Site Selective and Quantitative C–N Bond Cleavage of Spermine on a Cobalt Complex

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A C–N bond of spermine coordinated to cobalt(III) is cleaved through site-selective oxidation to yield 1,5-diazabicyclo[4.3.0]nonane and complexes containing 1,3-diaminopropane in an aqueous solution.

Oxidation of organic ligands by transition metal complexes has attracted much attention, in particular in industry and bioinorganic chemistry. We now report a novel site-selective oxidation of spermine on a cobalt complex under mild conditions, which results in quantitative C–N bond cleavage.

Spermine (4,9-diaza-1,12-diaminododecane, 3,4,3-tet) **1** is a naturally occurring tetraamine important to biological systems in growth and development, interaction with nucleic acids and stimulation of protein synthesis for example.[1] It is of interest to elucidate the coordination behaviour of such a biologically important compound to a transition metal complex.[2] During our studies of the unique properties of a metal complex containing polyamines,[3] we have prepared a cobalt(III) complex containing spermine.

A 200 ml aqueous solution of $K_3[Co(ox)_3]$[4] **2** (10 mmol) (ox = oxalato) and spermine (10 mmol) was stirred at room temp. for 12 h. The solution slowly changed from its original green to violet. Methanol (100 ml) and sodium perchlorate (3 g) were added to the solution and the resulting white precipitate was removed by filtration. Concentration of the filtrate gave violet crystals, which were recrystallized from water. Elemental analysis indicated the $[Co(ox)(spermine)]ClO_4$ constitution **3** (37%).† ^{13}C NMR spectroscopy‡ suggests that the tetraamine coordinates in the unsymmetrical *cis* (*cis*-β) form, which is analogous to $[Co(ox)(2,3,2\text{-tet})]^+$ **4** and $[Co(ox)(3,2,3\text{-tet})]^+$ **5**.[5,6] *cis*-β-$[Co(ox)(3,3,3\text{-tet})]ClO_4$ **6** was obtained by a similar procedure using 3,3,3-tet **7** (4,8-diaza-1,11-diaminoundecane) instead of spermine (90%).

A very interesting phenomenon was observed when an aqueous solution of **3** was left to stand at room temp. The change in **3** in D_2O solution was followed by ^{13}C NMR spectroscopy (see Fig. 1). The ten methylene signals of coordinated spermine gradually decreased, and new signals appeared. The change was completed after *ca.* 30 days.§ As the reaction proceeds, cobalt(II) oxalate (**8**, characterized by IR spectroscopy) was precipitated (40%). An organic compound **9** could be separated from the resulting solution by extraction with chloroform. **9** was transformed into **10** on acidification with HCl. ^1H, ^{13}C NMR, and mass spectroscopy

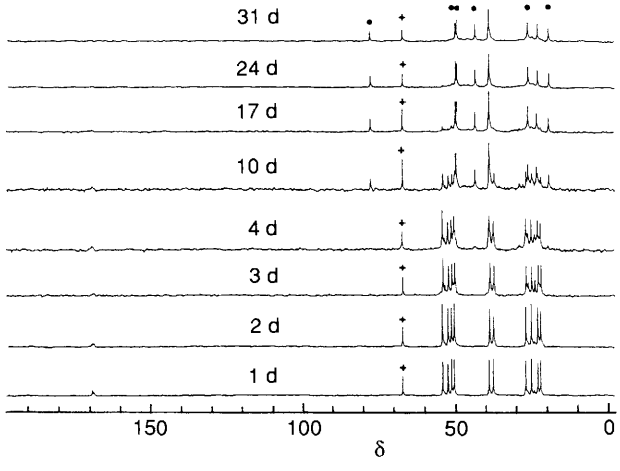
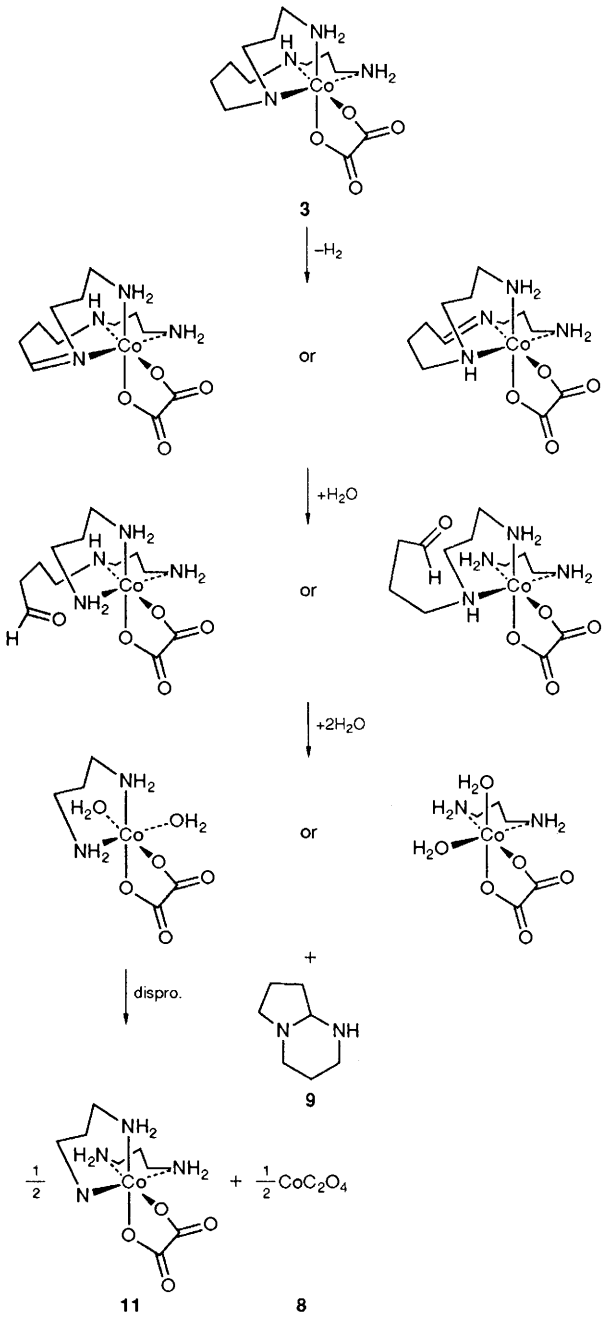


Fig. 1 ^{13}C NMR (22.5 MHz) spectra of **3** in D_2O stood at room temp. Signals marked with dots are due to **9**. The signal of C(7) in **9** is not observed owing to deuterium replacement.[14] +: internal standard (dioxane).

† CAUTION! Although these perchlorate salts are moderately stable, they are potential hazards and should therefore be handled with care and in small quantities.

‡ ^{13}C NMR spectra (D_2O, 22.5 MHz, dioxane δ 67.4) **3**: 169.1, 168.6, 54.4, 52.7, 51.5, 50.6, 38.9, 37.5, 26.8, 25.0, 22.9 and 22.0. **6**: 169.2, 168.5, 53.1, 50.8, 49.8, 48.2, 39.7, 39.0, 26.0, 25.1, and 22.7. λ_{max} (H_2O) **3**: 530(ε 84) and 375(154) nm; **6**: 532(103) and 373(182) nm.

§ At the final stage of the reaction, pH of the solution was 8.2. The same reaction proceeded at 50 °C, which was complete after *ca.* 10 h.



Scheme 1

indicated that **10** is 1-(3-aminopropyl)pyrrolinium, and **9** is 1,5-diazabicyclo[4.3.0]nonane.[11]¶

The ^{13}C NMR spectrum of the aqueous solution from which **9** was extracted gave two broad methylene signals at δ 39.5 and 26.3, whose intensities are about 2 : 1. This is characteristic of the 1,3-diaminopropane chelate. From the solution $[Co(ox)(1,3\text{-diaminopropane})_2]ClO_4$ **11** was isolated (10%) and characterized by elemental analysis and ^{13}C NMR spectroscopy.

The results suggest that the decomposition of **3** proceeds *via* oxidation of spermine on a cobalt complex. A C–N bond of coordinated spermine is oxidized to form an imine intermediate, which immediately undergoes hydrolysis. The resulting aldehyde moiety is released from the complex with the formation of an aminal **9**. The 1,3-diaminopropane moiety is retained in the complex, and partial disproportionation gives **11** and **8** (Scheme 1 ‖). It is remarkable that the oxidation is site specific and almost quantitative, which is apparent from ^{13}C NMR spectroscopy (Fig. 1).

It is important to note that a significant difference in reactivity was observed between the analogous compounds, **3** and **6**. No change was observed for the aqueous solution of **6** even after one month. Thus, the oxidative C–N bond cleavage is specific for the spermine chelate. Absorption maxima due to the d–d transition of **3** are very similar to those of **6**,‡ and are considerably shifted to lower energy than **4** or **5**.[6] Therefore, no significant difference between **3** and **6** in the ligand field and thus in the electronic structure around cobalt is suggested from these absorption spectroscopic data. The unusual reactivity of **3** should be attributed to the chelate structure of the coordinated tetraamine. The important factor is that the spermine chelate partly contains an energetically unfavourable seven-membered ring.[13]

The present result will be important in designing highly specific oxidation reactions using a metal complex, as well as in understanding the role of metal ions in amine oxidases.[9]

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References

1 C. W. Tabor and H. Tabor, *Ann. Rev. Biochem.*, 1984, **53**, 749; H. G. Wiliams-Ashman and Z. N. Canellakis, *Perspect. Biol. Med.*, 1979, **22**, 421; K. Igarashi, K. Sugawara, I. Izumi, C. Nagayama and S. Hirose, *Eur. J. Biochem.*, 1974, **48**, 495.
2 R. Boggs and J. Donohue, *Acta Crystallogr., Sect. B*, 1975, **31**, 320; M. L. Antonelli, S. Balzamo, V. Carunchio, E. Cernia and R. Purrello, *J. Inorg. Biochem.*, 1988, **32**, 153.
3 M. Yashiro, A. Shimada, T. Usui, S. Yano, K. Kobayashi, T. Sakurai and S. Yoshikawa, *J. Am. Chem. Soc.*, 1985, **107**, 4351; M. Yashiro, M. Ajioka, S. Yano, K. Toriumi, T. Ito and S. Yoshikawa, *Inorg. Chem.*, 1986, **25**, 1709.
4 D. M. Yost, *Inorg. Synth.*, 1939, **1**, 37.
5 M. Yashiro, S. Yano and S. Yoshikawa, *J. Am. Chem. Soc.*, 1986, **108**, 1096.
6 L. H. DeHayes and D. H. Busch, *Inorg. Chem.*, 1973, **12**, 2010.
7 K. Hasse and K. Schührer, *Biochem. Z.*, 1962, **336**, 20.
8 T. A. Smith, *Biochem. Biophys. Res. Commun.*, 1970, **41**, 1452.
9 T. A. Smith, *Phytochemistry*, 1972, **11**, 899.
10 S. J. Croker, R. S. T. Loeffler, T. A. Smith and R. B. Sessions, *Tetrahedron Lett.*, 1983, **24**, 1559.
11 S. Brandänge, L.-H. Eriksson and B. Rodriguez, *Acta Chem. Scand., B*, 1984, **38**, 526.
12 T. A. Smith, S. J. Crocker and R. S. T. Loeffler, *Phytochemistry*, 1986, **25**, 683.
13 H. Ogino and J. Fujita, *Bull. Chem. Soc. Jpn.*, 1975, **48**, 1836; H. Ogino, *J. Coord. Chem.*, 1987, **15**, 187.

¶ **9** and **10** are reported as metabolic products of spermine by amine oxidases of higher plants.[7–12]

‖ Because of the unsymmetrical coordination of the tetraamine, two sterically different sites are possible for the oxidation. Both are shown in Scheme 1 (left and right).