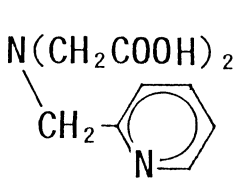
CHEMISTRY LETTERS, pp. 641-644, 1994.

Iron Chelates in Biological Systems. Its Relevance to Induction of Pathogenesis of Tissue Damage and Carcinogenesis

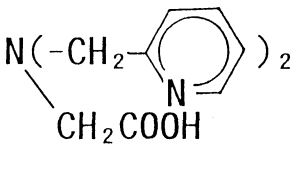
Yuzo NISHIDA,* Atsuko GOTO, Tetsuya AKAMATSU, Shigeru OHBA,†
Toyoaki FUJITA,† Tadashi TOKII,†† and Shigeru OKADA†††
Department of Chemistry, Faculty of Science, Yamagata University, Yamagata 990
†Department of Chemistry, Faculty of Science and Engineering, Keio University, Yokohama 223
††Department of Chemistry, Faculty of Science and Engineering, Saga University, Saga 840
†††Department of Pathology, Okayama University, Medical School, Okayama 700

Iron-nta(nitrilotriacetate) solution induces severe nephrotoxicity and high accidence of renal carcinoma in rats and mice, however, the effect by an iron-pac(2-aminomethylpyridine-N,N-diacetate) solution is negligible. These facts were interpreted in terms of different reactivity of the two compounds toward hydrogen peroxide.

Significance of the catalytic role of iron in the production of active molecular species of dioxygen in vivo for the pathogenesis of tissue damage and carcinogenesis has been suggested, since Awai and Okada reported that iron complex of nitrilotriacetate(nta) causes severe nephrotoxicity and high accidence of renal carcinoma in rats and mice.[1] In our previous paper,[2] we have isolated several iron(III)-nta complexes, and have determined[3] the crystal structure of $K_4[Fe_2O(nta)_2(CO_3)]$, and proposed that the unique reactivity of the solution should be due to its dimeric structure.[4] Later, we also have examined the effects of several other iron-chelates(see figures below)



(pac)



(dpa)

on iron-induced renal damage, and found that the effect by iron-(pac) or -(dpa) solution is negligible under the same experimental conditions in contrast with the iron-(nta) solution. In this report, we have determined the crystal structure of the iron-(pac) complex in order to elucidate the origin of the difference in the biological activity. The crystals of $Cs_2[Fe_2O(pac)_2(CO_3)]\cdot 7H_2O$ was isolated as green prisms from a solution containing ferric chloride, (pac) and Cs_2CO_3.[5] In Fig. 1, the ORTEP drawing of $[Fe_2O(pac)_2(CO_3)]^{2-}$ is shown; the complex is of a dimeric structure with μ-oxo and μ-carbonato bridges, which is very similar to that of the corresponding (nta) complex.[3] The structural parameters of the two compounds are compared in Table 1. It should be emphasized that Fe-O bond distances with oxo and carbonato ions are shorter by 0.02 — 0.03 Å in the (pac) complex than those in the (nta) complex. This fact should be the result of the higher Lewis acidity of the iron(III) ion induced by the (pac) chelate.[6] This is also reflected in the stability of the compounds; the μ-oxo species can exist in the solution of pH 6.0 in the case of (pac) complex, however, decomposition of the binuclear structure occurs under pH 6.5 in the case of (nta) complex.

Okada et al. have found[7] that much quantity of TBA(2-thiobarbituric acid)-active compound, which shows absorption maximum at 532 nm, is formed by the injection of iron-(nta) solution in Wistar rat, however the formation of TBA-active compound is negligible in the case of iron-(pac)

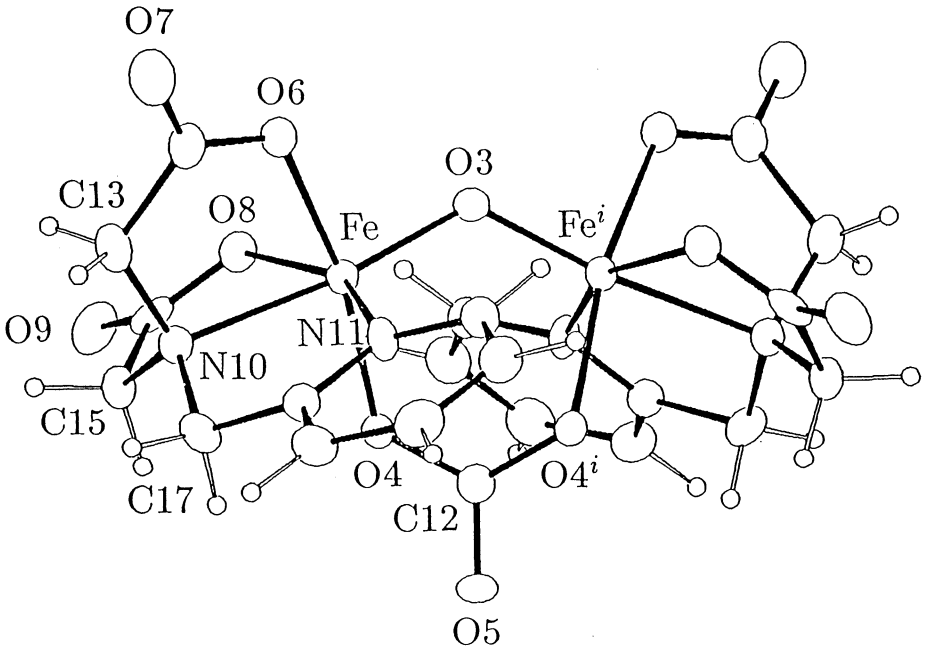


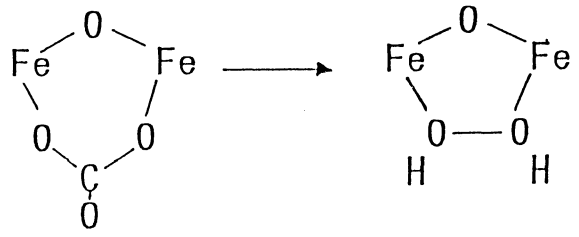
Fig. 1. Molecular structure of $[Fe_2O(pac)_2(CO_3)]^{2-}$.

Table 1. Selected bond lenghts(Å) of binuclear iron(III) compounds

	Fe-(nta)	Fe-(pac)
Fe-Fe	3.188(1)	3.186(3)
Fe-N10(tert-amine)	2.246(4)	2.235(8)
Fe-O3(oxo oxygen)	1.830(2)	1.800(4)
Fe-O4(carbonato)	2.005(3)	1.984(6)
Fe-O6(carboxylato)	2.025(3)	2.061(7)
Fe-O8(carboxylato)	2.020(3)	2.020(7)
Fe-O10(carboxylato)	2.082(3)	
Fe-N11(pyridine)		2.166(8)

solution. In order to elucidate the origin of the above fact, we have investigated the formation of TBA-active compounds by the iron(III)-chelates. As the results, we have found that presence of hydrogen peroxide in the system induces notable difference in the formation of TBA-active compounds between the iron(III)-(nta) and -(pac) solutions; i.e., the (nta)-solution produces much TBA-active compounds in the presence of hydrogen peroxide and 2'-deoxyribose, however TBA-active compounds are not formed in the (pac)-solution. In addition to this, we also have observed that iron(III)-(nta)/H_2O_2 solution produces nitrone radical in reaction with 2,2,6,6-tetramethyl-4-piperidinol, one of the singlet-oxygen spin trapping reagent,[8] but the formation of the radical is negligible in the case of iron(III)-(pac)/H_2O_2 system under the same experimental conditions.

We have already reported that some binuclear iron(III)-peroxide adducts exhibit unique reactivity (electrophilicity),[9] and several chemists have reported that binuclear iron(III)/H_2O_2 systems can catalyze hydroxylation reaction of alkanes.[10] We also found that the peroxide adduct of Mo(VI)[11] can also produce the nitrone radical in the reaction with substituted-piperidinols. Based on these results, it seems quite reasonable to assume that the formation of the nitrone radical by the iron-(nta)/H_2O_2 system should be due to formation of a peroxide adduct of iron-(nta) species, as shown below.



Since the Fe-O(carbonato ion) bonds are stronger in the (pac) complex, the formation of a peroxide adduct is unlikely, leading to the negligible activity of the (pac) complex for the formation of nitrone radical, and also for the formation of TBA-active compounds in reaction with 2'-deoxyribose. These are suggesting that tissue damage by the iron-(nta) solution in the biological system may be due to the presence of a dimeric iron(III) species and hydrogen peroxide.

References

1) M. Awai, M. Narasaki, Y. Yamanoi, and M. Seno, Am. J. Pathol., 95, 663(1979); S. Okada and O. Midorikawa, Jpn. Arch. Intern. Med., 29, 485(1982); M. Liu, S. Okada, and T. Kawabata, "Oxygen Radicals," ed by K. Yagi, M. Kondo, E. Niki, and T. Yoshikawa, Elsevier Science Publishers(1992), pp. 95-97.

2) Y. Nishida, K. Yoshizawa, and T. Akamatsu, Chem. Lett., 1991, 1521.

3) T. Fujita, S. Ohba, Y. Nishida, A. Goto, and T. Tokii, Acta Crystallogr., 1994, in press.

4) Y. Nishida and T. Akamatsu, J. Act. Oxyg. Free Radicals, 3, 376(1992).

5) Found: C, 24.56; H, 3.45; N, 5.24%. Calcd for $Cs_2Fe_2O(pac)_2(CO_3)\cdot 7H_2O$: C, 24.63; H, 3.35; N, 5.47%. Crystal data: monoclinic, space group C2/c; a=22.672(3), b=10.638(2), c=15.778(2) Å; β=107.90(1)°, V=3621.4(9) Å^3, Z=4. R=0.093 for 2516 observed reflections.

6) D. D. Cox and L. Que, Jr., J. Am. Chem. Soc., 110, 8085(1988); D. D. Cox, S. J. Benkovic, L. M. Bloom, F. C. Bradley, M. J. Nelson, L. Que, Jr., and D. E. Wallik, ibid., 110, 2026(1988).

7) S. Okada, to be submitted.

8) Y. Lion, M. Delmelle, and A. van de Vorst, Nature, 263, 442(1976).

9) Y. Nishida and M. Takeuchi, Z. Naturforsch., 42b, 52(1987); Y. Nishida, M. Nasu, and T. Akamatsu, ibid., 47b, 115(1992).

10) R. H. Fish, M. S. Konings, K. J. Oberhausen, R. H. Fong, W. M. Yu, G. Christou, J. B. Vincent, D. K. Coggin, and R. H. Buchanan, Inorg. Chem., 30, 3002(1991).

11) H. Tomioka, K. Takai, K. Ohshima, H. Nozaki, and K. Toriumi, Tetrahedron Lett., 21, 4843(1980).

(Received December 21, 1993)