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Syntheses of new water-soluble dicobalt complexes having two cobalt–carbon bonds and their ability for DNA cleavage

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Abstract—One-pot syntheses of new water-soluble dicobalt complexes having two cobalt–carbon bonds are reported. The complexes were characterized by ^{1}H NMR and UV–vis spectroscopies as well as ESI-MS. These complexes were photosensitive, and photo-cleavage of the cobalt–carbon bonds upon irradiation with visible light produced methyl radicals which were detected by ESR spin-trapping techniques. The dicobalt complexes exhibited high ability for DNA cleavage in comparison with that for the corresponding monocobalt complex. © 2003 Elsevier Science Ltd. All rights reserved.

Formation and cleavage of a metal–carbon σ-bond are important research targets in organometallic chemistry.[1] Especially, compounds with a cobalt–carbon bond, found as key intermediates in vitamin B_{12} enzymic reactions, have attracted much attention owing to facile cleavage of the cobalt–carbon bond upon irradiation with visible light.[2] Therefore, a variety of chelated complexes having a cobalt–carbon bond have been synthesized and used as a versatile radical source for organic syntheses.[3] Previously, we synthesized a new dicobalt complex having two cobalt–carbon bonds, and reported a unique catalysis of the dicobalt complex in organic media.[4,5] Recent growing requirement for organic synthesis has attracted attention on the utility of water as a clean solvent.[6] Thus, synthesis of water-soluble catalysis is of extreme importance in the organometallic chemistry. In this paper, the syntheses of new water-soluble organometallic compounds having two cobalt–carbon bonds are reported. Interestingly, these dicobalt complexes exhibited high efficiency for DNA cleavage by a pair of alkyl radical species via homolysis of the cobalt–carbon bonds in an aqueous solution.

Dicobalt complex **1** was synthesized by a condensation reaction between 3,3′,4,4′-tetraaminodiphenylmethane[7] and 5-(trimethylammoniomethyl)salicylaldehyde[8] in the presence of $Co(OAc)_2{\cdot}4H_2O$ and the following reaction with $NaBH_4$ and CH_3I as shown in Scheme 1. To a degassed H_2O (18 mL) solution of 3,3′,4,4′-tetraaminodiphenylmethane (22.4 mg, 0.1 mmol) and 5-(trimethylammoniomethyl)salicylaldehyde (92.2 mg, 0.4 mmol) was added $Co(OAc)_2{\cdot}4H_2O$ (50.7 mg, 0.2 mmol). After the solution was stirred for 2 h under nitrogen atmosphere at room temperature, CH_3I (240 μL, 4 mmol) and $NaBH_4$ (50.5 mg, 1.3 mmol) were added to it and stirred for 40 min at 313 K in the dark. The excess of $NaBH_4$ was decomposed by acetone (2 mL), and then addition of 1.6 M $NaClO_4$ aqueous solution (5 mL) to precipitate a dark-brown powder. The powder was washed with $CHCl_3$ and dried in vacuo.[†] Dicobalt complex **2** was also synthesized in the same manner as for **1** except for use of 3,3′,4,4′-tetraaminodiphenylethane[7] in place of 3,3′,4,4′-tetraaminodiphenylmethane.[†]

Compounds **1** and **2** were characterized by ^{1}H NMR spectroscopy (DMSO-d_6, 500 MHz). The reasonably

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[†] **1**: Yield, 81 mg (55%); ^{1}H NMR (DMSO-d_6, 500 MHz): δ 2.06 [s, 6H, $C\underline{H}_3$], 2.97 [s, 36H, -$NC\underline{H}_3$], 4.02 [s, 2H, Ph-$C\underline{H}_2$-Ph], 4.33 [s, 8H, Ph-$C\underline{H}_2$-N], 7.02 [s, 4H, Ph], 7.30 [s, 6H, Ph], 7.57 [d, 4H, Ph], 8.09 [s, 2H, Ph], 8.21[s, 2H, Ph], 8.71 [s, 2H, imine], 8.79[s, 2H, imine]; ESI-MS (*m*/*z*): $[M-4ClO_4]^{4+}$, 268.5; UV–vis (H_2O): [λ_{max}/nm], 280, 390, 575sh; IR, ν/cm^{-1}: 1617s (C=N), 1378 (C–O), 1113s, 627 (ClO_4). **2**: Yield, 96 mg (64%); ^{1}H NMR (DMSO-d_6, 500 MHz): δ 2.10 [s, 6H, $C\underline{H}_3$], 2.98 [s, 36H, -$NC\underline{H}_3$], 3.12 [s, 4H, Ph-$C\underline{H}_2C\underline{H}_2$-Ph], 4.33 [s, 8H, Ph-$C\underline{H}_2$-N], 6.98 [s, 4H, Ph], 7.26 [s, 6H, Ph], 7.54 [d, 4H, Ph], 8.07 [s, 2H, Ph], 8.10 [s, 2H, Ph], 8.70 [s, 2H, imine], 8.75 [s, 2H, imine]; ESI-MS (*m*/*z*): $[M-4ClO_4]^{4+}$, 272.6; UV–vis (H_2O): [λ_{max}/nm], 280, 389, 575sh; IR, ν/cm^{-1}: 1616s (C=N), 1379 (C–O), 1111s, 627 (ClO_4).

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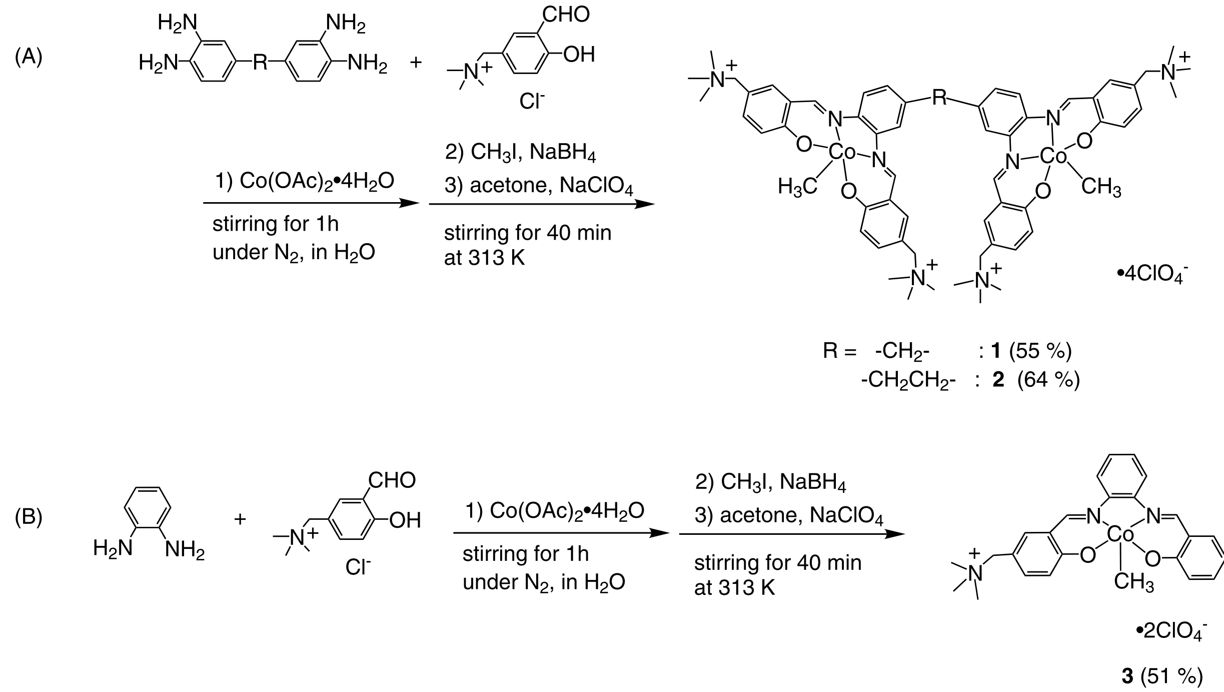
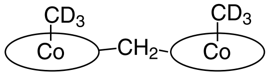


Scheme 1.

sharp NMR peaks indicated that the complexes are diamagnetic organocobalt low spin d^6 species. The methyl protons attached to the cobalt centers of **1** and **2** were observed at δ 2.06 and 2.10, respectively. These peaks disappeared on irradiation with visible light, and were not observed for the corresponding deuterium (Co-CD_3) complex **1**′ (Chart 1).[‡] The presence of labile cobalt–carbon bonds is also corroborated by the UV–vis spectrum, which shows absorptions at 280, 390, and 575(sh) nm in H_2O for **1**. This spectrum changed upon irradiation with visible light under aerobic conditions as shown in Figure 1, which is characteristic of the cleavage of the cobalt–carbon bonds. In addition, ESI-MS analysis directly confirmed the structure of **1**. Introduction of a MeOH solution of **1** into the ESI mass spectrometer in the dark affords a positive ion mass spectrum with the most prominent peak cluster at m/z 268.5, which has the mass value and isotope pattern consistent with the ion $\mathbf{1}^{4+}$. The corresponding peak cluster was observed at m/z 272.6 as for **2**. These results indicate the formation of the dicobalt complexes having two cobalt–carbon bonds.

Spin trapping experiments were performed to detect a radical species produced by photolysis of **1** upon irradiation with visible light. 5,5′-Dimethylpyrroline *N*-oxide (DMPO) was used as the spin-trapping reagent. Figure 2 shows the ESR spectrum of the DMPO spin adduct obtained by photolysis of **1** (1.0 mM) in the presence of DMPO (0.40 M) in H_2O. The ESR parameters for hyperfine splitting constants, $A_N = 16.5$ G and $A_H = 22.5$ G, are ascribed to the DMPO-CH_3 spin adduct[9] and clearly exhibit the formation of a methyl radical by the photo-cleavage of the cobalt–carbon bond for **1**. The



1'

Chart 1.

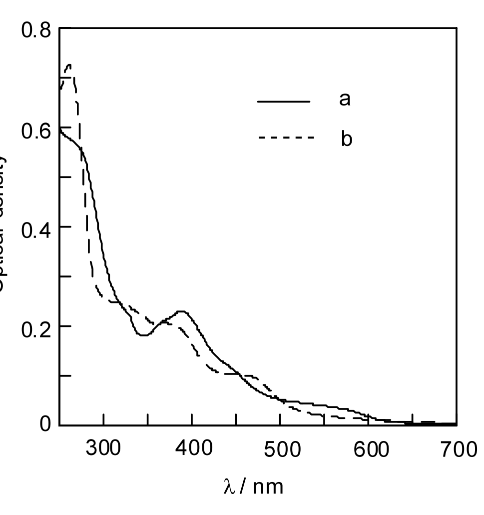


Figure 1. Electronic spectral change for the aerobic photolysis of **1**: (a) **1** in H_2O; (b) after irradiation with visible light.

[‡] **1**′ was synthesized in the same manner as for **1** except for use of iodomethane-d_3 in place of iodomethane as methylating reagent. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 3.03 [s, 36H, -NC$\underline{H}_3$], 4.13 [s, 2H, Ph-C$\underline{H}_2$-Ph], 4.37 [s, 8H, Ph-C$\underline{H}_2$-N], 7.01 [s, 4H, Ph], 7.30 [s, 6H, Ph], 7.57 [d, 4H, Ph], 8.07 [s, 2H, Ph], 8.22[s, 2H, Ph], 8.71 [s, 2H, imine], 8.79[s, 2H, imine]; ESI-MS (m/z): $[M-4ClO_4]^{4+}$, 270.6; UV–vis (H_2O): [λ_{max}/nm], 280, 386, 575sh; IR, ν/cm^{-1}: 1616s (C=N), 1383 (C–O), 1111s (ClO_4).

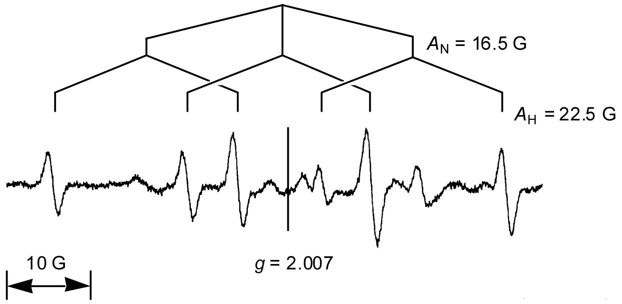


Figure 2. ESR spectrum of DMPO spin adducts of **1** (1.0 mM) in H_2O observed upon irradiation with a 500 W tungsten lamp for 40 s.

same behavior was observed in the case of **2** ($g = 2.007$, $A_N = 16.3$ G and $A_H = 22.2$ G; 10^4 G = 1 T).

Facile production of methyl radicals through the photolysis of **1** and **2** with visible light strongly prompted us to investigate the DNA cleavage in water since carbon-centered radical degradation of DNA is of significant current interest.[10–12] The DNA cleaving activity of the complexes was determined using a plasmid relaxation assay to monitor the conversion of circular supercoiled DNA (form I) to relaxed circular (form II). The complexes were photolyzed through a 500 W tungsten lamp for 5 min at a distance of 20 cm in the presence of pBR322 DNA at room temperature, and the amounts of strand scission were assessed by agarose gel electrophoresis as shown in Figure 3.[§] The complete conversion of form I (supercoiled DNA) to form II (open circular DNA) proceeded in the presence of **1** (lane 3 in Fig. 3). No DNA scission was observed when it was simply exposed to visible light in the absence of **1** (lane 1 in Fig. 3) or when it was kept in the dark even though **1** was present (lane 4 in Fig. 3). Thus, methyl radicals produced by the photolysis of **1** effectively cleaved the DNA strand. And it is quite interesting that the corresponding monocobalt complex **3**[¶] had low activity for DNA strand scission under the same conditions (lane 2 in Fig. 3). Therefore, dicobalt complexes having two cobalt–carbon bonds had high activity for DNA scission with visible light.

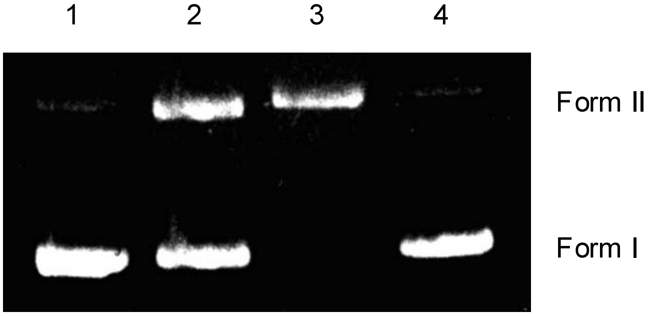


Figure 3. Gel-electrophoretic analysis of strand breaks generated in the photolysis (500 W tungsten lamp, room temp., 5 min) of supercoiled pBR 322 DNA (200 μM/bp in TBE buffer, pH 8) in the presence of alkylated complex. Lane 1, DNA alone; Lane 2, **3** (400 μM); Lane 3, **1** (200 μM); Lane 4, **1** (200 μM) in the dark.

In conclusion, new water-soluble dicobalt complexes **1** and **2** having two cobalt–carbon bonds were synthesized and characterized by various spectroscopic methods. The dicobalt complex **1** is capable of DNA cleavage with higher efficiency than the corresponding monocobalt complex **3** upon irradiation with visible light. The utility of the multi cobalt–carbon bonds system and low energy light, which can avoid the base damage induced by UV light, introduces a new strategy for construction of antitumor agents. Further work on the mechanism for the DNA cleavage by the dicobalt complex is currently in progress in our laboratory.

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[§] Quantification was accomplished by the Total Lab software program. The amount of supercoiled DNA was multiplied by a factor of 1.22 to correct the reduced ethidium bromide intercalation into the form I plasmid DNA.

[¶] The monocobalt complex **3** was synthesized by the condensation of *o*-phenylendiamine and 5-(trimethylammoniomethyl)salicylaldehyde in presence of $Co(OAc)_2 \cdot 4H_2O$ and subsequent reaction with $NaBH_4$ and CH_3I. Yield, 76mg (51%); ^1H NMR (DMSO-d_6, 500 MHz): δ 2.08 [s, 3H, $C\underline{H}_3$], 3.01 [s, 18H, -$NC\underline{H}_3$], 4.34 [s, 4H, Ph-$C\underline{H}_2$-N], 6.97 [d, 2H, Ph], 7.25 [s 2H, Ph], 7.34 [s, 2H, Ph], 7.56 [s, 2H, Ph], 8.13 [s, 2H, Ph], 8.76 [s, 2H, imine]; ESI-MS (m/z): $[M-2ClO_4]^{2+}$, 265.5; UV–vis (H_2O): [λ_{max}/nm], 264, 382, 575sh; IR, ν/cm^{-1}: 1616s (C=N), 1383s (C–O), 1111s, 627 (ClO_4).