Iron-Assisted Oxidative Radical C–C Bond Cleavage

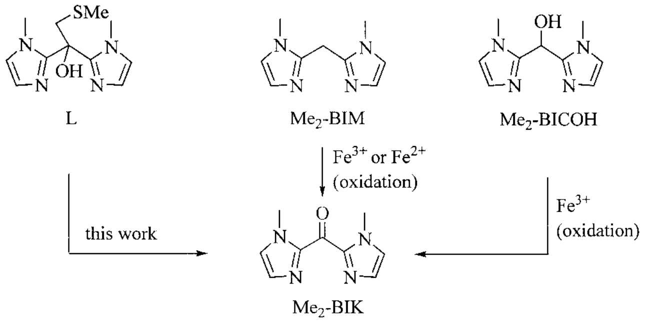
Laurent Bénisvy,[a,c] Jean-Claude Chottard,[a] Jérôme Marrot,[b] and Yun Li*[a]

Keywords: Iron / Multidentate ligand / Imidazole ligand / Thioether ligand / Radical fragmentation / X-ray diffraction

The N_2SO ligand, bis(*N*-methylimidazol-2-yl)-2-methylthioethanol (**L**), when coordinated to Fe^{3+} or Fe^{2+}, undergoes a radical C–C bond cleavage in air, to form bis(*N*-methylimidazol-2-yl) ketone (Me_2-BIK).

Introduction

Model complexes play an important role in the comprehension of mechanistic studies of metalloproteins. Iron complexes with polyimidazole and benzimidazole ligands are commonly used to mimic the active sites of various iron-containing proteins with histidine residues.[1,2] A variety of protein residues other than His also coordinate a metal ion in enzyme active sites. For example, a relatively unusual metal site [$N_2SM^{II}(H_2O)$] (N = Histidine, S = Cysteine, M = Zn, Co, Ni and Fe) is found in peptide deformylase (PDF).[3,4] Peptide deformylase (PDF) is responsible for the hydrolysis of an N-terminal formyl group during bacterial protein synthesis and has been under investigation as a new target for antibiotics. Our initial goal was to look at the coordination behavior of a mixed N,S,O multidentate ligand to Fe^{2+} or Fe^{3+}. However, because of the frustrating propensity of thiolato ($RS^–$) ligands to yield sulfur-bridged polymeric metal species and disulfide derivatives by radical coupling reactions, we chose to work with thioethers to avoid undesired side reactions. We have prepared the new tripodal N_2SO ligand, bis(*N*-methylimidazol-2-yl)-2-methylthioethanol (**L**, see Scheme 1), comprising donor atoms from *N*-methylimidazole, methylthioether and alcohol functionalities. **L** is an analogue of the previously reported N_2S ligands (N = imidazole, S = thiolate), that have been studied for Hg^{2+}, Cu^{2+}, Zn^{2+} and Fe^{2+} coordination.[5,6] These thiolato ligands presented both synthetic difficulties and the above-mentioned undesirable side reactions. In principle, **L** could coordinate to $Fe^{2+/3+}$ as a tridentate (N_2S or *NOS*), or as a bidentate (N_2 or *NO*). We have found that in aerated MeOH, in the presence of Fe^{2+} or Fe^{3+}, this ligand was converted into bis(*N*-methylimidazol-2-yl) ketone (Me_2-BIK). This reaction could be compared to the iron-catalyzed oxidations of bis(*N*-methylimidazol-2-yl)methanol (Me_2-BICOH)[7] and bis(*N*-methylimidazol-2-yl)methane (Me_2-BIM)[8] into Me_2-BIK. However, in the case of **L**, the formation of Me_2-BIK requires a carbon–carbon bond scission (Scheme 1).



Scheme 1. Different pathways for the formation of Me_2-BIK.

Results and Discussion

The synthesis of **L** was straightforward and was achieved in only one step by condensation of the anion of *N*-methylimidazole with ethyl (methylthio)acetate ($MeSCH_2COOEt$).

Under argon, the reaction of **L** with $Fe(ClO_4)_2\cdot xH_2O$ in degassed MeOH in a 3:1 ratio, led to a pale-yellow Fe^{II} complex (EPR silent). Its cyclic voltammogram in MeOH clearly shows the formation of an Fe^{II} complex, as there is an irreversible oxidation peak at ca. 0.180 V (vs. Fc^+/Fc) (Figure S1, see Supporting Information). In the presence of air, the Fe^{II} complex oxidized into a yellow, paramagnetic Fe^{3+} species. Its EPR spectrum in MeOH at 10 K is typical of rhombic high-spin Fe^{3+} species (g = 4.25). The cyclic voltammogram of this yellow complex in MeOH exhibits an irreversible reduction wave at –0.62 V (vs. Fc^+/Fc), con-

---

[a] Laboratoire de Chimie et Biochimie Pharmacologiques et Toxicologiques (CNRS UMR8601), Université René Descartes,
45, Rue des Saints Pères, 75270 Paris Cedex 06, France
E-mail: yun.xu-li@univ-paris5.fr
[b] Institut Lavoisier, Université Versailles Saint-Quentin,
45, Avenue des Etats-Unis, 78035 Versailles, France
[c] Present address: Max-Planck Institut für Bioanorganische Chemie,
Stiftstrasse 34-36, 45470 Mülheim, Germany

Supporting information for this article is available on the WWW under http://www.eurjic.org or from the author.

DOI: 10.1002/ejic.200400782

firming the +3 oxidation state (Figure S1 top, see Supporting Information). This yellow complex turned blue at room temperature. After several days, deep-blue crystals precipitated. The IR spectrum of the solid indicates the presence of a ketone function ($\nu_{C=O}$ = 1637 cm^{-1}). The cyclic voltammogram in CH_3CN solution shows a fully reversible one-electron oxidation process at $E_{1/2}$ = 0.44 V (vs. Fc^+/Fc) (Figure S2, see Supporting Information).

The X-ray structural determination of the blue complex revealed it to be $[Fe^{II}(Me_2\text{-BIK})_3](ClO_4)_2$. The Me_2-BIK ligand resulted obviously from the fragmentation of the CH_2SMe arm during the oxidation of **L**. An ORTEP[9] view of the $[Fe(Me_2\text{-BIK})_3]^{2+}$ cation at 298 K is shown in Figure 1. The unit cell includes eight mononuclear complex molecules. The iron is hexacoordinated in an N_6 environment with a distorted octahedral geometry. The six nitrogen donors originate from three Me_2-BIK molecules. The significant departure of the FeN_6 core from octahedral geometry is evidenced by the values of the bond angles, e.g. 83.91° for the N(26)–Fe–N(15) angle. The Fe–N distances range from 2.123 to 2.159 Å, clearly demonstrating that the iron is high-spin (HS, S = 2). For low-spin (LS, S = 0) octahedral $[Fe^{II}N_6]$ complexes, the average bond lengths are ca. 1.97 Å.[10] Moreover, the paramagnetism of $[Fe^{II}(Me_2\text{-BIK})_3](ClO_4)_2$ was also observed in the ^1H NMR spectrum (250 MHz, CN_3CN, 300 K), which spread over the range from 17 to 4 ppm (see Experimental Section).

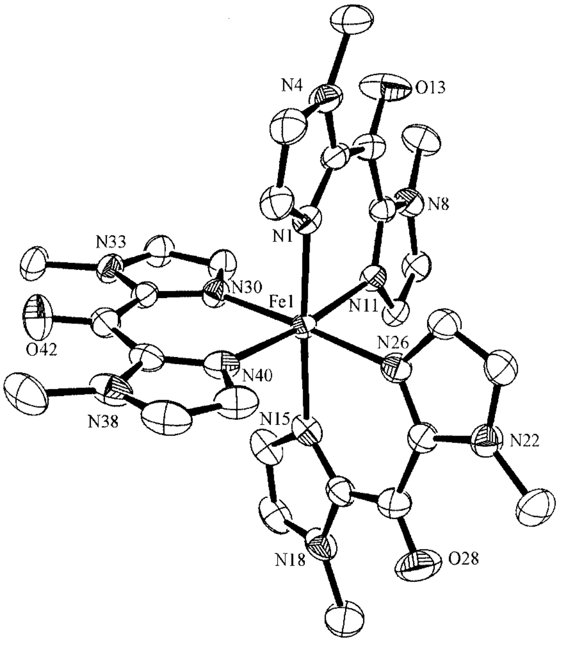
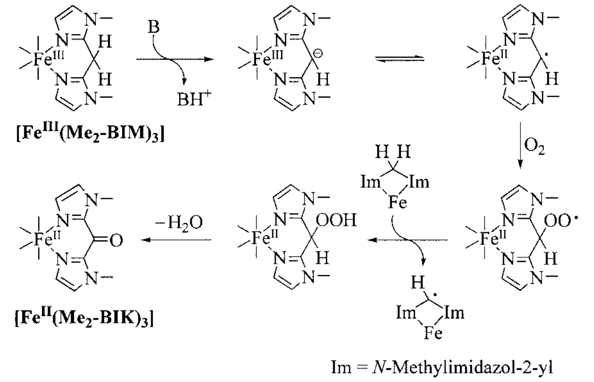


Figure 1. ORTEP view (ellipsoid at the 30% probability level) of $[Fe(Me_2\text{-BIK})_3]^{2+}$. H atoms are omitted for clarity. Selected bond distances (Å): Fe–N(1) 2.143(2), Fe–N(11) 2.125(2), Fe–N(15) 2.159(3), Fe–N(26) 2.132(2), Fe–N(30) 2.140(2), Fe–N(40) 2.123(3). Selected bond angles (°): N(1)–Fe–N(11) 84.53(9), N(1)–Fe–N(26) 92.88(9), N(1)–Fe–N(15) 176.61(9), N(1)–Fe–N(40) 90.56(9), N(1)–Fe–N(30) 91.02(9), N(11)–Fe–N(26) 91.07(9), N(11)–Fe–N(15) 94.45(8), N(11)–Fe–N(40) 172.67(9), N(11)–Fe–N(30) 88.92(8), N(26)–Fe–N(15) 83.91(9), N(26)–Fe–N(40) 94.62(9), N(26)–Fe–N(30) 176.09(9), N(15)–Fe–N(40) 90.75(9), N(15)–Fe–N(30) 92.19(9), N(40)–Fe–N(30) 85.71(9).

It is well-known that some octahedral iron(II)-N_6 complexes exhibit temperature-dependent "spin-equilibrium" (LS ↔ HS) behavior. This active research area has been widely reviewed.[11] The spin-crossover property of $[Fe(Me_2\text{-BIK})_3](BF_4)_2$, prepared classically from $Fe(BF_4)_2$ and 3 equiv. of Me_2-BIK[12] in CH_3CN, has been investigated earlier by Mössbauer spectroscopy in cooperation with our group.[13]

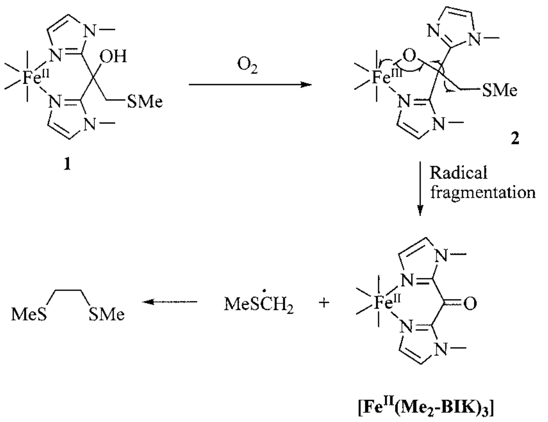
When Fe^{3+} or Fe^{3+}/Et_3N (3 equiv.) in MeOH were used instead of Fe^{2+}, the same cleavage reaction was observed. The addition of Et_3N accelerated the reaction and gave a better yield.

It has been previously reported that $[Fe(Me_2\text{-BIK})_3]^{2+}$ was a side-product formed during the complexation of Fe^{3+} by the N_2OH ligand (Me_2-BICOH) (Scheme 1).[7] We have also found that Me_2-BIM was converted into Me_2-BIK by $Fe^{2+/3+}$ under oxygen upon base catalysis (Scheme 2).[8] A comparable reaction has been observed with Cu^{II}-catalyzed oxidation of *bis*(*N*-methylbenzimidazol-2-yl)methane and *bis*(2-pyridyl)methane into the corresponding ketones.[14,15] In all these cases, the ligands present "benzylic"-type oxidizable hydrogen atom(s), and the mechanism involves most likely the "benzylic" radicals. However, the mechanism ought to be different in the present instance, since the "benzylic" carbon is fully substituted.



Scheme 2. Iron-assisted oxidation of Me_2-BIM into Me_2-BIK upon base catalysis (ref.[8]).

When the reaction was run under $^{18}O_2$ instead of air, no ^{18}O atom incorporation was found by electrospray mass spectroscopy. This result means that the oxygen atom in $[Fe^{II}(Me_2\text{-BIK})_3]^{2+}$ comes from the ligand. We suggest a radical mechanism for this C–C bond fragmentation which involves the following sequence (Scheme 3): [1] oxidation of the very unstable Fe^{II} complex **1** by O_2 to generate the intermediate Fe^{III} complex **2** with a switch of ligand in the coordination sphere, in agreement with the preference of Fe^{III} for the alcoholate rather than the imidazole ligand; [2] homolytic C–C bond cleavage, forming the (methylthio)methyl radical, assisted by the homolytic fragmentation of the Fe^{III}–O bond, to give the corresponding ketone function. The (methylthio)methyl radical is stabilized by the presence of the sulfur atom in the α-position of the radical and dimerizes into $CH_3SCH_2CH_2SCH_3$. The latter was detected in the mother liquor after the reaction, by electrospray MS (m/z = 123, M + H$^+$) and ^{1}H NMR spectroscopy ($CDCl_3$, δ = 2.653, and 2.151 ppm in a 2:3 ratio); the spectrum agreed with the literature data.[16] The driving force of the fragmentation likely results from the stability of $[Fe(Me_2\text{-}BIK)_3]^{2+}$ ($E_{1/2}$ = +0.44 V vs. Fc^+/Fc, CH_3CN), as well as the relative stability of the thioether α-carbon radicals.



Scheme 3. Proposed iron-assisted radical fragmentation mechanism for the formation of Me_2-BIK.

Conclusion

This study has shown that whatever the substituents on the "benzylic" type bridge of the bis(*N*-methylimidazol-2-yl)methane core, either H/H, H/OH or OH/CH_2SMe, its Fe(III)-catalyzed oxidation takes an appropriate pathway to form bis(*N*-methylimidazol-2-yl) ketone (Me_2-BIK). To avoid this fragmentation, a new ligand with one more carbon in the side arm (CH_2CH_2SMe instead of CH_2SMe) was synthesized. Its complexation towards Fe^{2+} and Fe^{3+} is under investigation.

Experimental Section

Synthesis of Ligand L: A solution of *n*BuLi (1.6 M *in* hexane, 7.3 mL, 11.7 mmol) was added dropwise to a solution of *N*-methylimidazole (0.96 g, 11.7 mmol) in anhydrous THF (10 mL) cooled to 0 °C. After 30 min at 0 °C under argon, $MeSCH_2CO_2Et$ (0.5 mL, 520 mg, 3.9 mmol) was added dropwise to the yellow solution at 0 °C. The temperature was allowed to rise slowly to room temperature and maintained at room temperature for 1 night. The mixture was extracted with EtOAc (3 × 50 mL), and the combined organic layers were washed with saturated aq. NaCl (2 × 50 mL), dried ($MgSO_4$), and the solvents evaporated to dryness. The crude product was filtered through silica gel ($MeOH\text{-}CH_2Cl_2$-conc. aq. NH_3 = 5:95:0.25 as the eluent). The pale-yellow solid obtained was recrystallized from EtOAc/cyclohexane (1:1) to give **L** as colorless crystals (403 mg, 41 %). M.p. (EtOAc/cyclohexane) 133 °C. MS (CI, NH_3): m/z = 253 (M + 1). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 6.97 (s, 2 H, H_{im}), 6.80 (s, 2 H, H_{im}), 5.40 (s, 1 H, D_2O exchangeable, OH), 3.66 (S, 2 H, CH_2), 3.29 (s, 6 H, NMe), 1.92 (s, 3 H, SMe) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 146.6 (C-2_{im}), 126.3 + 123.5 (C-4_{im} + C-5_{im}), 77.8 (C-OH), 44.6 (CH_2), 33.5 (NCH_3), 17.1 (SCH_3) ppm. $C_{11}H_{16}N_4OS$ (252.34): calcd. C 52.36, H 6.39, N 22.20, S 12.71; found: C 52.47, H 6.47, N 22.12, S 12.57.

$[Fe^{II}(Me_2BIK)_3](ClO_4)_2$: A solution of **L** (83 mg, 0.33 mmol) and $Fe^{II}(ClO_4)_2.xH_2O$ (37 mg, 0.11 mmol) in degassed MeOH (2.5 mL) was stirred under Ar. The initial pale-yellow solution turned yellow after 10 min at room temperature. Stirring was continued for 15 h, and the solvent was evaporated to dryness under reduced pressure. The yellow-brown solid was dissolved in MeOH (6 mL). Et_2O (12 mL) was carefully added to the surface of the MeOH solution, and the mixture was left unperturbed for 24 h. The blue precipitate was filtered, rinsed with Et_2O and vacuum-dried to afford $[Fe^{II}(Me_2BIK)_3](ClO_4)_2$ as a crystalline powder (40 mg, 44 %). UV/Vis (CH_3CN): λ_{max} (ε) = 591 (4305), 329 (40200), 284 (21607), 236 nm (15185 $M^{-1}cm^{-1}$). IR [KBr (cm^{-1})]: 1637 (ν_{CO}). ^{1}H NMR (250 MHz, CD_3CN, 300 K): δ = 17.00 (1 H, H_{im}), 7.22 (3 H, NCH_3), 4.06 (1 H, H_{im}) ppm. $C_{27}H_{30}Cl_2FeN_{12}O_{11}$ (825.35): calcd. C 39.29, H 3.66, N 20.36; found: C 39.12, H 3.81, N 20.53.

To produce the crystals of $[Fe^{II}(Me_2BIK)_3](ClO_4)_2$, the same procedure was used without addition of Et_2O. The MeOH solution was kept at room temperature for 1 week and deep-blue single crystals suitable for X-ray diffraction were collected.

X-ray intensity data were collected on a Bruker X8-APEX2 CCD area-detector diffractometer using Mo-K_α radiation (λ = 0.71073 Å). Seven sets of narrow data frames were collected using 0.5° increments of ω or φ. Data reduction was accomplished with SAINT V7.03.[17] The substantial redundancy in the data allowed a semi-empirical absorption correction (SADABS V2.10)[17] to be applied, on the basis of multiple measurements of equivalent reflections. The structure was solved by direct methods, developed by successive-difference Fourier syntheses, and refined by full-matrix least-squares on all F^2 data using SHELXTL V6.12.[18] Hydrogen atoms were included in calculated positions and allowed to ride on their parent atoms.

Crystal Data for $[Fe^{II}(Me_2BIK)_3](ClO_4)_2$: $C_{27}H_{30}Cl_2FeN_{12}O_{11}$, M = 825.35, blue parallelepipeds, orthorhombic, space group *pbca*, a = 15.2718(3), b = 11.8490(2), c = 38.3903(7) Å, Z = 8, $\alpha = \beta = \gamma$ = 90.00°, V = 6946.9(2) Å^3, D_c = 1.578 g cm^{-3}, T = 298 K, Mo-K_α radiation (λ = 0.71073 Å), 95217 reflections were measured, 6373 independent reflections [5466 $I > 2\sigma(I)$] were used in all calculations. R = 0.0492, R_w = 0.1385. G.O.F. = 1.038.

CCDC-240407 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see also footnote on the first page of this article): cyclic voltammograms of **1**, **2** (Figure S1) and $[Fe^{II}(Me_2\text{-}BIK)_3](ClO_4)_2$ (Figure S2).

---

[1] E. Y. Tshuva, S. J. Lippard, *Chem. Rev.* **2004**, *104*, 987–1011.
[2] M. Costas, M. P. Mehn, M. P. Jensen, L. Que, *Chem. Rev.* **2004**, *104*, 939–986.
[3] M. K. Chan, W. M. Gong, P. T. R. Rajagopalan, B. Hao, C. M. Tsai, D. H. Pei, *Biochemistry* **1997**, *36*, 13904–13909.
[4] P. T. R. Rajagopalan, S. Grimme, D. H. Pei, *Biochemistry* **2000**, *39*, 779–790.
[5] J. M. Downes, J. Whelan, B. Bosnich, *Inorg. Chem.* **1981**, *20*, 1081–1086.
[6] V. V. Karambelkar, R. C. diTargiani, C. D. Incarvito, L. N. Zakharov, A. L. Rheingold, C. L. Stern, D. P. Goldberg, *Polyhedron* **2004**, *23*, 471–480.
[7] S. M. Gorun, S. J. Lippard, *Inorg. Chem.* **1988**, *27*, 149–156.

[8] G. Guillot, E. Mulliez, P. Leduc, J. C. Chottard, *Inorg. Chem.* **1990**, *29*, 577–579.
[9] L. J. Farrugia, *J. Appl. Crystallogr.* **1997**, *30*, 565–565.
[10] E. Konig, *Prog. Inorg. Chem.* **1987**, *35*, 527–622.
[11] P. Gütlich, A. Hauser, *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2024–2054.
[12] S. M. Gorun, G. C. Papaefthymiou, R. B. Frankel, S. J. Lippard, *J. Am. Chem. Soc.* **1987**, *109*, 4244–4255.
[13] A. Bousseksou, C. Place, J. Linares, F. Varret, *J. Magn. Magn. Mater.* **1992**, *104–107*, 225–226.
[14] C. A. Sprecher, A. D. Zuberbühler, *Angew. Chem. Int. Ed. Engl.* **1977**, *16*, 189–189.
[15] F. L. Urbach, U. Knopp, A. D. Zuberbühler, *Helv. Chim. Acta* **1978**, *61*, 1097–1106.
[16] R. C. Chambers, G. L. Hill, *J. Am. Chem. Soc.* **1990**, *112*, 8427–8433.
[17] APEX2 version 1.0-8, Bruker AXS, Madison, WI, **2003**.
[18] SHELXTL version 6.12, Bruker AXS, Madison, WI, **2001**.

Received: September 23, 2004