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Preparation of Iron(III) Complex with Nitrilotriacetic Acid and Origin of Its Unique Reactivity

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We have succeeded in isolating the iron(III) complex with nitrilotriacetate(nta^{3-}) and concluded that this complex exists as a μ-oxo dimeric species in both the solid and solution states. The unique reactivity observed for this complex solution was discussed in relation to its dimeric structure.

It has been well known that the "Fe(III)-nta complex solution", prepared by mixing the iron(III) solution and nitrilotriacetic acid(H_3nta) exhibits unique reactivity. Awai et al.[1] have reported the development of glucosia and parenchymal cell iron deposition in rats treated with repeated injection of the "above solution." Okada et al.[2] have reported that the "Fe(III)-nta complex solution" is nephrotoxic and induces renal carcinoma in rats and mice. In animals treated with the "Fe(III)-nta complex solution", products of lipid peroxidation, such as thiobarbituric acid(TBA)-reactive substances, ethane or conjugated dienes, increased.[3] Furthermore, the generation of radical in the "Fe(III)-nta complex solution" has been demonstrated through electron spin resonance spectroscopy.[4] However, at present there is no comprehensive elucidation for the unique reactivity of the "Fe(III)-nta complex solution." In this study we have succeeded in isolating the crystal of Fe(III)-nta complex, and measured several physical properties of this complex in order to clarify the origin of unique reactivity.

The iron(III)-nta complex was isolated as follows: To an aqueous solution(50 ml) containing H_3nta(1.9 g, 0.01 mol) and $KHCO_3$(3 g, 0.03 mol) was added 2.2 g of $Fe_3O(CH_3COO)_6(H_2O)_3Cl\cdot 4H_2O$ with stirring. After one hour, the solvent was evaporated to almost dryness, and methanol(50 ml) was added to the residue. The precipitated KCl was removed by filtration, and the filtrate was kept to stand for several days. The precipitated dark

green crystals were filtered, and once recrystallized from a methanol solution. Found: C, 21.83; H, 3.15; N, 3.66; Fe, 14.5%. Calcd for $Fe_2O(CH_3COO)(nta)_2K_3 \cdot 4.5H_2O$: C, 22.09; H, 3.18; N, 3.68; Fe, 14.67%. The crystal water can be removed under vacuum over P_2O_5. Found: C, 24.94; H, 2.19; N, 4.18%. Calcd for $K_3Fe_2O(CH_3COO)(nta)_2$: C, 24.71; H, 2.22; N, 4.12%. By the similar way, the Cs-salt complex was also obtained. Found: C, 17.00; H, 2.45; N, 2.83; Fe, 11.3%. Calcd for $Cs_3Fe_2O(CH_3COO)(nta)_2 \cdot 3H_2O$: C, 16.56; H, 2.08; N, 2.76; Fe, 11.00%.

In Fig. 1, the temperature dependence of magnetic susceptibility of K-salt complex is shown. Magnetic moments are 2.03 and 0.79 μ_B at 292.8 and 81.4 K, respectively, suggesting that strong antiferromagnetic interaction is operating between two iron atoms.[5] The J-values were calculated based on the theoretical expression obtained from the isotropic Heisenberg exchange Hamiltonian, $\mathcal{H} = -2JS_1 \cdot S_2$, and are -87.9 and -80.2 cm^{-1}, for K-salt and Cs-salt, respectively. These large -J values are consistent with presence of strong antiferromagnetic interaction between two iron atoms, and also suggesting that two compounds are of a binuclear structure with μ-oxo bridge.[5] Preliminary X-ray structure determination on the Cs-salt has confirmed the presence of μ-oxo and μ-acetato bridges between two iron atoms.[6] In Fig. 2, the reflectance spectrum of the K-salt is shown. The spectral property is very similar to that in the solution with pH 7-8.[4] This is demonstrating that the Fe(III)-nta complex exists as a dimeric species with μ-oxo bridge in aqueous solution.

Halliwell et al.[7] have reported that the "Fe(III)-nta complex solution" has much higher effect on the degradation of DNA in the presence of H_2O_2 than any other Fe(III) chelates such as edta or cdta. In this study we

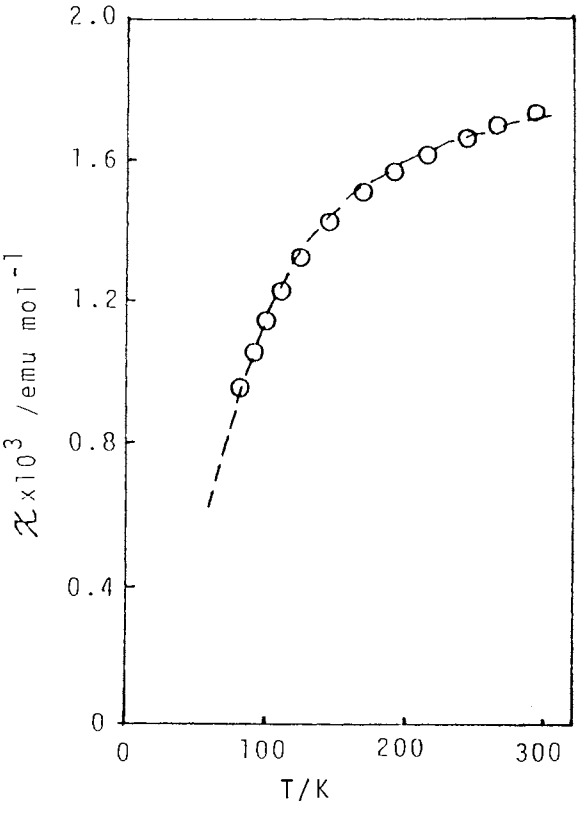

Fig. 1. Variation with temperature of molar susceptibility(per Fe) of $K_3[Fe_2O(CH_3COO)(nta)_2]$: O O O O experimental values;----calculated value based on isotropic Heisenberg equation for values of g=2.00, J= -87.9 cm^{-1}, and Nα=0 including 0.36 % of monomeric Fe(III) impurity.

have compared the ability for DNA degradation of iron(III) chelates in the presence of H_2O_2 by the use of TBA method.[8] The result in Fig. 3 clearly indicates that the binuclear structure is very important for degradation of DNA, which seems to be consistent with our report that the peroxide adduct of binuclear iron(III) complexes can cleave DNA.[9]

Awai et al.[4] have reported that the "Fe(III)-nta complex solution" reacts with DMPO, one of the spin-trapping reagents, to yield an ESR-detectable species. As shown in Fig. 4, the ESR signal in solution of $K_3[Fe_2O(CH_3COO)(nta)_2]$ and DMPO is very similar to that reported by Awai et al. In addition to this, we have observed that some binuclear iron(III) complexes such as $Fe_2(HPTB)^{5+}$,[10] react with DMPO, forming an ESR-detectable species (cf. Fig. 4-A), where H(HPTB) represents N,N,N',N'-tetrakis(2-benzimidazolylmethyl)-2-hydroxy-1, 3-diaminopropane. This also suggests that the formation of ESR-detectable species of DMPO is due to a dimeric structure of Fe(III)-nta complex.

As already reported by us,[11] several binuclear iron(III) complexes can catalyze the peroxidation of linolenic and linolic acid in the presence of dioxygen molecule. We in this study have confirmed that several binuclear iron(III) compounds with μ-oxo bridge show high ability for peroxidation of

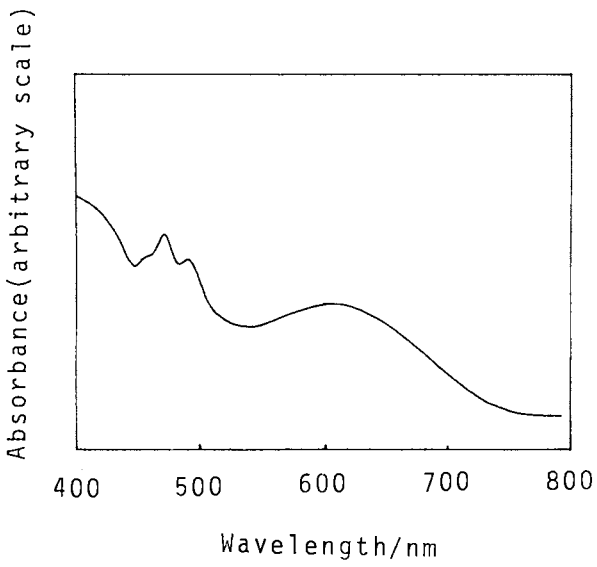

Fig. 2. Reflectance spectrum of $K_3[Fe_2O(CH_3COO)(nta)_2]$(room temperature).

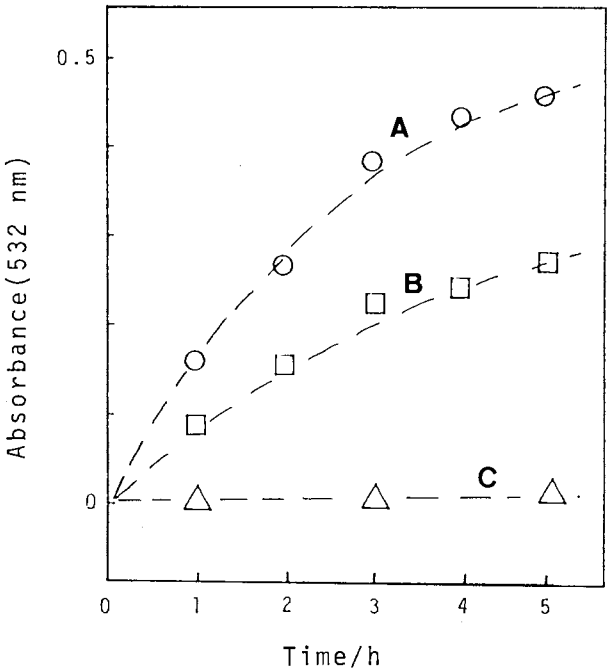

Fig. 3. Time course of absorbance at 532 nm of reaction mixture(10 ml of DNA solution(1 mg/1 ml), 10 ml of Fe(III) complex(0.004 M), and 10 ml of H_2O_2(1/10 M) were mixed) treated by 2-thiobarbituric acid(TBA).
A: $K_3[Fe_2O(CH_3COO)(nta)_2]$
B: $(enH_2)[Fe_2O(Hedta)_2]$[12]
C: Na[Fe(edta)]

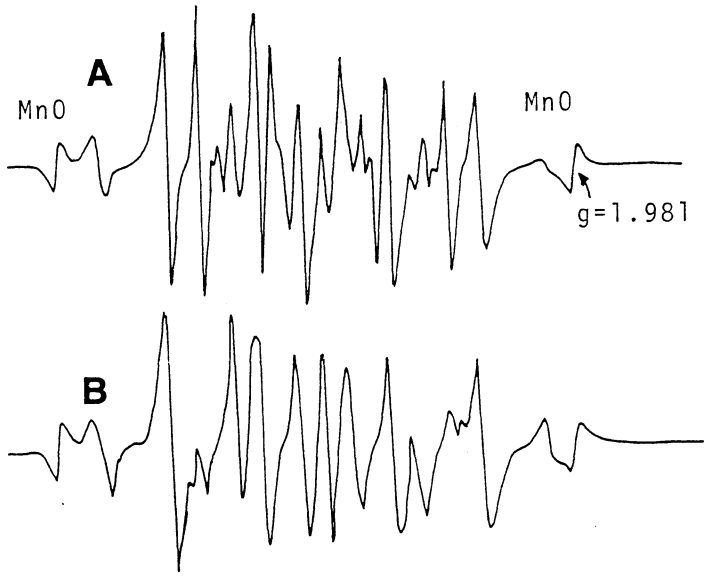

Fig. 4. ESR spectra(X-band, room temperature) of reaction mixture of 20 μl of Fe(III) complex(in ethanol/water=1/1, 1/500 M) and 10 μl of DMPO.
A: $Fe_2(HPTB)^{5+}$
B: $K_3[Fe_2O(CH_3COO)(nta)_2]$

linolenic acid. These are suggesting that the ability of the "Fe(III)-nta complex solution" for lipid peroxidation may be due to its dimeric structure.

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