STUDIA UBB CHEMIA, LVII, 1, 2012 (p. 213 - 217)

DFT VIBRATIONAL ANALYSIS OF METAL-HYDROPEROXO BLEOMYCIN COMPLEXES

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ABSTRACT. As part of our current efforts to understand the mechanisms of oxygen-oxygen bond cleavage in biological metal complexes, density functional theory (DFT) calculations are employed to calculate the vibrational spectra of the Fe(III)-hydroperoxo adduct of bleomycin and of its more stable cognate Co(III)-hydroperoxo, as models for the ABLM form of bleomycin thought to be key in its biological activity. In addition to bleomycin, we examine another Fe(III)-hydroperoxo complex, $[Fe(III)(N4Py)(OOH)]^{2+}$. The theoretical predictions show errors of 20-100 cm^{-1} with respect to experiment, and reproduce some of the experimental trends, with the important observation that the vibrational modes are far more complex than usually assumed.

Key words*: bleomycin, cobalt, iron, DFT, vibrational spectrum*

INTRODUCTION

Bleomycin is a drug whose action involves chelating a metal center and then damaging DNA within living cells. A key intermediate in bleomycin's anti-DNA action is a species known as activated bleomycin, ABLM, which, on the basis of spectroscopic and theoretical studies, appears well described as a bleomycin-ferric-hydroperoxo adduct (cf. Figure 1). ABLM's instability has to some extent precluded detailed structural characterization.[1-3] A somewhat more stable cognate, the Co(III)-hydroperoxo bleomycin adduct, has been characterized spectroscopically, and its inferred structural features appear very similar to those of ABLM.[4-12]

The reactivity of the Fe-O-OH moiety is central to bleomycin's therapeutic activity. Arguably, the most direct spectroscopic probe available to date for bonding in metal-hydroperoxo bleomycin adducts is vibrational spectroscopy. Although vibrational data is not available for the Fe-O-OH modes in ABLM, a detailed vibrational analysis of Co(III)-hydroperoxo bleomycin has recently been reported.[5,6] Here, we attempt to employ density functional (DFT) calculations to calculate the vibrational spectra of Fe(III)-hydroperoxo and Co(III)-hydroperoxo bleomycin. In addition to bleomycin, we examine an

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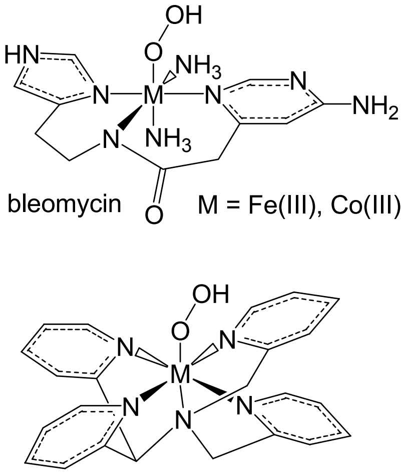
Fe(III)-hydroperoxo complex for which vibrational data *is* available, namely, $[Fe(III)(N4Py)(OOH)]^{2+}$.[13,14] The theoretical predictions show errors of 20-100 cm^{-1} with respect to experiment, and reproduce some of the experimental trends, with the observation that the vibrational modes are far more complex than usually assumed.

RESULTS AND DISCUSSION

Figure 1 shows the models employed in the present work. Table 1 lists key calculated geometrical parameters for the three models of Figure 1. These parameters are in good agreement with previously reported data on related iron-hydroperoxo species.[3,13-22]



$[Fe(III)(N4Py)(OOH)]^{2+}$

Figure 1. Models employed in the present work. The two ammonia ligands in the bleomycin structure are modelling terminal amine groups otherwise connected to the rest of the macro-chelate unit.

Table 2 lists calculated vibrational modes for the Co-OOH moiety. At the outset, we note that the $\nu_{\text{Co-OOH}}$ and $\nu_{\text{O-OH}}$ modes are far from pure: they are mixed with each other as well as with several other metal-nitrogen and bleomycin-based modes, such that several calculated vibrational modes have consistent $\nu_{\text{Co-OOH}}$ and $\nu_{\text{O-OH}}$ character. Resonance Raman experiments on Co(III)-OOH bleomycin as well as on various Fe(III)-OOH complexes have consistently identified *one* single experimentally detectable vibrational mode for $\nu_{\text{Co-OOH}}$ and *one* for $\nu_{\text{O-OH}}$.[3,6,10,13,14,23] The calculated frequencies are within 20-90 wavenumbers from the experimental data.

Table 1. Key calculated bond lengths (Å) and angles for the three models of Figure 1.

Co(III)-OOH bleomycin			
Co-O	1.90	Co-N(amide)[b]	1.96
O-OH	1.50	Co-N(imid)[c]	2.00
Co-O-OH	112°	Co-N(py)[d]	1.99
Co-NH$_3$(cis)[a]	2.04	Co-N(trans)[a]	2.04
Fe(III)-OOH bleomycin			
Fe-O	1.80	Fe-N(amide)[b]	1.96
O-OH	1.53	Fe-N(imid)[c]	2.03
Fe-O-OH	113°	Fe-N(py)[d]	2.03
Fe-NH$_3$(cis)[a]	2.09	Fe-N(trans)[a]	2.09
$[Fe(III)(N4Py)(OOH)]^{2+}$			
Fe-O	1.79	Fe-N(axial)	2.03
O-OH	1.48	Fe-N(py)[d]	2.00
Fe-O-OH	120°		

[a] positions cis and trans relative to the OOH ligand. [b] amide nitrogen atom.
[c] imidazole nitrogen atom. [d] pyridine/pyrimidine nitrogen atoms (for $[Fe(III)(N4Py)(OOH)]^{2+}$, the average of four distances is shown).

Table 2. Calculated vibrational modes for the bleomycin Co(III)-OOH model. Shown in bold is previously reported experimental data.[6,10]

vibration	Co(II)-OOH
ν_{Co-OOH}	517, 520 / **548**
ν_{O-OH}	744, 748, 750, 787 / **828**
ν_{OO-H}	3579

Table 3 lists calculated vibrational modes for the Fe-OOH moiety in the bleomycin model. Similar to the cobalt case discussed above, the ν_{O-OH} mode is far from pure, contrary to previous B3LYP results.[3] Table 4 lists vibrations calculated for the related complex, $[Fe(III)(N4Py)(OOH)]^{2+}$, for which experimental data exists.[14]

Table 3. Calculated vibrational modes for the bleomycin Fe(III)-OOH model. Shown in bold is previously reported theoretical data.[3]

vibration	Fe(III)-OOH
ν_{Fe-OOH}	465 / **575**
ν_{O-OH}	647, 664, 672, 737 / **879**
ν_{OO-H}	3568

A comparison of the O-OH stretching frequencies in the three models reveals that they do not correlate with the calculated bond length: the order is Co-OOH > Fe-OOH(bleomycin) > Fe-OOH(N4Py) for the calculated frequencies and Fe-OOH > Co-OOH(bleomycin) > Fe-OOH(N4Py) for the calculated O-O bond lengths. On the other hand, the experimentally-determined frequencies are in the order Co-OOH > Fe-OOH(bleomycin) > Fe-OOH(N4Py), in good agreement with experiment. A similarly good agreement with experiment is found when comparing the metal-oxygen(OOH) stretching frequency, with Fe-OOH(N4Py) > Co-OOH. This order correlates well with the distinctly shorter calculated metal-oxygen bond in the iron model compared to the cobalt.

Table 4. Calculated vibrational modes for the $[Fe(III)(N4Py)(OOH)]^{2+}$ model. Shown in bold is previously reported experimental data.[14]

vibration	Fe(III)-OOH
$v_{Fe\text{-}OOH}$	576 / **632**
$v_{O\text{-}OH}$	638, 688, 700, 707 / **790**
$v_{OO\text{-}H}$	3546

CONCLUSIONS

In models of activated bleomycin and in related structures, the theoretical predictions on vibrational spectra show errors of 20-100 cm^{-1} with respect to experiment in terms of peroxide-related vibrations, and reproduce some of the experimental trends; however, the vibrational modes are far more complex than usually assumed.

EXPERIMENTAL SECTION

Geometries were optimized and vibrational spectra were computed using the BP86 functional. This functional employs the gradient-corrected exchange functional proposed by Becke,[24] and the correlation functional by Perdew.[25] The 6-31G** basis set was used, as implemented in Spartan. [26] For the SCF calculations, a fine grid was used, and the convergence criteria were set to 10^{-6} (for the root mean square of electron density) and 10^{-8} (energy), respectively. For geometry optimization, convergence criteria were set to 0.001 a.u. (maximum gradient criterion) and 0.0003 (maximum displacement criterion).

ACKNOWLEDGEMENTS

Funding from the Romanian Ministry of Education and Research, (grant PCCE 140/2008) is gratefully acknowledged.

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