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Facile Conversion of syn-[Fe\(^{IV}\)(O)(TMC)]\(^{2+}\) into the anti Isomer via Meunier’s Oxo–Hydroxo Tautomerism Mechanism

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Abstract: The syn and anti isomers of [Fe\(^{IV}\)(O)(TMC)]\(^{2+}\) (TMC = tetramethyleclam) represent the first isolated pair of synthetic non-heme oxoiron(IV) complexes with identical ligand topology, differing only in the position of the oxo unit bound to the iron center. Both isomers have previously been characterized. Reported here is that the syn isomer [Fe\(^{IV}\)(O\(_{\text{syn}}\))(TMC)]\(^{2+}\) (2) converts into its anti form [Fe\(^{IV}\)(O\(_{\text{anti}}\))(TMC)]\(^{2+}\) (1) in MeCN, an isomerization facilitated by water and monitored most readily by \(^1\)H NMR and Raman spectroscopy. Indeed, when \(\text{H}_2\text{O}\) is introduced to 2, the nascent 1 becomes \(^{18}\)O-labeled. These results provide compelling evidence for a mechanism involving direct binding of a water molecule trans to the oxo atom in 2 with subsequent oxo–hydroxo tautomerism for its incorporation as the oxo atom of 1. The nonplanar nature of the TMC supporting ligand makes this isomerization an irreversible transformation, unlike for their planar heme counterparts.

In recent years, polyaza macrocyclic-based and polypropyridyl-based ligands have served as surrogates for ligands derived from a protein backbone and contributed significantly to our understanding of metal–oxygen intermediates (M\(^{n+}\)--OO\(^-\), M\(^{n+}\)--OHH, M\(^{n+}\)--OH) involved in the catalytic cycles of oxidative enzymatic systems. The ligand topology around the metal center can play an important role in governing the properties of these reactive intermediates. Tetramethyleclam (TMC)\(^{[3]}\) and its derivatives [TMC-L, where one of the four methyl groups in TMC is replaced by an alkyl group bearing a Lewis base that can act as the axial ligand (L) to the metal center] are one such family of ligands for which a variety of iron–oxygen species (such as \(\text{Fe}^{3+}\)--OO\(^-\)--\(\text{Fe}^{3+}\)--OHH\(^{[4]}\), \(\text{Fe}^{3+}\)--O\(^{[5]}\), and \(\text{Fe}^{3+}\)--O\(^{[6]}\)) has been characterized by various spectroscopic techniques, as well as X-ray crystallography in a few cases. The common structural features evident in all the crystallographically characterized Fe(TMC) complexes\(^{[3,4,6-8]}\) are a) the adoption of the trans-I (R,S,R,S) configuration\(^{[3]}\) with all alkyl groups on one side of the macrocycle and the amine groups forming an equatorial N4 plane around the iron center and b) anionic ligand binding to the iron center almost exclusively syn to the methyl groups. An exception to the latter feature is the prototypical oxoiron(IV) complex [Fe\(^{IV}\)(O\(_{\text{syn}}\))(TMC)(NCMe)](OTf)\(^{-}\) (1) reported by Rohde et al. in 2003.\(^{[9]}\) The crystal structure of which displays the dianionic oxo ligand bound to the iron center on the anti face of the TMC macrocycle. This complex has been extensively characterized with respect to structure and reactivity.\(^{[9]}\) Also, crystal structures of related [Fe\(^{IV}\)(O\(_{\text{anti}}\))(TMC)(OTf)](OTf)\(^{-}\) and [Fe\(^{IV}\)(O\(_{\text{anti}}\))(TMC)(OH\(_3\))]OTf\(^{-}\) complexes have recently been reported by Schindler and coworkers.\(^{[9]}\) However, the existence of the corresponding syn isomer was not unequivocally established until 2015 when the crystal structure of [Fe\(^{IV}\)(O\(_{\text{syn}}\))(TMC)(OTf)](OTf)\(^{-}\) was characterized by Prakash et al.\(^{[10]}\) To the best of our knowledge, the two [Fe\(^{IV}\)(O)(TMC)(OTf)]\(^{2+}\) isomers represent the first pair of crystallographically characterized oxoiron(IV) complexes with the identical ligand topology but with the oxo atom occupying different faces of the TMC macrocycle (Scheme 1). In this work, we focus on the interesting observation that the syn isomer converts into its anti isomer upon standing. This isomerization is irreversible and is dramatically accelerated by the addition of water. We provide compelling evidence for a proposed mechanism that directly involves a water molecule in this conversion process and is related to the oxo–hydroxo tautomerism mechanism first conceived by Bernadou and Meunier.\(^{[11]}\)
The syn isomer 2 is generated by adding 1 equivalent of 2-BuSO₂C₆H₄IO to an MeCN solution of Fe₄(TMC)(OTf)₂ at 298 K. The formation of 2 is indicated by a near-IR band at 815 nm (ε = 380 M⁻¹ cm⁻¹), and it converts into 1 over 6 h at 298 K with several isosbestic points (see Figure S1 in the Supporting Information). This conversion can also be monitored by ¹H NMR spectroscopy, where 2 exhibits a set of seven paramagnetically shifted resonances with a 1:1:2:2:2:2:6 intensity ratio (Figure 1, left; see Figure S2).

There is also a minor amount of 1 present in the solution of 2, representing about 20% of the Fe in the sample, and it increases over time with a concomitant decrease of 2 such that the starting 4:1 ratio of 2 to 1 becomes 1:10 after 6 hours at 298 K (Figure 1). The growth and the decay of the respective N-CH₃ peaks at ~41 and ~50 ppm in the conversion of 2 (squares) into 1 (circles) in CD₃CN as monitored by ¹H NMR spectroscopy at 298 K. Solid lines represent single exponential fits to the experimental data.

To test this idea, we monitored the conversion of 2 into 1 in the presence of added water. A 10 mM solution of 2 in CD₃CN containing 0.1 M H₂O was monitored by ¹H NMR spectroscopy, and 2 converted into 1 at 298 K within 1400 s (kobs = 2.0 × 10⁻⁵ s⁻¹; Figure 2A), a 20-fold rate acceleration relative to the reaction in pure CD₃CN (kobs = 1.1 × 10⁻⁷ s⁻¹, Figure 1). Monitoring this conversion by Raman spectroscopy under the same conditions, except for the use of H₂¹⁸O (Figure 2B), shows that the 858 cm⁻¹ peak associated with v(Fe=O) of [¹⁸O]-2 decays over time with concomitant formation of a new peak at 804 cm⁻¹, corresponding to the v(Fe=O) of [¹⁸O]I. These changes occur at a rate (Figure 2C) comparable to that deduced from the NMR data in Figure 2A. That the peak at 804 cm⁻¹ grows over time at the...
Figure 2. A) Plot of intensity changes for the N-Me protons observed by 1H NMR spectroscopy versus time in the conversion of 2 (squares) into 1 (circles) (10 mM 2 in CD3CN with 0.10 M H2O at 298 K). B) Raman spectral changes observed for a 10 mM solution of 2 (generated in MeCN with 1 equiv 2-BuSO2CF3H2O added as a solid) containing 0.10 M H2O over a period of 22 min at 298 K. Numbers to the right of each spectrum indicate how many minutes after sample preparation the spectra were collected. The peaks at 858, 839, and 804 cm⁻¹ are associated with v(Fe=O)’s of [16O2], [18O]1, and [16O]1, respectively. No peak corresponding to [16O]2 (820 cm⁻¹) was observed. C) Time profile for the decay of the 858 cm⁻¹ peak (squares) and the growth of the 804 cm⁻¹ peak (circles). No significant change was observed in the intensity of the 839 cm⁻¹ peak (triangles). Lines represent single exponential fits to the data.

expense of the peak at 858 cm⁻¹ (Figure 2B) provides direct evidence for H2O 18 binding to 2 and subsequent incorporation of the O atom from H216O as the oxo atom of 1. That the peak corresponding to [18O2] (expected at 820 cm⁻¹ based on Hooke’s law) is not observed in the Raman experiment rules out the corresponding cis-binding mechanism as proposed by Seo et al.[16] (Scheme 2, bottom) for 16O incorporation from H218O into 1 in a label-exchange reaction. Instead, our data fit well with the mechanism shown in Scheme 3 where H216O binds the iron center trans to the oxo moiety of 2 (species I), undergoes tautomerization to form a transient trans-FeIV(18OH)(18OH) species (II), and eventually yields FeIV(16O) with the exchanged 16O atom occupying the position trans to the initial oxo moiety (species III). The original oxo atom becomes a water molecule at the end of the reaction and is displaced by the MeCN solvent. Of note is the relative invariance in the intensity of the peak at 839 cm⁻¹, which derives from [16O]1 that is observed from the start, showing that this minor component of the reaction mixture is not involved in the 16O-exchange process under these conditions.

Additional experiments following changes in the UV-vis-NIR absorption, NMR, and Raman spectra show that the rate of conversion of 2 into 1 is accelerated with an increase in the concentration of the added water (Figure 3, left; see Table S1). A linear fit of the accumulated data gives a second rate constant of 3.5 × 10⁻³ M⁻¹ s⁻¹, supporting the involvement of a water molecule in the conversion. In contrast, a study starting with different amounts of 2 in the presence of 0.1 M H2O shows the conversion to be independent of [2] (see Table S1). Interestingly, when 0.1 M D2O is added instead of H2O, a KIE of 2 is observed (see Figure S3), implicating a role for the subsequent proton transfer events in the conversion. An Eyring analysis of the temperature dependence of the rate constants between 258 and 298 K by following spectral changes in the near IR region in MeCN solutions containing 0.25 M H2O affords activation parameters of ΔH* = 18(2) kJ mol⁻¹ and ΔS* = −225(20) J mol⁻¹ K⁻¹ (Figure 3, right) for the conversion of 2 into 1. The large and negative value of ΔS* demonstrates the key role of a water molecule in effecting this conversion, consistent with the mechanism shown in Scheme 3. Interestingly, the above results resemble those reported for H218O exchange into the Fe=O unit of 1 under comparable conditions,[12] suggesting closely related mechanisms that differ only in having a trans- or a cis-dihydroxoiron(IV) intermediate (Scheme 2).[14]

We have also probed whether the pathway shown in Scheme 3 is energetically viable using computational methods. For this purpose, all structures have been optimized at the TPSS-D3(BJ)/def2-TZVP level of theory in the gas phase[15] and are depicted in Figure 4. The calculated structural parameters agree with those established by crystallography (see Table S2).[16] We note here that two conformations of the TMC ligand have been considered, where the ethylene linkages are oriented in either a crossed or parallel conformation (see Figures S4 and S6). We only show the parallel conformation in Figure 4 for simplicity and provide energetic values for the crossed conformation in square brackets.

To obtain accurate energies, we computed the free energies of solvation with the SMD solvation model[16] to simulate MeCN solvation for the gas-phase structures. To improve the accuracy of the electronic energies we recomputed them using the random phase approximation (RPA)[17] in a post Kohn–Sham fashion (i.e., using the TPSS KS orbitals; RPA@TPSS) with the def2-QZVP basis set.[18] For a detailed description and justification of the computational procedure, see the Supporting Information.
At this correlated wavefunction level of theory, we indeed find that the anti isomer 1 is energetically the lowest in energy and thus thermodynamically favored. More importantly, the primary conclusion to be drawn from the calculations is that 1, II, and III are clearly energetically accessible intermediates at room temperature for the isomerization from 2 into 1. Although we have not attempted to follow the specific series of deprotonations and reprotonations (or extended proton shuttling events) necessary to interconvert the tautomers of the H$_2$O-bound intermediates; such proton transfers generally are facile in polar solvents. One additional feature to consider is the varying concentrations of MeCN and H$_2$O, as the outlined process involves the loss/gain of a solvent molecule. In the energetics in Figure 4 we have not taken this into account, as this will strictly depend on the ratio of MeCN to H$_2$O. We note, however, that with an increasing H$_2$O concentration and a decreasing MeCN concentration I, II, and III become energetically more favorable by several kJ·mol$^{-1}$.

In conclusion, the conversion of the syn isomer 2 into its anti form 1 in the presence of added water has been investigated by UV-vis absorption, Raman, and $^1$H NMR spectroscopy. Addition of water clearly accelerates the transformation, and the rate of conversion has a first-order dependence on water concentration (Figure 3, left panel). The authors declare no conflict of interest.

**Keywords:** isomers · iron · macrocycles · reaction mechanisms · tautomerism

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