Site-Selective Oxidative N-Dealkylation in a Cobalt(III) Polyamine Hydrolytic Agent

Antonia M. Calafat and Luigi G. Marzilli*

Department of Chemistry, Emory University, Atlanta, Georgia 30322

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Site-selective and quantitative C–N bond cleavage occurs at one of the C–N(tertiary) bonds of half the $[Co^{III}(trpn)(H_2O)_2]^{3+}$ complex (trpn = tris(3-aminopropyl)amine) dissolved in D_2O under acidic conditions. The cleavage leads to 100% consumption of $[Co(trpn)(H_2O)_2]^{3+}$ and 100% formation of Co^{2+} quantified by assessing solution paramagnetism with *t*-BuOH (*tert*-butyl alcohol) as an internal and external ^1H NMR standard as well as by direct measurement with optical spectroscopy. In contrast, the analogous tren complex (tren = tris(2-aminoethyl)amine) does not exhibit C–N bond cleavage. The major organic products produced by $[Co(trpn)(H_2O)_2]^{3+}$, trpn and bpn (3,3'-iminobis(propylamine)), formed in a 1:1 ratio, were identified and characterized using ^1H NMR spectroscopy as well as modern 2D NMR methods (COSY, HOHAHA, HMBC, HMQC). bpn was presumably formed by an oxidative N-dealkylation of half the trpn at the tertiary amine, since an essentially identical ^1H NMR spectrum was obtained on treatment of trpn with 1 equiv of Br_2. This oxidant is known to cleave C–N bonds by oxidative N-dealkylation. In addition, two identifiable minor byproducts were formed in the two types of trpn N-dealkylation reactions. The major byproduct was unstable but was identified as the hydrated form of β-aminopropionaldehyde, the metabolite of spermine produced by mammalian polyamine oxidases. Also formed was β-alanine, an oxidation product of β-aminopropionaldehyde. Furthermore, Br_2 accelerated the C–N cleavage reaction for $[Co(trpn)(H_2O)_2]^{3+}$, but even under these conditions $[Co(tren)(H_2O)_2]^{3+}$ was stable. The tren ligand was readily cleaved by Br_2 to form initially diethylenetriamine and hydrated aminoacetaldehyde; these products were eventually oxidized to ethylenediamine and glycine. Co^{III} coordination does not prevent trpn oxidation by Br_2 but does prevent such oxidation of tren. We speculate that an intramolecular one-electron oxidation of the tertiary N of coordinated trpn by Co^{III} initiates the oxidation process. Ironically, factors that favor hydrolytic efficiency in Co(III) polyamine complexes produce electron-deficient Co^{III} centers; such centers facilitate the initial electron transfer and hence oxidative N-dealkylation.

Introduction

In recent years extensive effort has been devoted to facilitating the hydrolysis of phosphate esters because of the utility of phosphodiester hydrolysis in probing DNA and RNA sequences and structure.[1] One of the most effective agents promoting phosphodiester hydrolysis is the complex $[Co(trpn)(H_2O)_2]^{3+}$ (trpn = tris(3-aminopropyl)amine) (Chart I).[2] However, when we examined the potential application of this complex for the phosphodiester hydrolysis of two true biological substrates, namely cyanocobalamin (vitamin B_{12}) and aquocobalamin, we found it decomposed, releasing some free trpn ligand and Co^{2+} under reasonable initial reaction conditions (pH 5–7, temperature 20–45 °C).[3] The decomposition was not clean, and the released trpn raised the pD. Therefore several questions were unanswered: If Co^{2+} is formed by a redox reaction, what are the reducing agent(s) and the oxidized product(s)? The identification of the decomposition products could be useful in determining the reductant as well as a possible mechanism for the "deligation" process. The instability of $[Co(trpn)(H_2O)_2]^{3+}$ was also observed during studies

Chart I
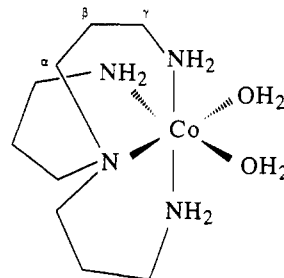
of the hydrolysis of acetonitrile to acetamide[4] and was attributed to an amide-promoted deligation of the trpn in the Co^{III}–amine complex. Recently, deligation of trpn has been reported in an attempt to hydrolyze dimethyl phosphate with $[Co(trpn)(H_2O)_2]^{3+}$.[5]

We report the discovery that under acidic conditions $[Co(trpn)(H_2O)_2]^{3+}$ completely converts into Co^{2+} and organic byproducts. Identification by 1D and 2D NMR techniques of the major organic byproducts as trpn and bpn (3,3'-iminobis(propylamine)) demonstrates site-selective cleavage at the C–N(tertiary) bond of half the coordinated trpn. The observation of site-selective cleavage of C–N bonds of coordinated polyamines[6,7] and tertiary amines[8] is rare. The products observed for a Co(III) spermine complex are those found in spermine metabolism involving amine oxidases of higher plants.[6]

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Experimental Section

The synthesis and analytical data of $[Co(trpn)(H_2O)_2](ClO_4)_3$ have been reported.[3] $[Co(tren)(H_2O)_2](ClO_4)_3 \cdot 3H_2O$ (tren = tris(2-aminoethyl)amine) was synthesized according to reported procedures.[9] Anal. Calcd for $C_6H_{28}Cl_3CoN_4O_{17}$: C, 12.14; H, 4.75; N, 9.44. Found: C, 12.14; H, 4.51; N, 9.22. *tert*-Butyl alcohol (*t*-BuOH) and tren, from Aldrich, were used without further purification.

UV–visible spectra were obtained using a Perkin-Elmer Lambda 3B instrument equipped with a Model 3600 data station.

pH-meter readings were obtained directly from the NMR sample in 5-mm NMR tubes with a 0.3 mm × 20 cm pH electrode (Ingold). In D_2O, the value was corrected by using the relationship pD = pH + 0.4.[10] The pD was adjusted with NaOD and DClO$_4$.

Reaction of the coordinated trpn ligand in $[Co(trpn)(H_2O)_2]^{3+}$ in D_2O was conveniently monitored by ^{1}H NMR spectroscopy at slightly elevated temperature.[3] Unless indicated, the experiments were carried out at 48 °C. The reaction was carried out at a 1:1 ratio of HClO$_4$ to $[Co(trpn)(H_2O)_2]^{3+}$ (5, 20 mM), as well as at a 4:1 ratio of HClO$_4$ to $[Co(trpn)(H_2O)_2]^{3+}$ (5, 10, 20 mM). Moreover, the reaction at a 1:3 ratio of HClO$_4$ to $[Co(trpn)(H_2O)_2]^{3+}$ (20 mM) was examined. The reaction was carried out at 1:1 and 4:1 molar ratios of triflic acid to $[Co(trpn)(H_2O)_2]^{3+}$ (5 mM). Furthermore, the reaction was also carried out in H_2O at a 4:1 molar ratio of HClO$_4$ to $[Co(trpn)(H_2O)_2]^{3+}$ (20 mM). In addition, the behavior of $[Co(trpn)(H_2O)_2]^{3+}$ (5 and 20 mM) was studied in the absence of acid at 45 °C. In all cases, except for a 4:1 ratio of acid to $[Co(trpn)(H_2O)_2]^{3+}$ in which the final pD was ~2, the pD increased to a final value ~8. Buffers were avoided since they are reported to cause dimerization of the cobalt complex.[2]

In addition, the reaction was followed by ^{1}H NMR using the *t*-BuOH signal in D_2O (1.242 ppm relative to TSP (sodium 3-(trimethylsilyl)tetradeuteriopropionate). On Co^{2+} formation, the ^{1}H NMR signal of internal *t*-BuOH shifted downfield relative to an external *t*-BuOH standard. This method was quantitated from a calibration line on the basis of known Co^{2+} concentrations {$\Delta\delta$ (ppm) = $-7.9595e^{-3} + 4.0427e^{-2} [Co^{2+}]$ (mM); r = 0.999 for 3 points}.

NMR Spectroscopy. ^{1}H NMR spectroscopy was performed using Nicolet NT-360 and General Electric QE-300, GN-500, and Ω-600 spectrometers. The 2D NMR experiments were performed on General Electric GN-500 and NT-360 spectrometers at ~25 °C, without sample spinning. Proton and carbon chemical shifts were referenced to internal TSP. Exact chemical shifts for the trpn and bpn ^{13}C resonances were obtained from the 1D spectrum (QE-300). The 2D spectra were processed with the FTNMR and Felix programs (Hare Research Inc., Woodinville, WA).

COSY Spectroscopy.[11] The COSY spectrum on the NT-360 resulted from a 512 × 1024 data matrix size with 24 scans (preceded by 4 dummy scans) per t_1 value. Presaturation of the residual HOD peak was used. A sine bell and a Gaussian function were used prior to Fourier transformation in the t_2 and t_1 dimensions, respectively.

HOHAHA Spectroscopy.[12] The HOHAHA spectrum on the GN-500 resulted from a 512 × 1024 data matrix size with 48 scans (preceded by 4 dummy scans) per t_1 value. Delay time between scans was 1.0 s. An MLEV-17 mixing sequence of 92.4 ms preceded and followed by 2.0-ms trim pulses was used. A total of 1.5 W (70 dB) of power provided a 70-μs 90° [1]H pulse width. A Gaussian function was used prior to Fourier transformation in both the t_1 and t_2 dimensions.

HMQC ([1]H-Detected Heteronuclear Multiple Quantum Coherence) Spectroscopy.[13] The one-bond [1]H–[13]C shift correlation spectrum on the GN-500 resulted from a 512 × 1024 data matrix size with 512 scans per t_1 value. The delay time between scans was 1.2 s, and 41 W (63 dB) of ^{13}C rf power and a 38-μs 90° [13]C pulse width were used. A sine bell squared filter was used prior to Fourier transformation in both the t_2 and t_1 dimensions.

HMBC ([1]H-Detected Multiple-Bond Heteronuclear Multiple Quantum Coherence) Spectroscopy.[14] The multiple-bond [1]H–[13]C shift correlation spectrum on the GN-500 resulted from a 512 × 1024 data matrix size with 512 scans per t_1 value. Delay time between scans was 1.2 s, and 41 W (63 dB) of power and a 38-μs 90° [13]C pulse width were used. Values of Δ_1 (delay between the first 90° [1]H pulse and the first 90° [13]C pulse) and Δ_2 (delay between the first and second 90° [13]C pulses) were 3.3 and 50 ms, respectively. A sine bell squared filter was used prior to Fourier transformation in both t_1 and t_2 dimensions.

Results and Discussion

The $[Co(trpn)(H_2O)_2]^{3+}$ cation reacted under all conditions, leading to the formation of paramagnetic Co^{2+}, as evidenced initially by a change in the color of the solution from violet to pink, as well as extensive ^{1}H NMR line broadening at high pD (pD ~ 8). The presence of Co^{2+} was established spectroscopically. The electronic spectrum of the solution resulting from the complete reaction under acidic conditions (pD ~ 2; see below) of $[Co(trpn)(H_2O)_2]^{3+}$ showed a band at ~505 nm and a shoulder at ~475 nm, in agreement with a high-spin six-coordinate Co^{2+} compound.[15] In addition, the visible spectrum was identical to that of a solution of Co^{2+} at the same pD in the presence of the major organic products (trpn and bpn; see below).

We first sought experimental conditions leading to complete conversion of $[Co(trpn)(H_2O)_2]^{3+}$. Previous work indicated that addition of 0.1 equiv of Co^{2+} had no effect on the rate of the conversion.[3] Since no noticeable amounts of Co^{2+} were detected in the initial $[Co(trpn)(H_2O)_2]^{3+}$, it was clear that the Co^{2+} was generated as a result of the reduction of the Co(III) originally in $[Co(trpn)(H_2O)_2]^{3+}$. Thus, the amount of Co^{2+} formed was used as a measure of the extent of reaction. The *t*-BuOH method indicated the following: (a) When solutions of $[Co(trpn)(H_2O)_2]^{3+}$ (5 and 20 mM) were left to react in the absence of acid (final pD ~8), ~60% of the Co(III) was reduced to Co^{2+}. (b) For 1:1 solutions of HClO$_4$ to $[Co(trpn)(H_2O)_2]^{3+}$ (5 mM, final pD ~8), a higher amount of Co^{2+} (~90%) formed. (c) For 4:1 solutions of HClO$_4$ (80 mM) to $[Co(trpn)(H_2O)_2]^{3+}$ (final pD ~2), 100% Co^{2+} was formed. The quantitation of the amount of Co^{2+} by optical spectroscopy gave 20 mM Co^{2+}, confirming that consumption of $[Co(trpn)(H_2O)_2]^{3+}$ was complete.

Co^{2+} was also observed when the reaction was carried out in H_2O instead of D_2O. Likewise, the same results were obtained when triflic acid instead of HClO$_4$ was used. These experiments rule out an adventitious oxidant or reductant.

The identification of the organic reaction products could both give insight into the nature of the redox process and facilitate the identification of the reductant of Co(III). The ^{1}H NMR spectrum of a solution (pD ~ 4, after lyophilization) resulting from the complete conversion of $[Co(trpn)(H_2O)_2]^{3+}$ (20 mM) in the presence of HClO$_4$ (80 mM) showed several resonances in the 5.5–1.5 ppm region (Figure 1). Comparison to the ^{1}H NMR spectra of authentic trpn and bpn at the same pD allowed us to identify the resonances of trpn (3.32, 3.09, 2.13 ppm) and bpn (3.16, 3.09, 2.08 ppm) in the complex mixture. The multiplicity and chemical shifts of these signals and those for trpn and bpn at different pD's were used to obtain an initial assignment for all the ^{1}H resonances of trpn and bpn. Thus, the multiplets at 2.13 and 2.08 ppm were assigned to the β-H resonances of trpn and bpn, respectively. Triplets at 3.16 and 3.09 ppm were assigned to the α- and γ-H resonances of the bpn, respectively. Likewise, the triplets at 3.32 and 3.09 ppm were assigned to the α- and γ-H resonances of trpn, respectively.

In addition, minor ^{1}H signals at 5.20, 3.25, 2.80, and 1.94 ppm are not attributable to either trpn or bpn. These could (or could not) be due to several products. Integration indicated that these

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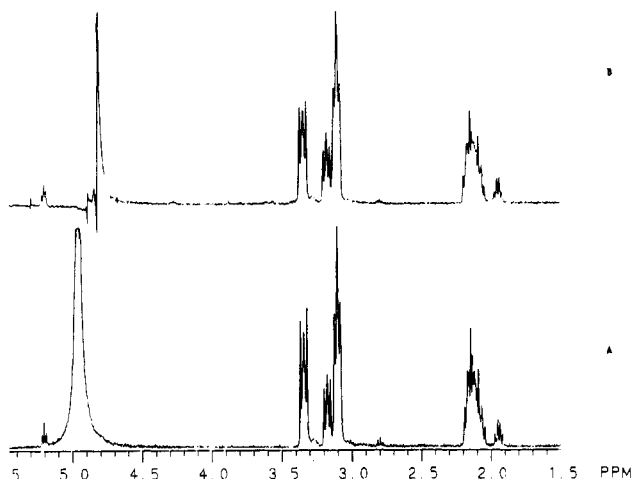(15) Lever, A. B. P. *Inorganic Electronic Spectroscopy*, 2nd ed.; Elsevier: Amsterdam, New York, 1984.

Figure 1. ^{1}H NMR spectrum of (A) a D_2O solution at pD $\sim$ 2 of lyophilized products resulting from the decomposition in H_2O of [Co(trpn)(H$_2$O)$_2$]$^{3+}$ (20 mM) in the presence of HClO$_4$ (80 mM) (the spectrum is identical to that at pD $\sim$ 4) and (B) a D_2O solution of equimolar trpn and Br$_2$ (40 mM) at pD $\sim$ 2 after 22 h at 48 °C. The signal at 4.8–5 ppm is HOD.

Table I. ^{1}H and ^{13}C NMR Chemical Shifts and Signal Assignments for Tris(3-aminopropyl)amine (trpn), 3,3′-Iminobis(propylamine) (bpn), and β-Aminopropionaldehyde ("BAPA") at pD 4.3[a]

	^{1}H NMR			^{13}C NMR		
	trpn	bpn	"BAPA"	trpn	bpn	"BAPA"
α	3.32	3.16	5.20	52.7	47.5	91.7
β	2.13	2.08	1.94	24.3	26.4	36.6
γ	3.09	3.09	3.10	39.6	39.5	38.7

[a] Shifts relative to internal TSP.

signals were not due to one stoichiometric product. In order to investigate these, 2D NMR experiments were carried out.

Product Studies by 2D NMR Spectroscopy. 2D COSY, HOHAHA, HMQC, and HMBC were used to assign the ^{1}H and ^{13}C NMR spectra. The ^{1}H and ^{13}C assignments of the major organic byproducts in D_2O at pD $\sim$ 4 are shown in Table I. The ^{1}H nuclei are designated by the carbon atom to which they are attached.

Assignment of the ^{1}H NMR Spectrum of the Product Mixture. The COSY spectrum (supplementary material) confirmed the initial β-H assignments for trpn and bpn. In order to unequivocally assign the α- and γ-H's, ^{13}C data were needed (see below).

In the COSY and HOHAHA spectra, the minor signals gave only one spin system. The two minor signals in the 1D spectrum in this spin system are the triplet at 5.2 and the quartet at 1.94 ppm, which integrated for two protons relative to the triplet. In the COSY and HOHAHA (Figure 2) spectra, the quartet showed correlations to the triplet and to a signal at 3.10 ppm (obscured in the 1D ^{1}H NMR spectrum by the more intense γ-H resonances of bpn and trpn). Thus, the three signals at 5.2, 3.1, and 1.94 ppm are for the same compound. We now consider the possible nature of a product with this shift and coupling pattern. The formation of bpn as well as Co^{2+} and trpn is consistent with an oxidative N-dealkylation of coordinated trpn at the tertiary nitrogen to give bpn and an aldehyde.[16] If in fact an oxidative N-dealkylation of trpn had occurred, these signals should correspond either to an aldehyde, namely β-aminopropionaldehyde (BAPA), or to a reaction product of BAPA ("BAPA"). Thus, the quartet at 1.94 ppm is assigned to the β-H's, and the obscured signal at 3.10 ppm to the γ-H's of such a BAPA derivative.

Aldehydic protons appear in the downfield region of the ^{1}H NMR spectrum at a chemical shift of $\sim$9–10 ppm, but no such

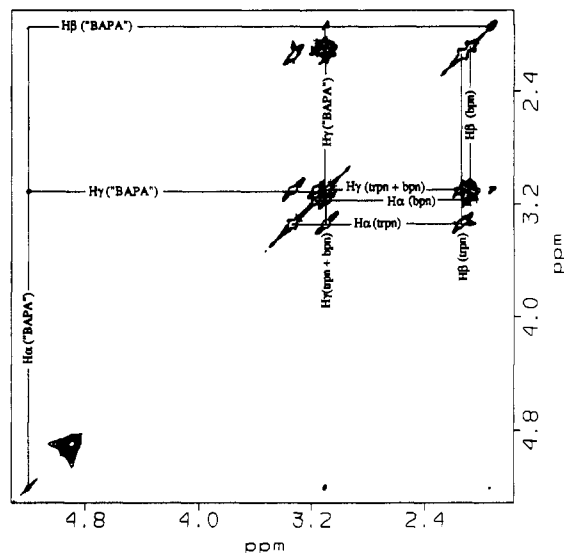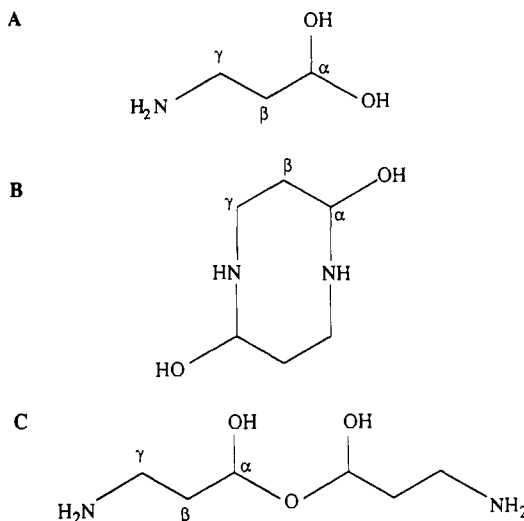**Figure 2.** HOHAHA spectrum after symmetrization of a D_2O solution (pD $\sim$ 4, after lyophilization) resulting from the complete conversion of [Co(trpn)(H$_2$O)$_2$]$^{3+}$ (20 mM) in the presence of HClO$_4$ (80 mM), showing the trpn, bpn, and "BAPA" connectivities.

Chart II

signal was observed. Therefore, the product is not BAPA. However, carbonyl compounds in aqueous solutions are reversibly hydrated.[17,18]

$$RHC(OH)_2 \rightleftharpoons RHC{=}O + H_2O$$
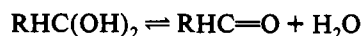
The resonance of a proton bound to a *gem*-diol carbon atom is 4.6–5 ppm upfield relative to that of an aldehydic proton.[17] Likewise, the α- and β-H's signals shift upfield upon hydration by less than 1 ppm.[17] Thus, the major byproduct signals at pD $\sim$ 4 could be due to hydrated BAPA (hBAPA, A in Chart II), namely H$_2$NCH$_2$CH$_2$CH(OH)$_2$. They also could be due to any species with the two heteroatoms O or N on the C, such a cyclized or linear dimer (B and C in Chart II). However, both dimeric species (B and C) should have more complex spectra, especially the cyclized dimer, since the methylene protons are inequivalent. The carbon bearing the heteroatoms is asymmetric and meso and *d,l* dimer forms should exist. The signals of "BAPA" did not

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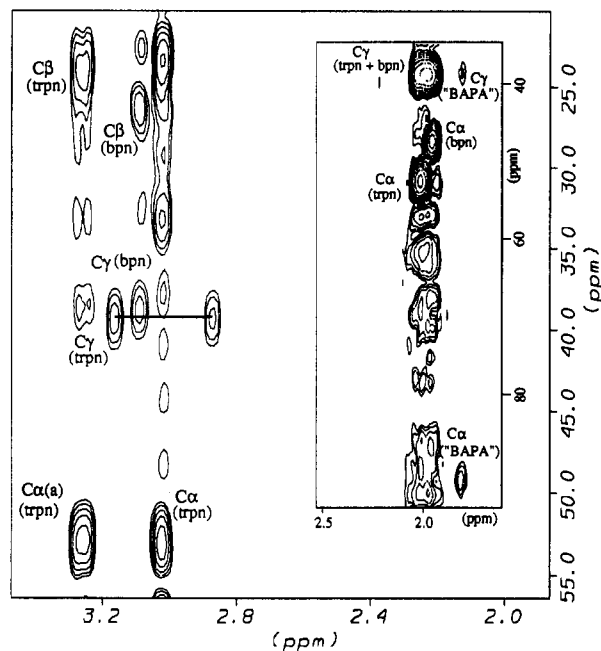
Figure 3. Part of the HMBC spectrum of a D_2O solution (pD ~ 4, after lyophilization) resulting from the complete conversion of [Co-(trpn)(H_2O)$_2$]$^{3+}$ (20 mM) in the presence of $HClO_4$ (80 mM), showing the trpn and bpn ^{13}C–^1H correlations. The inset shows some of the "BAPA" connectivities.

show any greater complexity in a ^1H NMR spectrum recorded at higher field, namely 600 MHz. Furthermore, the ^1H chemical shift values of "BAPA" are in good agreement with those reported for a related compound, namely β-aminopropanal diethyl acetal.[19] Therefore, the results highly favor hBAPA.

The other minor signals at 3.25 and 2.8 ppm in the 1D spectrum correspond to the same spin system. The shift and multiplicity of these resonances are in agreement with those of β-alanine (β-ala), formed by further oxidation of BAPA. The signals were too small to have detectable cross peaks in the COSY and HOHAHA spectra.

Assignment of the ^{13}C NMR Spectrum of the Product Mixture. Most of the ^{13}C signals of the products were assigned from the HMQC spectrum. However, the assignment of the γ-C's of the three products was difficult using HMQC, since the γ-C signals overlap in the ^1H and ^{13}C dimensions. The HMBC spectrum, which displays two- and three-bond ^1H–^{13}C correlations, was used to confirm the assignments and also to assign some of the signals.

The 1D ^{13}C NMR spectrum of trpn has peaks at 52.7, 39.6, and 24.3 ppm, whereas that of bpn has peaks at 47.5, 39.5, and 26.4 ppm. In the HMBC spectrum (Figure 3), the signal at 2.08 ppm, assigned above to β-H of bpn, shows correlations to two carbon resonances at 47.5 and 39.5 ppm. In the HMQC (supplementary material), the bpn proton signal at 3.09 ppm, assigned above to γ-H, correlates to the carbon signal at 39.5 ppm, which must be γ-C of bpn. The carbon signal at 26.4 ppm was assigned to β-C of bpn from its correlation with β-H (2.08 ppm) in the HMQC spectrum. With two of the three carbon resonances of bpn assigned, the one at 47.5 ppm was assigned to α-C. The same strategy was followed for assigning the carbon resonances of trpn. The assignment of the α- and γ-C's confirmed the ^1H NMR assignments since C's attached to tertiary amines are more downfield than C's attached to primary amines.[20] This assignment is confirmed by the interesting observation that the α-H of trpn (3.32 ppm) shows a three-bond correlation to α-Cα

(or α-Cb) (the symmetry equivalent carbons) in the HMBC spectrum. No such correlation was observed for α-H of bpn. The observed HMBC, COSY, and HOHAHA connectivities are given in the supplementary material.

The signals at 91.7 and 36.6 ppm, in the HMQC spectrum (supplementary material), were assigned to α- and β-C of "BAPA" from their correlations with the α-H (5.20 ppm) and β-H (1.94 ppm) signals, respectively. The ^{13}C chemical shift value of the α-C of "BAPA" (91.7 ppm) is in good agreement with the chemical shift expected for a *gem*-diol (89–93.5 ppm).[21] In the HMBC spectrum (Figure 3), the proton signal at 1.94 ppm, assigned above to β-H of "BAPA", shows correlations to two carbon resonances at 91.7 (α-C) and 38.7 ppm. Since α- and β-C were assigned above, the resonance at 38.7 ppm must be γ-C. The ^{13}C chemical shift values for the β- and γ-C resonances of "BAPA" are in good agreement with literature values for similar compounds (e.g. $ClH_2CCH_2CH(OCH_2CH_3)_2$ and $HOCH_2CH_2CH_2NH_2$).[20] The shifts are not consistent with the cyclized product because the γ-C shift would be further downfield if the N were a secondary amine.[20]

When the pD of a solution resulting from complete reaction of [Co(trpn)(H_2O)$_2$]$^{3+}$ (20 mM) in the presence of $HClO_4$ (80 mM) was increased and kept at pD ~8 for 7 h at room temperature, the ^1H NMR signals of "BAPA" were not observed after lowering the pD to ~2. Moreover, no signals assignable to "BAPA" were observed in the ^1H NMR spectrum of a product solution resulting from the reaction of [Co(trpn)(H_2O)$_2$]$^{3+}$ (20 mM) under acidic conditions (80 mM $HClO_4$, pD final ~2.5) after being kept at 5 °C for 1 month. In both experiments, the trpn and bpn ^1H NMR resonances were unaffected. These observations suggested that "BAPA" was not stable at high pD and low temperatures.[21] When [Co(trpn)(H_2O)$_2$]$^{3+}$ was left to react in the absence of acid or in the presence of up to only 1 equiv of acid, signals of both trpn and bpn but no signals of "BAPA" were found in the ^1H NMR spectra of the final solutions (pD ~8). This observation is consistent with the relative instability of "BAPA" at high pD.

Finally, it should be noted that no ^{13}C–^1H signals in either the HMBC or HMQC spectra indicated inequivalent protons for "BAPA". Taken together with the properties of the compound, these results leave little doubt that "BAPA" is hBAPA.

Other Oxidants. The products formed by [Co(trpn)(H_2O)$_2$]$^{3+}$ (Co^{2+}, trpn, bpn, "BAPA") are consistent with an oxidative N-dealkylation of a tertiary nitrogen to give a secondary nitrogen and an aldehyde.[16] Aliphatic tertiary nitrogens can be oxidized to a secondary nitrogen and an aldehyde by neutral permanganate,[22] aqueous bromine,[23] potassium hexacyanoferrate(III),[24] and (batho)$_2$Cu^{II} (batho = 2,9-dimethyl-4,7-diphenyl-1,10-phenanthrolinedisulfonate),[25,26] among other agents. The reaction proceeds via a two-electron oxidative N-dealkylation to a secondary amine and an aldehyde through an iminium species:[26]

$$R_2N-(CH_2)_2R' \xrightarrow{-2e} [R_2N^+=CHCH_2R'] \xrightarrow{H_2O}$$

$$R_2NH + R'CH_2CHO + 2H^+$$
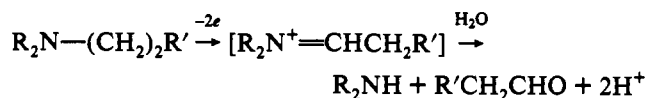
In order to determine whether the same products would be formed by oxidative N-dealkylation of trpn with a known oxidant,

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we studied the oxidation by aqueous Br_2. The ratio and products of the reaction for 1:1 solutions of trpn:Br_2 (40 mM) at pD ~ 2 and 48 °C were the same as those formed by $[Co(trpn)(H_2O)_2]^{3+}$ under acidic conditions (Figure 1) suggesting that an oxidative N-dealkylation of coordinated trpn indeed occurs in $[Co(trpn)(H_2O)_2]^{3+}$. We also tested trpn (20 mM) with Br_2 (40, 80 mM). With an excess of bromine, signals of bpn, "BAPA", and β-ala were identified in the ^1H NMR spectra. Moreover, with time (e.g. after 10 days for a 1:4 ratio of trpn to Br_2), only signals of bpn and β-ala were observed. In addition, other signals, probably due to brominated products, were also present. Further addition of Br_2 to 1:1 solutions led to the disappearance of the "BAPA" signals and the appearance of signals of β-ala. This result is consistent with the instability of the "BAPA" species, which is oxidized to β-ala in the presence of an excess of Br_2. Furthermore, the reaction between bpn (20 mM) and Br_2 (40 mM) was found to be much slower than that of trpn under the same conditions. Integration of the ^1H NMR signals agrees with the presence in solution of mostly unchanged bpn and small amounts of β-ala, consistent with the lower reactivity of secondary amines toward oxidative N-dealkylation.[26] The signals of tn (1,3-propanediamine, $H_2NCH_2CH_2CH_2NH_2$) (the other product of the bpn oxidative cleavage) were obscured by those of bpn.

In addition, quantification of the time dependence of Co^{2+} formed in the reactions of $[Co(trpn)(H_2O)_2]^{3+}$ (10 mM) with Br_2 at room temperature and pD ~2 was studied. For Br_2 concentrations of 120 and 200 mM, the reaction had progressed ~50% after 94 h and ~68% after 24 h, respectively. These results show that the rate of the reaction accelerated as the Br_2 concentration increased. However, the reaction rate decreased with time, and a more complete kinetic study was not pursued.

Reaction of Br_2 (80 mM) with $[Co(tren)(H_2O)_2]^{3+}$ (20 mM) and tren (20 mM) at pD ~2 was also studied. The reaction of tren with Br_2 was very similar to that of trpn under the same conditions. After 1.5 h at 48 °C, no ^1H NMR signals of tren remained; signals corresponding to diethylenetriamine (dien) were observed, suggesting that an oxidative N-dealkylation of tren had occurred. Moreover, a triplet at 5.3 ppm and a doublet at 3.05 ppm were observed and are assigned to the hydrated form of the aminoacetaldehyde ($H_2NCH_2CH(OH)_2$), the other product of the oxidative cleavage of tren. With time, signals of ethylenediamine and glycine, resulting from the oxidative N-dealkylation of dien and further oxidation of the aminoacetaldehyde, respectively, were also observed. In contrast, $[Co(tren)(H_2O)_2]^{3+}$ did not react with Br_2 even after 136 h at 48 °C.

Rate and Mechanism. The rate of the reaction of $[Co(trpn)(H_2O)_2]^{3+}$ accelerated with time as the pD increased (supplementary material). Under very acidic conditions, the reaction of coordinated trpn is better behaved but is relatively slow for obtaining kinetic data. However, we measured the initial part of the reaction. For solutions that were 10 mM in $[Co(trpn)(H_2O)_2]^{3+}$, integration of the ^1H NMR signals of trpn and complex indicated that the rate was first order in $[Co(trpn)(H_2O)_2]^{3+}$ and was the same for 80 and 160 mM $[H^+]$ (Figure 4). In addition, lowering the $[Co(trpn)(H_2O)_2]^{3+}$ concentration to 5 mM in the presence of $HClO_4$ (80 mM) did not affect the rate constant (Figure 4). These results gave an observed first-order rate constant of ~$3.7 \pm 0.1 \times 10^{-3} h^{-1}$ at 48 °C, under acidic conditions.

The mechanism shown in eqs 1–5 for the reaction of coordinated trpn is suggested on the basis of both the mechanism for the oxidative N-dealkylation of tertiary amines[16,27] and the observed products. (In eqs 1–5, R = $CH_2CH_2CH_2NH_2$; the uncoordinated amines are protonated, but the H^+ are shown for bookkeeping purposes.)
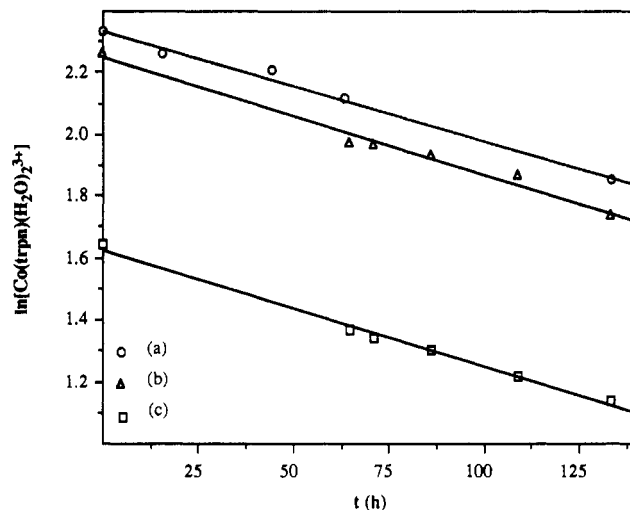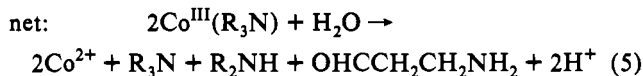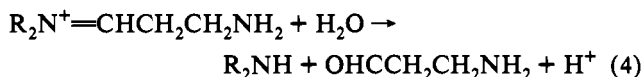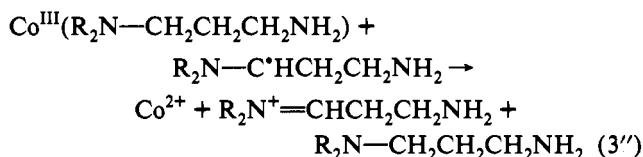
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Figure 4. Plots of the ln{$[Co(trpn)(H_2O)_2]^{3+}$ concentration} vs time (h) for solutions at 10 mM $[Co(trpn)(H_2O)_2]^{3+}$ (a, b) and 5 mM $[Co(trpn)-(H_2O)_2]^{3+}$ (c). $[HClO_4]$ = 80 mM in (b) and (c) and 160 mM in (a). Observed rate constants were (a) 3.56, (b) 3.82, and (c) 3.77 × $10^{-3} h^{-1}$.

$$Co^{III}(R_2N—CH_2CH_2CH_2NH_2) \rightleftharpoons$$
$$Co^{II}(R_2N^{+\bullet}—CH_2CH_2CH_2NH_2) \quad (1)$$

$$Co^{II}(R_2N^{+\bullet}—CH_2CH_2CH_2NH_2) \rightarrow$$
$$Co^{II}(R_2N—C^{\bullet}HCH_2CH_2NH_2) + H^+ \quad (2)$$

$$Co^{III}(R_2N—CH_2CH_2CH_2NH_2) +$$
$$Co^{II}(R_2N—C^{\bullet}HCH_2CH_2NH_2) \rightarrow$$
$$2Co^{2+} + R_2N^+=CHCH_2CH_2NH_2 +$$
$$R_2N—CH_2CH_2CH_2NH_2 \quad (3)$$

or

$$Co^{II}(R_2N—C^{\bullet}HCH_2CH_2NH_2) \rightarrow$$
$$Co^{2+} + R_2N—C^{\bullet}HCH_2CH_2NH_2 \quad (3')$$

$$Co^{III}(R_2N—CH_2CH_2CH_2NH_2) +$$
$$R_2N—C^{\bullet}HCH_2CH_2NH_2 \rightarrow$$
$$Co^{2+} + R_2N^+=CHCH_2CH_2NH_2 +$$
$$R_2N—CH_2CH_2CH_2NH_2 \quad (3'')$$

$$R_2N^+=CHCH_2CH_2NH_2 + H_2O \rightarrow$$
$$R_2NH + OHCCH_2CH_2NH_2 + H^+ \quad (4)$$

net: $\quad 2Co^{III}(R_3N) + H_2O \rightarrow$
$$2Co^{2+} + R_3N + R_2NH + OHCCH_2CH_2NH_2 + 2H^+ \quad (5)$$

In this proposal, step 2 is rate determining. The first intermediate, the aminium radical at the tertiary nitrogen of coordinated trpn, is formed in step 1. The tertiary N probably is no longer coordinated. The $Co^{II}(R_2N^{+\bullet}—CH_2CH_2CH_2NH_2)$ species is deprotonated by H_2O in strong acid and also by OH^- or by free amine at higher pH, such as when decomposition increases the pH. In this mechanism, the $Co^{II}(R_2N—C^{\bullet}H-CH_2CH_2NH_2)$ intermediate is oxidized by the second $[Co(trpn)(H_2O)_2]^{3+}$ complex (step 3) or in two steps ((3') and (3'')). The iminium ion formed in (3) or (3'') is hydrolyzed to give unstable BAPA and bpn.[27] Thus, equivalent amounts of trpn,

bpn, and BAPA-derived products should be found after the complete consumption of $[Co(trpn)(H_2O)_2]^{3+}$ under acidic conditions (eq 5). This was true for trpn and bpn. However, quantification of the "BAPA" was hampered by the relative instability of "BAPA", but at least 50% of the expected amount was clearly present. The presence of β-ala, formed probably by further oxidation of "BAPA", agrees with this "BAPA" relative instability. Integration of the signals for both β-ala and "BAPA" gave a ratio of 1 to 5.5 (β-ala:"BAPA").

Otherwise, the forward reaction in the first step could be an alternative rate-determining step (mechanism in supplementary material). This alternative mechanism does not account for the increased rate of $[Co(trpn)(H_2O)_2]^{3+}$ complex decomposition observed under the higher pH conditions usually used in substrate hydrolysis studies.

Conclusions and Consequences. We have discovered an interesting rare example of site-selective cleavage of an N–C bond in a coordinated polyamine.[6,7] It should be noted that BAPA is a product expected from spermine and spermidine metabolism involving tissue polyamine oxidases (e.g., rat liver or human placental enzymes).[28] The results are intriguing because a previous example of selective cleavage in a Co(III) polyamine complex (i.e., a spermine complex) gave a different product, one characteristic of amine oxidases of higher plants.[6] The low reaction rate probably precludes the use of the $[Co(trpn)(H_2O)_2]^{3+}$ complex as a model for studying processes relevant to amine oxidases. However, our proposed mechanism appears to us to be more reasonable than that proposed for cleavage of the N–C bond in a Co(III) complex of spermine.[6] In that mechanism, the initial step proposed is the release of H_2, but the driving force for this step is not specified. Furthermore, the formation of only 50% Co^{2+} is not explained.

The results reported here suggest that the reaction of coordinated trpn in $[Co(trpn)(H_2O)_2]^{3+}$ under acidic conditions is initiated by a slow intracomplex redox process, in which Co(III) and coordinated trpn are the oxidant and reductant, respectively.

Under higher pH conditions where the use of $[Co(trpn)(H_2O)_2]^{3+}$ for hydrolysis reactions is feasible, the overall reaction of the coordinated trpn is faster. It is likely that a redox process similar to that found at low pH occurs, but the situation is more complex than at low pH. Since the redox process involves the agent itself, it seems unlikely that $[Co(trpn)(H_2O)_2]^{3+}$ would be a useful hydrolytic agent except for relatively easily hydrolyzed substrates.

It is somewhat ironic that factors favoring hydrolytic efficiency by Co(III) species may eventually doom the use of Co(III) as a useful metal center for hydrolytic reactions. The six-membered chelate rings produce a weak field and minimize electron donation to the Co(III). A weak ligand field may be needed to provide rapid H_2O ligand exchange, and an electron deficient Co(III) may promote substrate hydrolysis. This is exactly the situation which would make the Co(III) a better oxidant. The stability of $[Co(tren)(H_2O)_2]^{3+}$ against oxidative N-dealkylation by Br_2 supports this idea; tren has stronger ligand field strength than trpn[29] and therefore is not expected to favor an oxidative N-dealkylation process. New ligands for Co(III) hydrolytic agents should be designed to avoid the possibility of competing oxidative N-dealkylation.

Supplementary Material Available: Tables of the observed HMBC, COSY, and HOHAHA connectivities in a D_2O solution resulting from the complete conversion of $[Co(trpn)(H_2O)_2]^{3+}$ in the presence of $HClO_4$, HMQC and symmetrized COSY spectra of the same solution, a plot of the concentration of $[Co(trpn)(H_2O)_2]^{3+}$ vs time at different initial concentrations of $HClO_4$, and a set of equations for one alternative mechanism for the C–N cleavage reaction (5 pages). Ordering information is given on any current masthead page.

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