Table I. NMR Spectral Data of TTX, 6-*epiTTX*, and 11-deoxyTTX[a]

| | TTX[b] | | | | 6-*epi*-TTX[c] | | | | 11-deoxyTTX[c] | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | hemilactal | | lactone | | hemilactal | | lactone | | hemilactal | | lactone | |
| | C | H | C | H | C | H | C | H | C | H | C | H |
| 2 | 156.6 | | 155.9 | | 156.5 | | 155.8 | | 156.4 | | - | |
| 4 | 75.1 | 5.50 (d 9.4) | 74.8 | 5.50 (d 9.4) | 75.1 | 5.55 (d 9.4) | 75.1 | 5.55 (d 8.9) | 75.0 | 5.49 (d 9.4) | 74.8 | 5.51 (d 9.6) |
| 4a | 40.7 | 2.35 (d 9.5) | 46.5 | 2.35 (d 9.5) | 41.8 | 2.01 (d 9.0) | 46.9 | 2.13 (d 9.0) | 40.5 | 2.37 (d 9.4) | 46.2 | 2.37 (d 9.4) |
| 5 | 73.8 | 4.25 (br s) | 69.2 | 4.03 | 75.4 | 4.30 (d 1.6) | 68.4 | 4.03 (br s) | 77.5 | 4.08 (br s) | 72.0 | 3.87 (br s) |
| 6 | 71.5 | | -[d] | | 72.8 | | 77.0 | | 69.1 | | - | |
| 7 | 79.7 | 4.08 (t 1.8) | 82.5 | 4.55 (br s) | 82.0 | 4.08 (br s) | 85.5 | 4.62 (br s) | 83.6 | 3.91 (t 1.6) | 86.8 | 4.35 (t 2.0) |
| 8 | 72.8 | 4.30 (d 1.5) | 71.5 | 4.44 (br s) | 72.9 | 4.17 (br s) | 71.7 | 4.26 (br s) | 72.6 | 4.30 (d 1.6) | 71.3 | 4.46 (d 2.3) |
| 8a | 59.7 | | 60.4 | | 59.6 | | 60.1 | | 59.1 | | 59.8 | |
| 9 | 70.9 | 3.96 (s) | 74.0 | 4.57 (s) | 70.8 | 4.00 (s) | 73.7 | 4.59 (s) | 70.8 | 3.94 (s) | 73.9 | 4.55 (s) |
| 10 | 110.8 | | 176.1 | | 110.7 | | 175.8 | | 110.6 | | 175.4 | |
| 11 | 65.5 | 4.02 (d 12.6) 4.04 (d 12.6) | 65.2 | 3.77 (d 12.6) 4.01 (d 12.6) | 65.1 | 3.74 (s) | 66.2 | 3.68 (d 14.0) 3.69 (d 14.0) | 25.1 | 1.64 (s) | 24.5 | 1.51 (s) |

[a] $^{13}C$ NMR 75.5 MHz, $^{13}CD_3COOD$ = 22.4 ppm (GN-300); $^1H$ NMR, $CHD_2COOD$ = 2.06 ppm. Information in parentheses denotes multiplet and $J$ in Hz. [b] $^1H$ NMR 360 MHz (NT360) and solvent 1% $CF_3COOD$, 4% $CD_3COOD/D_2O$. [c] $^1H$ NMR 300 MHz (GN-300), and solvent 4% $CD_3COOD/D_2O$. [d] Unassignable carbons.

$\delta$ 3.74 ($CH_2$-11) enhanced signal intensities of H-4a (10.6%) and H-8 (10.3%) of **4**, while irradiation of $CH_2$-11 of TTX gave no NOE on both protons. All these data support the structural assignment of **4**.

The other analogue, 11-deoxyTTX (**6**), crystallized as colorless needles from 4% HOAc [202 °C dec, $[\alpha]^{25}_D$ +5.37° (*c* 0.34, 0.05 N HOAc)]; the $LD_{50}$ to mice was 71 $\mu$g/kg (ip); the molecular formula by high resolution FABMS $C_{11}H_{17}N_3O_7$ ($MH^+$, *m/z* 304.1145, found 304.1155) corresponded to a monodeoxy derivative of TTX. Proton COSY of **6** showed that the coupling patterns, including a W-type coupling between H-4a and H-9, are essentially the same as those of TTX (Table I), thus suggesting their structural resemblance. Homo and heteronuclear COSY spectra of **6** indicated that the $CH_2$-11 signals in TTX were replaced by a methyl signal (Table I). Comparison of $^{13}C$ NMR spectra of **6** and TTX further supported reduction at C-11. A signal assignable to C-6 was shifted upfield, and those of C-5 and C-7 were shifted downfield, while other signals of **6** agreed with those of TTX within 0.6 ppm (Table I). Me-11 was assigned equatorial conformation because no NOE was observed between H-4a and Me-11. These data establish the structure of the new analogue as 11-deoxyTTX, **6**. The spectral data indicated that **6** also exists as hemilactal–lactone tautomers (7:3). Two analogues derivable from **6** with acid were also isolated from the newts and identified as 4-*epi*-11-deoxyTTX (**7**)[8] and 4,9-anhydro-11-deoxyTTX (**8**).[9]

Biosynthesis of TTX supposedly involves arginine and a C5 unit derived from either amino acids, isoprenoids, shikimates, or branched sugars.[10] The occurrence of 6-epi and 11-deoxy analogues renders branched sugars unlikely precursors, and the shikimate pathway does not seem plausible because it rarely yields 1,2,4-trialkylcyclohexanes. An isoprenoid unit is favored because it possesses both an $sp^2$ carbon oxidizable to either TTX or 6-*epi*TTX and a methyl that remains in 11-deoxyTTX. The analogues will also be important for structure-activity relationships because chemical transformations of TTX are difficult.

**Acknowledgment.** We are grateful to Prof. P. J. Scheuer for reading the manuscript. The present work was supported by a grant-in-aid from the Ministry of Education, Science and Culture.

(8) 11-deoxy-4-*epi*TTX (**7**); SIMS (Hitachi M-80) $MH^+$ *m/z* 304; $^1H$ NMR of a hemilactal form $\delta$ 5.13 (H-4, d, $J_{4-4a}$ = 4.9 Hz), 2.87 (H-4a d, $J_{4a-4}$ = 5.0 Hz), 4.13 (H-5, d, $J_{5-7}$ = 1.5 Hz), 3.91 (H-7, t, $J_{7-5}$, $J_{7-8}$ = 1.5 Hz), 4.29 (H-8, d, $J_{8-7}$ = 1.5 Hz), 3.96 (H-9, s), 1.64 (Me-11, s).

(9) 4,9-anhydro-11-deoxyTTX (**8**): SIMS (Hitachi M-80) $NH^+$ *m/z* 286; $^1H$ NMR of a hemilactal form $\delta$ 5.51 (H-4, s), 2.95 (H-4a, d, $J_{4a-5}$ = 3.0 Hz), 4.15 (H-5, dd, $J_{5-4a}$ = 3.0 Hz, $J_{5-7}$ = 2.0 Hz), 4.01 (H-7, t, $J_{7-5}$, $J_{7-8}$ = 2.0 Hz), 4.63 (H-8, d, $J_{8-7}$ = 2.0 Hz), 4.56 (H-9, s), 1.61 (Me-11, s). The signals of **5**, **7**, and **8** were assigned by $^1H$-$^1H$ COSY measured with a GN-300 spectrometer by using 4% $CD_3COOD$ in $D_2O$ as the solvent.

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## Models for the $Fe^{II}Fe^{III}$ and $Fe^{II}Fe^{II}$ Forms of Iron-Oxo Proteins

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*Received December 3, 1987*

The importance of redox active, binuclear iron centers in proteins is well established.[1] In an attempt to probe these centers, several crystallographically characterized synthetic analogues of the binuclear iron center in methemerythrin and ribonucleotide reductase have been reported, demonstrating the thermodynamic stability of the ($\mu$-oxo)bis($\mu$-carboxylato)diiron(III) unit.[2-4] Analogues of mixed valence sites in semimethemerythrin and reduced purple acid phosphatases have also been reported, but none are structurally characterized.[5-7] In addition, only one model

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**Table I.** Comparison of the Structural Parameters of $[Fe^{II}Fe^{III}BPMP(OPr)_2]^{2+}$ (**1**) and $[Fe^{II}Fe^{II}BPMP(OPr)_2]^{+}$ (**2**)

| bond length (Å) or angle (deg) | 1 | 2 |
|---|---|---|
| Fe1–O1 | 2.090 (2) | 2.062 (1) |
| Fe1–O2 | 2.029 (2) | 2.035 (2) |
| Fe1–O3 | 2.145 (3) | 2.150 (2) |
| Fe1–N1 | 2.195 (3) | 2.259 (2) |
| Fe1–N2 | 2.186 (3) | 2.232 (2) |
| Fe1–N3 | 2.141 (3) | 2.165 (2) |
| Fe2–O1 | 1.943 (2) | 2.052 (1) |
| Fe2–O4 | 1.945 (2) | 2.045 (2) |
| Fe2–O5 | 1.983 (2) | 2.138 (2) |
| Fe2–N4 | 2.185 (3) | 2.250 (2) |
| Fe2–N5 | 2.155 (3) | 2.241 (2) |
| Fe2–N6 | 2.128 (3) | 2.178 (2) |
| Fe1–Fe2 | 3.365 (1) | 3.348 (2) |
| Fe1–O1–Fe2 | 113.1 (1) | 108.93 (6) |

for the $Fe^{II}Fe^{II}$ site in deoxyhemerythrin has been crystallized and structurally determined.[6,8] We have approached the synthesis of such analogues by using a binucleating ligand strategy, a method that has been successful in mimicking the active site properties of binuclear copper proteins.[9–11] Reported herein is the first example of a structurally characterized triply bridged $Fe^{II}Fe^{III}$ complex, $[Fe^{II}Fe^{III}BPMP(OPr)_2](BPh_4)_2$ **1**,[12] the structure of the corresponding $Fe^{II}Fe^{II}$ complex **2**, and their physical properties.

Complex **1** was obtained by treating a methanolic solution of HBPMP[13] with 2 equiv of $Fe(NO_3)_3{\cdot}9H_2O$ and 3 equiv of sodium propionate. Reduction of one Fe(III) center occurs spontaneously presumably by oxidation of the solvent. Metathesis with $NaBPh_4$ and recrystallization by vapor diffusion of methanol into an acetone solution of **1** yielded dark crystals.[14] Complex **2** was prepared by a similar procedure except that the reaction was performed under a dinitrogen atmosphere and $Fe(BF_4)_2{\cdot}6H_2O$ was used as the iron precursor. Recrystallization by vapor diffusion of acetone into a dichloromethane solution of **2** under $N_2$ yielded orange crystals.[15]

Complexes **1** and **2** have been characterized crystallographically, and their important structural parameters are compared in Table I.[16,17] The overall structures of **1** and **2** are similar (shown in Figure 1 for **1**), with both complexes containing the increasingly

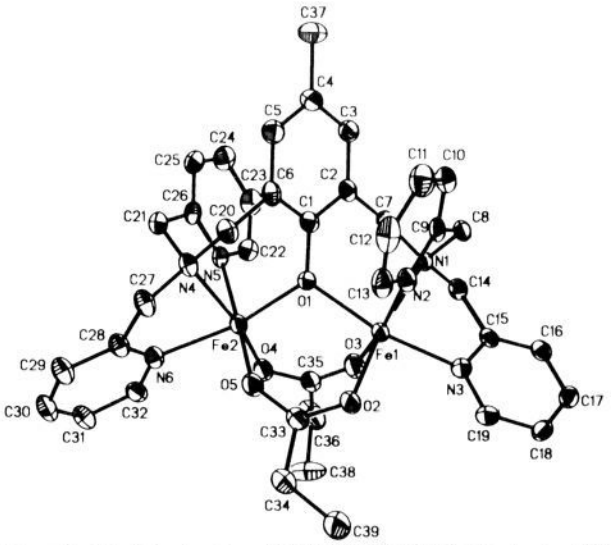


**Figure 1.** Plot of the structure of $[Fe^{II}Fe^{III}BPMP(OPr)_2]^{2+}$, showing 50% probability ellipsoids. The hydrogen atoms are omitted for clarity.

familiar ($\mu$-phenoxo)bis($\mu$-dicarboxylato)diiron core. The X-ray structure analysis of **1** is indicative of a mixed valence complex. It shows significant differences in the Fe–O bond lengths for the two Fe centers, with average Fe–O values of 1.957 (2) Å for Fe(III)–O and 2.088 (2) Å for Fe(II)–O. For comparison, the average Fe(III)–O bond length found in $[(HBpz_3Fe)_2OH(OAc)_2]^{+}$ is 1.970 Å,[18] while the average Fe(II)–O bond lengths observed for $[Fe_2(OH)(OAc)_2(Me_3TACN)_2]^{+}$ and $[Cr^{III}Fe^{II}(OH)(OAc)_2(Me_3TACN)_2]^{2+}$ are 2.083 (5) Å[6] and 2.064 (6) Å,[19] respectively. The Fe–Fe distance for **1** is 3.365 (1) Å, which is comparable to the 3.44-Å distance found in semimethemerythrin azide by EXAFS.[20]

In **2**, the iron–ligand bond lengths for both metal ion centers are now similar to those found for the Fe(II) site in **1** and $[Fe_2(OH)(OAc)_2(Me_3TACN)_2]^{+}$. The increased bond lengths at Fe2 in **2** causes a decrease in the Fe1–O1–Fe2 angle relative to **1** (108.93 (6)° versus 113.1 (1)°) and a slight shortening of the Fe–Fe distance to 3.348 (2) Å. This Fe–Fe distance is similar to that found for $[Fe_2(OH)(OAc)_2(Me_3TACN)_2]^{+}$ (3.32 (1) Å),[6] and is consistent with the distance deduced for deoxyhemerythrin by X-ray diffraction measurements.[21]

The physical properties of the complexes corroborate the crystallographic results. The two complexes display electrochemistry expected for a redox pair, with nearly identical cyclic voltammograms. Two reversible one-electron waves are observed at 690 and −10 mV versus SCE which correspond to $Fe^{III}Fe^{III}/Fe^{II}Fe^{III}$ and $Fe^{II}Fe^{III}/Fe^{II}Fe^{II}$ couples, respectively.[22] Complex **1** exhibits an electronic spectrum in $CH_3CN$ with features at 385 (sh, $\epsilon$ 2200 $M^{-1}$ $cm^{-1}$), 554 ($\epsilon$ 950 $M^{-1}$ $cm^{-1}$), and 1340 nm ($\epsilon$ 280 $M^{-1}$ $cm^{-1}$), the latter being assigned to an intervalence charge transfer band, while the spectrum of **2** contains only one band at 441 nm ($\epsilon$ 2500 $M^{-1}$ $cm^{-1}$) with no prominent features in the near-IR region. The Mössbauer spectrum of **1** at 55 K is consistent with the mixed valence formulation, revealing two quadrupole doublets of equal intensity having $\delta$ values of 0.48

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(15) Elemental Anal. Calcd for $[Fe_2BPMP(OPr)_2](BPh_4){\cdot}0.8CH_2Cl_2$ (**2**), $C_{63.8}H_{64.6}B_2Cl_{1.6}Fe_2N_6O_6$: C, 65.22; H, 5.55; N, 7.15. Found: C, 65.18; H, 5.60; N, 6.88. A $^1H$ NMR spectrum of **2** confirms the presence of the $CH_2Cl_2$ solvent of crystallization.
(16) $[Fe_2BPMP(OPr)_2](BPh_4)_2{\cdot}CH_3COCH_3$ (**1**) crystallized in the space group $P\bar{1}$ with the following cell constants: $a$ = 13.489 (9) Å, $b$ = 13.514 (6) Å, $c$ = 25.258 (15) Å, $\alpha$ = 77.23 (4)°, $\beta$ = 77.89 (5)°, $\gamma$ = 61.43 (4)°, $Z$ = 2, $V$ = 3914.2 Å$^3$. With the use of 9531 of 13728 reflections, for which $I(\text{obsd}) > \sigma(I)$, collected at 182 K with Mo K$\alpha$ ($\lambda$ = 0.71073 Å) radiation out to $2\theta$ = 50° on an Enraf-Nonius CAD4 X-ray diffractometer, the structure was solved by the Patterson method and refined anisotropically to $R$ = 0.051 and $R_w$ = 0.063.
(17) $[Fe_2BPMP(OPr)_2](BPh_4){\cdot}0.8CH_2Cl_2$ (**2**) crystallized in the space group $P\bar{1}$ with the following cell constants: $a$ = 12.607 (6) Å, $b$ = 15.113 (13) Å, $c$ = 16.601 (6) Å, $\alpha$ = 81.42 (6)°, $\beta$ = 88.88 (4)°, $\gamma$ = 67.89 (5)°, $Z$ = 2, $V$ = 2879.4 Å$^3$. From 11192 reflections (of 13865 where $I(\text{obsd}) > \sigma(I)$) collected at 175 K, the structure was solved by the Patterson method and refined anisotropically to $R$ = 0.058 and $R_w$ = 0.074.
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and 1.13 mm/s and $\Delta E_Q$ values of 0.50 and 2.69 mm/s, respectively. In addition, the Mössbauer spectrum of **2** shows only one quadrupole doublet ($\delta$, 1.20 mm/s; $\Delta E_Q$, 2.72 mm/s) associated with the high spin ferrous centers. The magnetic moments of **1** and **2** at 200 K are 6.62 and 6.88 $\mu$B/complex, respectively. Complex **1** does not exhibit any EPR features at $g < 2$, a result that is similar to that found for the previously reported mixed-valence complex, $[Fe_2HXTA(OAc)_2]^{2-}$ [5] and the reduced uteroferrin-phosphate complex.[23] Complex **2**, on the other hand, exhibits a broad EPR signal at low field with maximum amplitude at 500 G.[24] This is reminiscent of the signal found for deoxyhemerythrin azide, which is proposed to arise from a $\Delta M_s = 8$ transition.[25] Detailed magnetic and spectroscopic studies of these complexes are in progress.

In summary, **1** and **2** represent the first structurally characterized $Fe^{II}Fe^{III}$ and $Fe^{II}Fe^{II}$ redox pair that contain the biologically important triply bridged diiron core. The two complexes have significant differences in their structural and physical properties. Furthermore, the dependence of the physical properties on the bridging and terminal ligands in these complexes should provide important insights into the magnetic and electronic interactions of such binuclear iron centers in biology.

**Acknowledgment.** This work was supported by the National Institutes of Health Grant GM-38767. A.S.B. is grateful for a N.I.H. Postdoctoral Fellowship (GM-11533). We thank Dr. Vasilios Papaefthymiou for the Mössbauer measurements, Dr. Edmund Day and Jacques Bonvoisin for the magnetic measurements, and Professor Doyle Britton and Paul Boyle for their efforts on the X-ray crystal structure determinations.

**Supplementary Material Available:** Tables of atomic positional and thermal parameters for $[Fe^{II}Fe^{III}BPMP(OPr)_2](BPh_4)_2 \cdot CH_3COCH_3$ and $[Fe^{II}Fe^{II}BPMP(OPr)_2](BPh_4) \cdot 0.8CH_2Cl_2$ (20 pages). Ordering information is given on any current masthead page.

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## Alteration of Bleomycin Cleavage Specificity in a Platinated DNA Oligomer of Defined Structure

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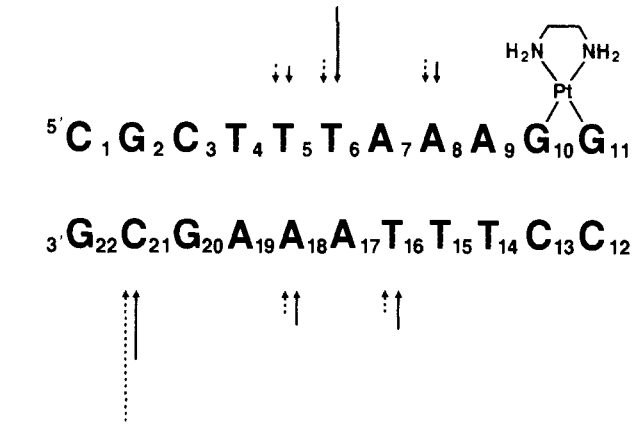
The bleomycins (BLMs) are antitumor antibiotics that are thought to act via metal ion and oxygen-dependent oxidative damage to DNA.[2,3] At least for Fe·BLM, available evidence suggests that degradation involves oxygenation of the deoxyribose moiety at C-4′H.[4] Bleomycin-mediated DNA degradation occurs with considerable selectivity for the pyrimidines in a subset of all 5′-GT-3′ and 5′-GC-3′ sequences.[5,6] Interestingly, the extent of cleavage at preferred sites differed among individual bleomycin congeners,[6f,7] including some having a different spectrum of activity

**Chart I**[a]




[a] Fe·BLM-mediated strand scission of a platinated (↑) and nonplatinated (↟) DNA oligomer. The extent of cleavage at individual positions was proportional to the length of the arrows shown. The extent of DNA cleavage was determined by HPLC analysis and quantification of individual products (Table I and ref 15). In order to identify the site(s) of enhanced Fe(II)·BLM modification in the platinated oligonucleotide, each of the strands in the duplex was separately 5′-$^{32}$P end labeled and annealed to its complementary unlabeled strand. The four duplexes (platinated and unplatinated, with the individual strands $^{32}$P-end labeled) were subjected to Fe(II)·BLM $A_2$ digestion, and the relative extents of cleavage at individual positions were determined by densitometry of polyacrylamide gels (Table II).[20] The HPLC and sequence analysis data were found to correlate well.

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