt corrinoid whose FAB MS parent ion (*m*/*z* = 1313.2) agreed with the formulation of **1** (*m*/*z* = 1313.4). Its ^{1}H, ^{15}N HMQC spectrum (available as Supporting Information) confirmed that this product lacked a *c* amide, but its ^{1}H and ^{13}C NMR spectra could not be

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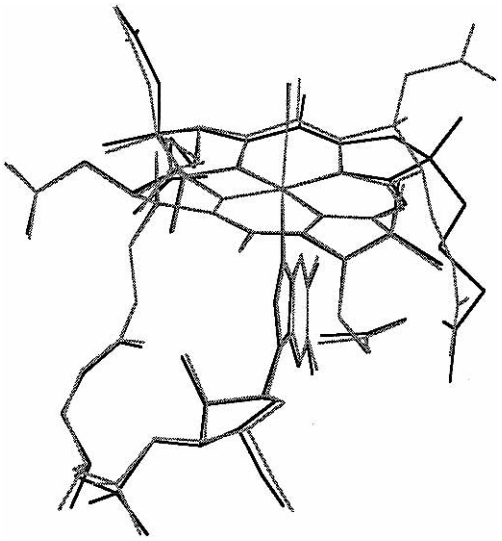


Figure 3. Superposition of CNCbl-8-butanamide (dark lines) with CNCbl (light lines).

Table 1. Crystal Data for CNCbl-8-butanamide, **6**

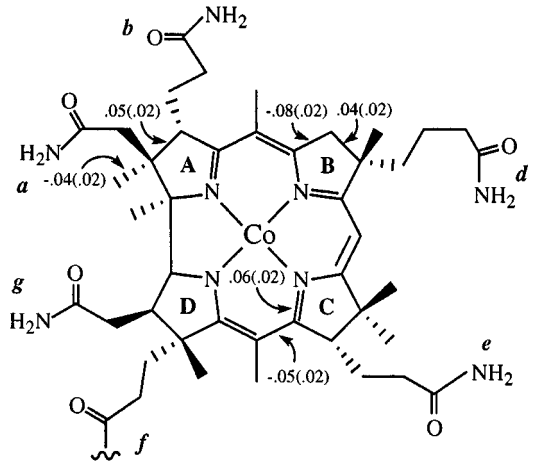
empirical formula	$C_{61}H_{87}N_{12}O_{13}PCo\cdot C_3H_6O\cdot 17H_2O$
fw	1650.68
temperature (K)	295(2)
λ(Mo Kα) (Å)	0.710 73
space group	$P2_12_12_1$
a (Å)	16.041(11)
b (Å)	21.94(2)
c (Å)	25.43 (2)
V (Å^3)	8948(10)
Z	4
crystal size (mm^3)	0.80 × 0.40 × 0.40
D (g cm^{-3})	1.225

reconciled with **1**. As a result, a single-crystal X-ray diffraction study was undertaken to determine the structure of this product.

The complex crystallizes in the orthorhombic system, space group $P2_12_12_1$, with 4 molecules in the unit cell. Crystal data are given in Table 1, atomic coordinates are given in Table 2, and the structure and numbering scheme are shown in Figure 2. The structure is revealed to be an isomer of **1** resulting from a remarkable apparent rearrangement in the B pyrrole ring and its substituents. The resulting complex is devoid of substituents at C(7) but instead has an "upwardly" projecting methyl group at C(8), and its *d* side chain at the same position is expanded from a propionamide to a butanamide. This compound is hereafter referred to as CNCbl-8-butanamide. This structure is completely in accord with the ^{1}H and ^{13}C NMR spectra obtained (available as Supporting Information), the former of which, for instance, shows an isolated spin system readily assignable to the C(37)H$_2$−C(38)H$_2$−C(39)H$_2$ butanamide side chain.

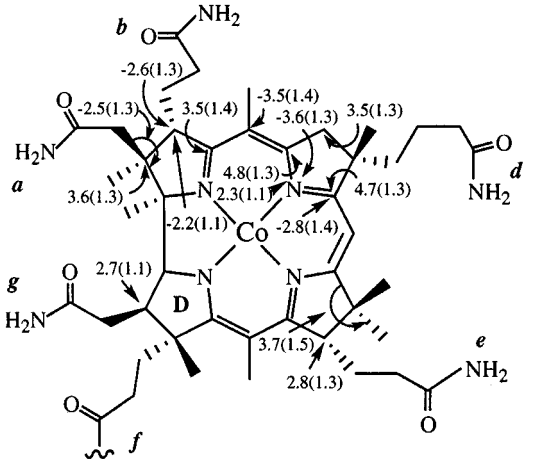
A comparison of the structure of CNCbl-8-butanamide to that of CNCbl itself[41] shows that the inner sphere geometries are nearly identical. The only significant (>2 esd) differences are an elongation of the axial Co-N(23) bond of 0.031 ± 0.013 Å, an increase in the N(24)−Co−N(23) bond angle of 1.2 ± 0.5°, and a decrease in the N(22)−Co−N(23) bond angle of 1.2 ± 0.5° in the 8-butanamide derivative. However, superposition of the two structures (Figure 3) shows that there is a significant difference in the corrin ring conformation most noticeable as a decrease in the corrin fold angle about the Co···C(10) axis. This angle has been defined by Glusker[42] as the angle between the normals to the least-squares planes through N(21), C(4), C(5), C(6), N(22), C(9), and C(10), and through N(24), C(16), C(15), C(14), N(23), C(11), and C(10). In CNCbl, this angle is 18.0°, but it is reduced to 9.9° in CNCbl-8-butanamide.[43]

Structures **7** and **8** show the significant differences between CNCbl-8-butanamide and CNCbl in bond distance and bond angle, respectively, for the corrin ring and its attachments, as



7

$d_{CNCbl\text{-}8\text{-}butanamide} - d_{CNCbl}$



8

$angle_{CNCbl\text{-}8\text{-}butanamide} - angle_{CNCbl}$

the signed difference between the bond length or angle in CNCbl-8-butanamide and in CNCbl (±esd). These comparisons show that, in addition to the geometry changes at the site of the rearrangement in the B pyrrole, there are some significant geometry changes in the corrin nucleus and its substituent atoms quite remote from the site of the structural changes, particularly in the A pyrrole ring. In addition, the bond length differences in the corrin nucleus suggest that the significant flattening of the corrin ring in CNCbl-8-butanamide, indicated by the decrease in the corrin fold angle and clearly evident in Figure 3, is largely due to lengthening of the C(14)−N(23) (0.06 Å)

(41) Kräutler, B.; Konrat, R.; Stupperich, E.; Fäber, G.; Gruber, K.; Kratky, C. *Inorg. Chem.* **1994**, *33*, 4128.

(42) Glusker, J. P. In *B_{12}*; Dolphin, D., Ed.; Wiley-Interscience: New York, 1982; Vol. 1 p 23.

(43) For CNCbl-8-butanamide, the rms deviation for the plane including N(21) and N(22) (the "northern" plane) is 0.034 Å and the rms deviation for the plane including N(23) and N(24) (the "southern" plane) is 0.043 Å. The range of observed values for the corrin ring fold angle is 1.9−23.8°.[42,44]

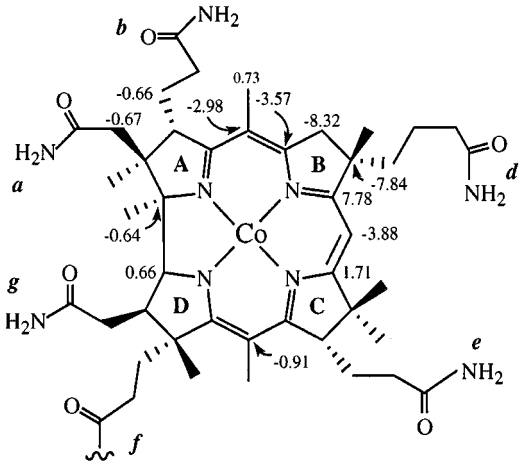
(44) Brown, K. L.; Evans, D. R.; Zubkowski, J. D.; Valente, E. J. *Inorg. Chem.* **1996**, *35*, 415.

Table 2. Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for CNCbl-8-butanamide (**6**), Where *U*(eq) Is Defined as One-Third of the Trace of the Orthogonalaized $\mathbf{U}_{ij}$ Tensor

atom	*x*/*a*	*y*/*b*	*z*/*c*	*U*(eq)	atom	*x*/*a*	*y*/*b*	*z*/*c*	*U*(eq)
Co	7456(1)	5808(1)	7506(1)	35(1)	C(16)	6535(6)	6968(4)	7495(5)	33(3)
C(64)	7620(7)	5962(5)	8214(5)	44(3)	C(17)	6729(6)	7659(4)	7481(5)	37(3)
N(65)	7727(7)	6080(5)	8654(4)	79(4)	C(18)	7647(6)	7658(4)	7252(4)	31(3)
P	5011(3)	7641(2)	4648(1)	57(1)	C(19)	7975(5)	7037(4)	7450(5)	39(3)
O(2P)	5291(5)	7311(4)	5181(3)	61(3)	C(20)	8507(6)	6717(4)	6548(4)	38(3)
O(3P)	4869(5)	8301(4)	4871(3)	53(2)	N(21)	8544(5)	6051(3)	7338(3)	29(2)
O(4P)	5723(6)	7670(4)	4284(3)	88(3)	N(22)	7822(5)	5000(4)	7635(3)	44(3)
O(5P)	4241(5)	7363(4)	4456(3)	72(3)	N(23)	6302(5)	5649(4)	7642(3)	34(2)
O(6R)	5118(5)	5891(4)	5843(3)	63(2)	N(24)	7229(5)	6640(4)	7429(4)	40(2)
O(7R)	6536(5)	6775(3)	5771(3)	55(2)	C(25)	10047(7)	7301(5)	6954(4)	48(3)
O(8R)	3937(9)	5801(6)	5047(5)	161(5)	C(26)	9657(7)	7039(5)	7877(4)	48(3)
C(1R)	5909(7)	5809(5)	5613(4)	47(3)	C(27)	10552(9)	7159(6)	8080(5)	56(4)
C(2R)	6168(7)	6434(5)	5367(4)	44(3)	O(28)	11187(6)	6921(4)	7934(4)	87(3)
C(3R)	5299(7)	6672(5)	5205(5)	50(4)	N(29)	10543(6)	7598(5)	8456(4)	82(4)
C(4R)	4720(7)	6429(5)	5616(5)	48(3)	C(30)	10339(7)	5968(5)	6695(5)	58(4)
C(5R)	3859(9)	6242(7)	5465(7)	105(6)	C(31)	11271(7)	6008(7)	6632(5)	84(5)
N(1B)	6488(6)	5589(4)	5998(4)	41(3)	C(32)	11533(9)	5714(8)	6095(6)	69(4)
C(2B)	6555(7)	5791(5)	6495(4)	38(3)	O(33)	11752(8)	5201(5)	6058(5)	138(5)
N(3B)	7228(5)	5595(4)	6738(3)	38(2)	N(34)	11468(8)	6081(6)	5713(5)	111(5)
C(4B)	8399(7)	4927(4)	6382(4)	42(3)	C(35)	10209(6)	4882(5)	7641(5)	57(4)
C(5B)	8684(7)	4617(5)	5925(5)	50(3)	C(36)	7641(8)	3739(5)	8441(5)	83(4)
C(6B)	8201(8)	4606(5)	5476(5)	53(4)	C(37)	7485(9)	3423(4)	7521(6)	69(3)
C(7B)	7469(9)	4912(5)	5457(4)	54(3)	C(38)	7504(10)	3529(5)	6952(5)	75(4)
C(8B)	7215(6)	5234(4)	5895(5)	38(3)	C(39)	7187(9)	2982(7)	6631(6)	90(5)
C(9B)	7665(6)	5239(4)	6361(4)	31(3)	C(40)	7373(10)	3046(7)	6053(7)	78(5)
C(10B)	9495(7)	4278(6)	5948(5)	74(4)	O(41)	8098(7)	2993(6)	5885(4)	111(4)
C(11B)	8494(8)	4294(6)	5002(5)	82(5)	N(42)	6731(10)	3138(7)	5723(6)	150(6)
C(1P)	4649(7)	8807(5)	5674(5)	60(4)	C(46)	5082(9)	5233(6)	8535(6)	123(7)
C(2P)	4247(8)	8422(6)	5240(5)	64(4)	C(47)	4560(8)	4585(5)	7813(7)	122(8)
C(3P)	3503(8)	8768(6)	4992(5)	78(4)	C(48)	4398(6)	5740(5)	7159(4)	53(3)
C(1)	8660(6)	6695(5)	7146(4)	32(3)	C(49)	3493(7)	5562(5)	7109(5)	69(4)
C(2)	9631(7)	6836(6)	7288(4)	44(3)	C(50)	2937(7)	5864(7)	7514(7)	64(4)
C(3)	10002(7)	6166(4)	7241(4)	38(3)	O(51)	2612(7)	5536(4)	7829(4)	90(3)
C(4)	9258(6)	5796(5)	7405(4)	35(3)	N(52)	2806(5)	6461(4)	7480(5)	68(3)
C(5)	9328(6)	5160(5)	7580(4)	45(3)	C(53)	4958(6)	7080(4)	7644(4)	44(3)
C(6)	8659(7)	4791(5)	7661(5)	43(4)	C(54)	6740(7)	7870(5)	8055(4)	43(3)
C(7)	8705(7)	4137(5)	7788(5)	58(3)	C(55)	6136(7)	8048(4)	7158(4)	37(3)
C(8)	7771(7)	3939(5)	7884(5)	52(4)	C(56)	5923(7)	7836(5)	6602(4)	51(3)
C(9)	7329(7)	4532(5)	7759(5)	50(3)	C(57)	5179(8)	8169(6)	6362(5)	50(3)
C(10)	6469(8)	4582(5)	7813(5)	53(4)	O(58)	4506(6)	8131(4)	6584(4)	80(3)
C(11)	6008(7)	5098(5)	7778(4)	42(3)	N(59)	5302(7)	8498(5)	5942(4)	63(3)
C(12)	5091(7)	5148(6)	7932(5)	60(4)	C(60)	8176(6)	8205(5)	7381(5)	61(4)
C(13)	4827(6)	5754(5)	7686(4)	45(3)	C(61)	7913(8)	8790(7)	7112(6)	58(4)
C(14)	5644(6)	6083(5)	7646(4)	38(3)	O(62)	7815(6)	8802(4)	6636(4)	88(3)
C(15)	5735(6)	6686(4)	7588(5)	35(3)	N(63)	7813(5)	9269(4)	7403(5)	76(4)

and C(7)−C(8) (0.04 Å) bonds. The only other bonds involved in the planes used to define the corrin fold angle which are significantly altered, C(6)−C(7) and C(14)−C(15), are both shortened in the 8-butanamide and cannot therefore contribute to the flattening of the corrin.

While it is reasonably easy to envision how geometry changes in the B pyrrole might engender significant romote changes in geometry elsewhere in the corrin nucleus itself, it is more difficult to see how substituent atoms, such as C(26) and C(30), might be affected by a remote mechanism. This suggests that such peripheral changes might be due to differences in crystal packing forces. However, as seen in structure **9**, which shows the significant differences in ^{13}C chemical shifts as the signed difference between the 8-butanamide and CNCbl, significant differences in ^{13}C chemical shift at C(26) and C(30) suggest that geometry differences involving these atoms persist in solution. In addition, the ^{13}C NMR differences shown in **9** reveal a clear correlation between geometry changes (**7** and **8**) and chemical shift changes at sites remote from the area of structural change, suggesting that chemical shifts of these carbons are largely determined by conformation in the corrin ring.



9

$\delta_{^{13}C(CNCbl\text{-}8\text{-}butanamide)} - \delta_{^{13}C(CNCbl)}$

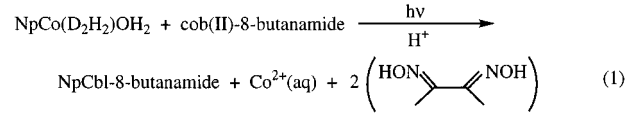
Thermolysis of NpCbl-8-butanamide. For reasons which remain unclear, the neopentyl derivative of **6**, NpCbl-8-butanamide, could not be obtained in good yield by the usual oxidative addition of neopentyl bromide to reduced CNCbl-8-butanamide.[16c,17] However, this derivative was obtained in adequate yield by photolysis of neopentyl(aquo)cobaloxime in

Table 3. Rate Constants for the Thermolysis and Equilibrium Constants for the Base-Off/base-On Reaction of NpCbl-8-butanamide in Aqueous Solution[a]

	T (°C)	k_{obs} (s^{-1})[b]	K_{meas}[c]	k_{on} (s^{-1})[d]
	14.9	$(2.16 \pm 0.06) \times 10^{-5}$	4.825 ± 0.026	$(2.61 \pm 0.07) \times 10^{-5}$
	20.3	$(5.26 \pm 0.12) \times 10^{-5}$	4.492 ± 0.019	$(6.44 \pm 0.16) \times 10^{-5}$
	25.1	$(1.08 \pm 0.03) \times 10^{-4}$	4.225 ± 0.013	$(1.34 \pm 0.04) \times 10^{-4}$
	30.0	$(2.24 \pm 0.02) \times 10^{-4}$	3.977 ± 0.011	$(2.80 \pm 0.03) \times 10^{-4}$
	30.0	$(2.17 \pm 0.02) \times 10^{-4}$ [e]		
	35.1	$(4.71 \pm 0.07) \times 10^{-4}$	3.742 ± 0.008	$(5.97 \pm 0.09) \times 10^{-4}$
	40.0	$(9.10 \pm 0.34) \times 10^{-4}$	3.535 ± 0.006	$(1.17 \pm 0.04) \times 10^{-3}$
	44.9	$(1.81 \pm 0.03) \times 10^{-3}$	3.346 ± 0.005	$(2.36 \pm 0.03) \times 10^{-3}$
$\Delta H^{\ddagger}$, (kcal mol^{-1})		26.1 ± 0.1		26.7 ± 0.1
$\Delta S^{\ddagger}$, (cal mol^{-1} K^{-1})		11.0 ± 0.3		13.2 ± 0.2

[a] At pH 7.5 (0.1 M phosphate buffer), ionic strength 1.0 M (KCl). [b] Weighted average of four determinations at each temperature in aerobic solution, except as noted. [c] Measured equilibrium constant for conversion of the base-off to the base-on species at pH 7.5. See text. [d] Rate constant for thermolysis of the base-on species after correcting for the presence of the base-off species at pH 7.5. [e] Under anaerobic conditions in the presence of 1.0×10^{-3} M H-TEMPO.

the presence of the cobalt(II)−8-butanamide complex in dilute acid. Under these conditions, photolytic transfer of the neopentyl radical to the corrinoid is favored by the fact that the photolysis product of neopentyl(aquo)cobaloxime, diaquocobalt(II) cobaloxime, is unstable in acid, decomposing to Co^{2+}(aq) and protonated dimethylglyoxime (eq 1).[6b,45,46] The identity of

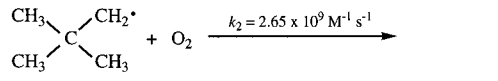


(1)

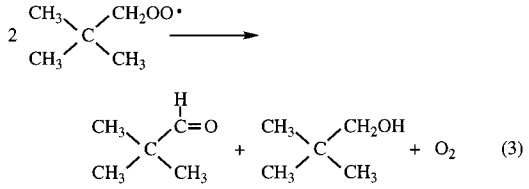
the NpCbl-8-butanamide product, which is not amenable to NMR characterization,[17c,d] is confirmed by quantitative analysis of its thermolysis products (vide infra).

Neopentylcobalt corrinoids are well-known to thermolyze homolytically, to produce a Np• radical and a cobalt(II) product.[11,15,16c,17,35] Because both a β-heteroatom[6,47−50] and β-hydrogens[51,52] are lacking in the organic ligand, homolytic carbon−cobalt bond scission is the only pathway available for decomposition.[53] Under aerobic conditions, the neopentyl radical rapidly reacts with oxygen ($k = 2.65 \times 10^9$ M^{-1} s^{-1})[54] to form the neopentylperoxy radical, which undergoes disproportionation to pivalaldehyde and neopentyl alcohol (eqs 2 and 3). As described previously,[17c,35] the aldehyde product resulting from aerobic thermolysis of NpCbl derivatives may be trapped as its Schiff's base with aniline (*N*-(2,2-dimethylpropylidene)benzeneamine) and quantified by GC. The yield of pivalaldehyde from aerobic NpCbl-8-butanamide thermolysis at 30 °C was found to be 44 ± 3%, in accord with the stoichiometry of eqs 2 and 3.

Under anaerobic conditions, the neopentyl radical may be rapidly trapped with an excess of the nitroxide trap H-TEMPO

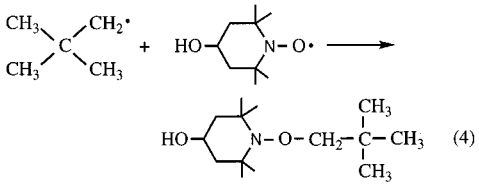


(2)



(3)

(eq 4).[16c,17c,d,35] Thermal decomposition of NpCbl-8-butanamide



(4)

anaerobically in the presence of 1 mM H-TEMPO at 30 °C was found to produce Np-H-TEMPO in 97 ± 4% yield. We conclude from these experiments that the organocobalt corrinoid resulting from photolysis of neopentyl(aquo)cobaloxime in the presence of cobalt(II) Cbl-8-butanamide in dilute acid is indeed NpCbl-8-butanamide and that the latter complex undergoes thermolysis homolytically to produce the neopentyl radical.

Thermolysis of NpCbl-8-butanamide was most conveniently monitored spectrophotometrically under aerobic conditions at the wavelengths of maximal absorbance change (258 and 322 nm). Reactions were run in quadruplicate at each of seven temperatures from 15 to 45 °C, and the weighted average of the observed rate constant at each temperature was used as the best estimate of k_{obs}. The results are shown in Table 3. An Eyring plot (Figure 4) gave the observed activation parameters, $\Delta H^{\ddagger}_{obs} = 26.1 \pm 0.1$ kcal mol^{-1} and $\Delta S^{\ddagger}_{obs} = 11.0 \pm 0.3$ cal mol^{-1} K^{-1}.

In order to determine if dissolved oxygen in these reaction mixtures functions as a kinetically competent trap for the Np• radical, reacting sufficiently fast with Np• to prevent back-reaction to NpCbl-8-butanamide, thermolysis kinetics were also studied anaerobically at 30 °C in the presence of 1.0×10^{-3} M H-TEMPO. This condition is known to provide kinetically competent trapping of Np•.[16c,17c,e] The rate constant obtained, $(2.17 \pm 0.02) \times 10^{-4}$ s^{-1}, is essentially identical to that observed aerobically at the same temperature ($(2.24 \pm 0.02) \times 10^{-4}$ s^{-1}).

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(53) Although organocobalt reagents with β-hydrogens can decompose to give products of apparent β-elimination origin, it is now clear that the proximal event in thermolysis of such species is homolytic Co−C bond dissociation.[51,52]
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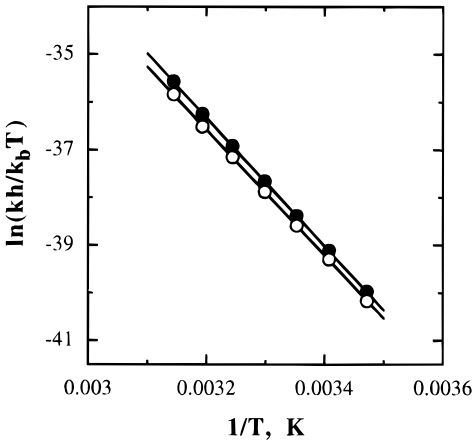

Figure 4. Eyring plots of k_{obs} (open symbols) and k_{on} (solid symbols) for the thermolysis of NpCbl-8-butanamide, where h is Planck's constant and k_b is Boltzmann's constant. The solid lines are linear-least squares regressions: k_{obs}, slope = −13 160 ± 48 K, intercept = 5.53 ± 0.16, r^2 = 0.999; k_{on}, slope = −13 430 ± 28 K, intercept = 6.64 ± 0.09, r^2 = 0.999.

Thus, as is the case for other NpCbl analogs, dissolved O_2 functions as a kinetically competent trap for carbon−cobalt bond homolysis in NpCbl-8-butanamide.

Cobalamins are well-known to undergo axial nucleotide detachment and protonation in acidic solution (the base-on/base-off reaction).[47,55−58] For NpCbl and its derivatives,[11b,15,16c,17] it is clear that the base-off species is a significant contributor even at neutral pH where the axial ligand is unprotonated.[58b] In addition, it is well-known that the base-off species of NpCbl and its derivatives is 2−3 orders of magnitude less reactive for carbon−cobalt bond thermolysis than the base-on species.[11b,16c,17a,c,e] Consequently, the reactivity of the base-off species can be neglected and the rate constant for thermolysis of the base-on species, k_{on}, can be calculated directly from the observed rate constant, k_{obs}, provided that accurate estimates of the equilibrium constant (K_{meas} = [base-on]/base-off]) for the base-on/base-off reaction in neutral solution are available.[16c,17a,c−e]

We have used the now standard NMR method[16c,17c−e] to determine the enthalpy (ΔH_{meas}) and entropy (ΔS_{meas}) changes associated with the base-off/base-on equilibrium of NpCbl-8-butanamide. This method is based on the sensitivity of the corrin ring C(10) hydrogen of cobalamins to axial ligand substitution.[59,60] Since the enthalpy of formation of the base-on species of RCbl's is negative,[26,58a,c] the base-off species is favored as temperature is increased. Thus, the ^{1}H NMR resonance of the C(10) hydrogen of an RCbl shifts increasingly toward the value of the C(10) hydrogen chemical shift of the analogous RCbi$^+$ (as a model of the base-off species) as the temperature increases. Consequently, temperature-dependent measurements of the relative chemical shift of the C(10) hydrogen of an RCbl and its RCbi$^+$ partner permit evaluation of the position of the base-on/base-off equilibrium and its thermodynamic parameters.

In the absence of a free radical trap, NpCbl and its derivatives are indefinitely stable toward thermolysis. As a result, the chemical shift of the C(10) hydrogen of Np-Cbl-8-butanamide was determined relative to that of Np-Cbi-8-butanamide$^+$ in sealed NMR tubes under anaerobic conditions at 19 precisely measured temperatures from 9 to 60 °C. The data were analyzed as described in detail elsewhere[17c−e] to provide the values ΔH_{meas} = −2.22 ± 0.22 kcal mol^{-1} and ΔS_{meas} = −4.58 ± 0.47 cal mol^{-1} K^{-1}. These data were used to calculate the values of K_{meas} at the temperatures at which kinetic measurements of NpCbl-8-butanamide were made (Table 3). Using these values of K_{meas} and the observed thermolysis rate constants, rate constants for the thermolysis of the base-on species, k_{on}, were calculated (Table 3) and used to determine the activation parameters for thermolysis of the base-on species via an Eyring plot (Figure 4). The values obtained were $\Delta H^{\ddagger}_{on}$ = 26.7 ± 0.1 kcal mol^{-1} and $\Delta S^{\ddagger}_{on}$ = 13.2 ± 0.2 cal mol^{-1} K^{-1}.

Discussion

The failure to obtain the *c* side chain-truncated analog of CNCbl, **1**, by decarboxylation of CNCbl-*c*-COO$^-$ (**4**) prompted us to attempt the hydrodeamination of the *c*-amino derivative, **5**. Treatment of **5** with hydroxylamine-*O*-sulfonic acid in base readily removed the amino group but, to our surprise, led to the extensively rearranged product, **6**, instead of the expected product of simple deamination, **1**. If we assume that treatment of **5** with hydroxylamine-*O*-sulfonate leads initially to the proximal radical, **10** (Scheme 2), presumably via hydrazine[61] and diazene[62] intermediates, then a plausible rearrangement route to CNCbl-8-butanamide can be suggested (Scheme 2). There is ample precedent for the rapid rearrangement of methylenecyclopentyl radicals to methylenecyclohexyl radicals via cyclopropyl intermediates both in carbocyclic[63−65] and in oxygen heterocyclic[64] systems. Here, the macrocycle may facilitate the rearrangement by providing stabilization of the intermediate cyclopropyl radical by vinylogous delocalization of the unpaired electron density onto the neighboring pyrrole nitrogen, as suggested in Scheme 2 by the tautomer shown for radical **11**.

Attempts were made to intercept the proximal radical, **10**, with 2,2-dimethylpropanethiol, but these were unsuccessful. This is not surprising considering the estimated unimolecular rate constant (∼2 × 10^5 s^{-1})[64] for the **10** → **11** insertion and the fact that the transition state for this reaction may be significantly stabilized by delocalization. The stereochemistry observed at C(8) of the rearranged product, **6**, is accounted for by this mechanism as the individual insertion and ring-opening steps must occur with the indicated stereochemistry. The inability of 2,2-dimethylpropanethiol to quench the proximal radical despite the fact that it would be expected to react with a second-order rate constant of about 1 × 10^7 M^{-1} s^{-1} [66] suggests that

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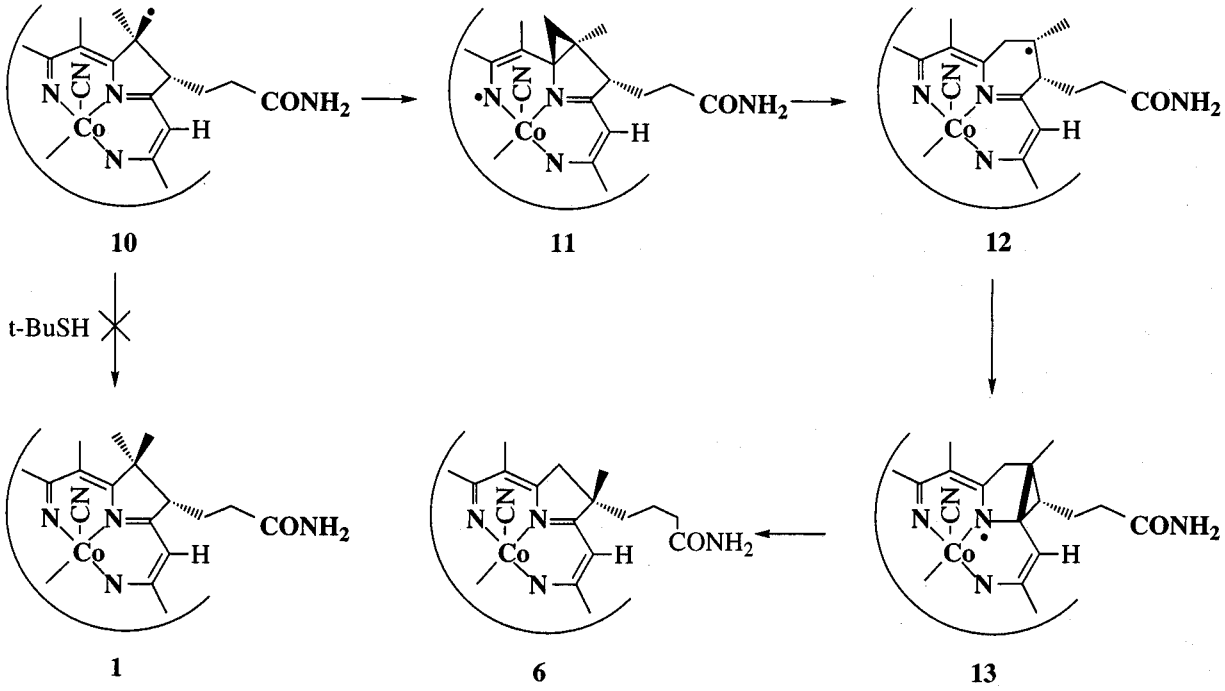
Scheme 2



formation of the cyclopropyl intermediate, **11**, may be very fast indeed, and it may consequently be impossible to obtain **1** by any route including the methylene radical, **10**.

Nonetheless, the 8-butanamide derivative, **6**, provides the needed opportunity to quantify the importance of the *c* side chain to the entropy of activation for carbon−cobalt bond homolysis since it lacks a *c* side chain and is, in fact, devoid of substituents at C(7). Our earlier work on analogs of NpCbl structurally modified in the *c* side chain[17e] strongly suggests that restrictions of *c* side chain thermal mobility by steric interactions with the bulky organic ligand contribute significantly to the entropic activation of carbon−cobalt bond cleavage. The question has been just how important a single side chain is in determining the net entropy of activation. The 8-butanamide analog now allows us to address this question for the *c* acetamide side chain.

While the origin of the difficulties encountered in synthesizing the neopentyl derivative of CNCbl-8-butanamide by standard oxidative addition methodology remains unclear, ample amounts of this complex can be obtained by trapping the Np• radical derived from photolysis of neopentylcobaloxime with 8-butanamidocob(II)alamin. As anticipated, NpCbl-8-butanamide undergoes thermolysis strictly via carbon−cobalt bond homolysis, as evidenced by the measured yields of Np-H-TEMPO from H-TEMPO-trapped anaerobic thermolysis and of pivalaldehyde (analyzed as its Schiff's base with aniline) from aerobic thermolysis. Furthermore, as was the case with NpCbl itself and other NpCbl analogs (including the *c* side chain-altered analogs and the 13-epi and 8-epi analogs),[17] dissolved oxygen in aerobic aqueous solution proved kinetically competent for trapping of Np• radicals produced by thermolysis.

In our study of the *c* side chain-modified analogs NpCbl-*c*-COX,[17e] molecular mechanics calculations showed that the Co−C bond length and Co−C−C bond angle were independent of the nature and size of the side chain substituent, X, and unaffected by rotation of the *c* side chain about the C(7)−C(37) bond.[67] In addition, and as anticipated from the molecular mechanics results,[69] the enthalpy of activation for carbon−cobalt bond homolysis was found to be independent of the *c* side chain substituent with an average value of $\Delta H^{\ddagger}_{on} = 28.4 \pm 1.1$ kcal mol^{-1}.[17e,70] For the new NpCbl-8-butanamide derivative, the enthalpy of activation is slightly lower at 26.7 ± 0.1 kcal mol^{-1}, a difference of 1.7 ± 1.1 kcal mol^{-1}. The origin of this slight (6 ± 4%) reduction and its significance to understanding the factors which control the energetics of carbon−cobalt bond homolysis in NpCbl are unclear. However, the effect of the structural modifications in the current NpCbl-8-butanamide derivative on the entropy of activation is much larger, the observed value (13.2 ± 0.2 cal mol^{-1} K^{-1}) being 6.1 ± 0.6 cal mol^{-1} K^{-1} lower than that for NpCbl itself ($\Delta S^{\ddagger}_{on} = 19.3 \pm 0.6$ cal mol^{-1} K^{-1}).[17d] Thus, the absence of a *c* side chain decreases the entropy of activation for NpCbl homolysis by 32 ± 3%. We conclude that approximately one-third of the entropic driving force for carbon−cobalt bond homolysis in NpCbl is due to steric restriction of *c* side chain thermal motion in the ground state, assuming that any secondary effects of the missing *c* side chain on the entropy of activation are negligible.

Carbon−cobalt bond homolyses are well-known to be at least partly under diffusion control, and solvent cage effects can be important determinants of observed reactivities.[6,16c,20,25,52,71] The observed enthalpy and entropy of activation for diffusion-controlled reactions can both be substantially altered from intrinsic values by solvent cage effects when cage efficiencies are large.[71a] Garr and Finke[52] have shown that such cage effects can be quite large indeed for alkylcobalt corrinoid homolysis in ethylene glycol. However, recent work in aqueous solution has shown quite small cage efficiencies for such species in this

(67) The average values for all five NpCbl analogs and all rotations of the *c* side chain were 2.068 ± 0.002 Å and $132.0 \pm 0.5°$, compared to the observed Co−C bond length and Co−C−C bond angle in neopentyl(pyridine)cobaloxime[68] of 2.060 ± 0.006 Å and $130.3 \pm 0.4°$.

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(70) For NpCbl itself, the measured value of $\Delta H^{\ddagger}_{on}$ is 28.3 ± 0.2 kcal mol^{-1}.[17d]

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medium.[73b] In addition, since the rate of diffusional separation of a caged {Np•, cob(II)alamin} radical pair and a caged {Np•, 8-butanamidocob(II)alamin} radical pair would not be expected to be significantly different, differential solvent cage effects for NpCbl and NpCbl-8-butanamide thermolysis cannot be expected to be significant. We conclude that the difference in the observed values of $\Delta S^{\ddagger}_{on}$ for NpCbl and NpCbl-8-butanamide thermolysis are unlikely to be due to differences in solvent cage effects but instead most likely represent the influence of the *c* side chain on the entropic course of the reaction.

The large contribution ($32 \pm 3\%$) to the entropy of activation of NpCbl thermolysis from *c* side chain thermal mobility revealed here suggests that the majority of the entropic driving force for carbon−cobalt bond homolysis may come from the steric restriction of acetamide side chain mobility, at least for NpCbl. Under the simplest of assumptions, i.e., that all three acetamide side chains contribute the same amount of positional entropy to the ground state, virtually all of the entropy of activation for NpCbl thermolysis would be attributable to this mechanism. However, this is unlikely to be the case since the *g* acetamide is known from X-ray crystal structure determinations of Cbl's to be pseudoequatorial as opposed to the *a* and *c* acetamides which are "upwardly" pseudoaxial.[42] As a result, the *g* side chain points further away from the organic ligand and would be expected to experience less restriction of its thermal motion by steric interaction with the organic ligand. Recent molecular mechanics calculations on AdoCbl[8] bear this out. Here, the strain energy barriers for rotation of the *g* side chain past the Ado ligand are found to be significantly smaller than those for the *a* and *c* side chains, suggesting that *g* side chain motions are indeed less hindered by steric contact with the organic ligand. However, the strain energy barriers for *a* side chain rotation are comparable to those for the *c* side chain, and so the contribution of the *a* side chain to the entropic activation of carbon−cobalt bond homolysis is expected to be quite significant. Thus, despite the fact that the lack of a synthetic entre to the *a* and *g* side chains[17e] precludes a quantitation of their contributions to the activation entropy for carbon−cobalt homolysis, it seems clear that acetamide side chain thermal motions dominate the entropic activation of carbon−cobalt bond homolysis, at least for NpCbl. Whether or not the AdoCbl-dependent enzymes manipulate acetamide side chain motions to catalyze carbon−cobalt bond cleavage is, of course, unknown. Possible mechanisms whereby these enzymes might accomplish such catalysis have been discussed elsewhere.[17c]

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Supporting Information Available: Additional structural diagrams and tables of crystal data and structure refinement details, anisotropic temperature factors, bond angles and bond lengths between adjacent non-hydrogen atoms, all atomic coordinates and isotropic thermal parameters torsion angles, ^{1}H and ^{13}C NMR assignments, NMR correlations, and amide ^{1}H and ^{15}N NMR assignments for CNCbl-8-butanamide (38 pages). Ordering information is given on any current masthead page.

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