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The nature of the M–NO bond in [M(Imidazole)(PPIX)(L)]^{q} complexes (M = Fe^{2+}, Ru^{2+}; L = NO^{+}, $NO^{\cdot}$ and NO^{-}; PPIX = Protoporphyrin IX)

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ABSTRACT

Aiming at understanding the effect of the replacement of iron by ruthenium in the Protoporphyrin IX (PPIX) system of the heme group, in this work density functional theory calculations were performed to investigate the structures, nature of the M–NO bond and electronic spectra of the complexes [**M**(Im)(PPIX)(**L**)]^{q}, where **M** = Fe^{2+} and Ru^{2+}, Im = Imidazole ring, PPIX = Protoporphyrin IX of the heme group and **L** = NO^{+}, NO and NO^{-}. Energetic and structural results obtained at the B3LYP/SBKJC/6-31G(d) level of theory indicates that the NO coordinates preferentially through the nitrogen atom and its oxidized form NO^{+} produces more stable complexes. Charge and energy decomposition analysis revealed that, independent of the coordination mode, the interaction of NO species with the ruthenium fragment is stronger than with iron. TD-DFT calculations predict that the transition that can lead to photodissociation of the Ru–NO bond occurs at 419 nm and if the NO coordinates to ruthenium in its oxidized form this transition is blue-shifted to 384 nm. The results obtained in this work also gives support to conclude that ruthenium complexes with the protoporphyrin IX (PPIX) system can strongly bind NO, which can be used to capture NO species, and releasing it upon irradiation with visible light.

1. Introduction

Nitric oxide (NO) is a molecule of great chemical and biological interest, which has stimulated the scientific community mainly due to its biochemical functions and possible therapeutic applications [1–4]. NO is classified as a messenger molecule and it is well known to play important roles in several important biochemical and physiological processes in the human body as, for instance, modulation of the immune and endocrine response, cardiovascular control, regulation of blood pressure, neurotransmission, induction of apoptosis, among others [5–10].

Physiologically, NO is synthesized by the nitric oxide synthase (NOS). Depending on its concentration and local of production several ambiguous effects may occurs, as for instance: (i) high concentration of NO can affect the cardiac function [11,12], (ii) the intracellular concentration of NO must remain low to avoid parallel oxidative reactions as the formation of highly reactive nitrogen oxide species (RNOS) [13] leading to a oxidative stress in the cell, (iii) NO can bind to the cytochrome P450, inhibiting this enzyme and causing several damages [14] and (iv) the NO can reversibly compete with oxygen to the binding site of cytochrome oxidase, during the cellular breathing and, in high concentrations, in conjunction with superoxide species, can generate reactive species of oxygen, which are involved in the mitochondrial toxicity and cellular death [15,16]. Due to the extreme instability of NO in biological environment and its short half-life (approximately 5 s) it is difficult to study its physiological effects. These facts have encouraged the synthesis of coordination compounds that can capture or release NO in biological systems in a controlled manner, acting thus as prodrugs [17–19].

Transition metal compounds to act in the controlled binding/release of NO must satisfy some pre-requisites as: (i) high affinity for NO, (ii) thermodynamical stability in physiological conditions, (iii) low toxicity, (iv) being soluble in water and (v) being permeable to the membrane. In addition, they must be susceptible (labile) to chemical [20], electrochemical [21] or photochemical [22–23] stimuli to promote the release of NO. Ruthenium complexes have shown very promising for this purpose [24]. Nitrosyl ruthenium compounds have been presented to be thermodynamically stable but photodynamic active, releasing NO when exposed to ultraviolet irradiation and in some cases, visible irradiation. As examples, the compounds *trans*-[$(Ru(NH_3)_4(L)(NO)]^{3+}$ (L = pyridine, 4-methyl-pyridine) in an aqueous solution and irradiated in the near ultraviolet (300–370 nm) result in dissociation of NO and producing the compound *trans*-[$(Ru(NH_3)_4(L)(H_2O)]^{3+}$ [25]. Cameron et al. reported the use of ruthenium complexes as potential and effective scavengers of NO in biological systems

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[26]. In another interesting work, Clarke and coworkers [27] report that the administration of the complex *trans*-[Ru^{II}(cyclam)Cl(NO)]$^{2+}$ reduces blood pressure in Wistar rats, especially in hypertensive rats. Notably, the slower rate of release of NO from this complex followed by reduction produces a hypertensive effect 20 times longer than that generated by sodium nitroprusside, used to lower blood pressure. Then, these results suggest that ruthenium cyclam complexes could be used as a "NO-buffer" system to control physiological levels of available NO.

The nitrosyl group can coordinate to a transition metal as NO^+, $NO^{\cdot}$ or NO^-. Feltham and Enemark [28] proposed the $\{M–NO\}^n$ formulation to describe the bonding of NO to metals. In this formulation n is the sum of the metal d-electrons and the nitrosyl π^* electrons. NO can also form metastable compounds coordinating η^1 through the oxygen and η^2-NO [29,30]. The nature of metal–nitrosyl bond have been the subject of interest for several theoretical studies [31–35]. For instance, Caramori et al. [35] have employed quantum chemical calculations at the DFT level of theory for *trans*-[$Ru^{II}(NH_3)_4(L)NO]^q$ and *trans*-[$Ru^{II}(NH_3)_4(L)NO]^{q-1}$ complexes with L = NH_3, Cl^{-1}, and H_2O to study the nature of the Ru–NO^{+1} and Ru–NO chemical bonding through the energy decomposition analysis (EDA). They showed that both the orbital term and Pauli repulsion contribute to the weakening of the NO bond and, the NO ligand is more susceptible to dissociation in comparison to NO^+, due to the increasing Pauli repulsion contribution.

Many of the bioregulatory activities of NO involve its interaction with iron heme proteins [36]. For instance, the activation of the soluble Guanilyl Cyclase (sGC), an enzyme involved in vasodilation requires the formation of a nitrosyl complex with the Fe(II)(PPIX) portion of the enzyme, where PPIX is the protoporphyrin IX [37]. NO also acts as inhibitor for several other iron-heme enzymes such as, cytochrome P450, cytochrome oxidase, catalase, among others [38–42]. These enzymes are thus natural targets for the synthesis of biomimetic compounds to be used in the controlled binding/release of NO. Understanding the nature of the interaction involving the NO molecule with these metalloporphyrins is thus a crucial ingredient in the development of new compounds for this purpose. Mechanistic studies [43,44] and Flash photolysis kinetic experiments [43,45] have contributed to the measurements of the rate constants involved in the binding and releasing of NO in synthetic metalloporphyrins complexes and iron heme proteins. Ford and co-workers [43] have shown that the rate of biding of NO (k_{on}) to iron heme proteins can have different values, depending on factors like the oxidation state of the metal, availability of a vacant site for the NO coordination, *trans* effect of the ligands, etc. For instance, $k_{on} = 8.3\ M^{-1}\ s^{-1}$ for cytochrome oxidase, $3.0 \times 10^7\ M^{-1}\ s^{-1}$ for catalase and $1.8 \times 10^9\ M^{-1}\ s^{-1}$ for the compound Fe^{II}(TPPS)NO (where TPPS is tetra(4-sulfonatophenyl)porphine). The rate constant for the release of NO (k_{off}) also varies widely. For instance, $k_{off} = 1.7 \times 10^2\ s^{-1}$ for catalase, $2.9 \times 10^{-5}\ s^{-1}$for cytochrome oxidase and ~0 for the compound Fe^{II}(TPPS)NO. The knowledgement of the rate by which the NO molecule can bind to and released from these molecules is very important since several other physical and chemical processes can compete to the NO depletion in the cell.

Despite of iron porphyrins be present in the active site of these iron heme enzymes, nitrosyl complexes of iron porphyrins are thermally labile, which is not a desirable property specially for the photochemical delivery of NO. Ruthenium porphyrin analogs emerges as an important alternative and, indeed, several mechanistics and photochemical studies have been performed on ruthenium porphyrins analogs of iron heme proteins [44]. The low toxicity and greater stability of metallodrugs containing ruthenium to be used in the binding/release of NO are attributed to the similarities with iron.

Although several mechanistic and photochemical studies on synthetic compounds of metalloporphyrins with NO and binding of NO to iron heme enzymes, the thermal mechanism by which the Metal–NO bond forms and breaks in these compounds in the living systems is still not well understood. The understanding of the nature of the bond involving NO and the metallic center in these metalloporphyrins is thus crucial for understanding the thermal delivery/binding of NO, which will have an impact on the design of new biomimetic compounds. In this regard, electronic structure calculations may play an important role.

Aiming at understanding the nature of the Metal–NO bond in metalloporphyrins, in this work we have applied quantum mechanical calculations to investigate the electronic structure, spectroscopic properties and nature of the **M**–NO bond in the complexes [**M**(Im)(PPIX)(**L**)]^q, where **M** = Fe^{2+} and Ru^{2+}, Im = Imidazole ring, PPIX = Protoporphyrin IX of the heme group and **L** = NO^+, $NO^{\cdot}$ and NO^-. The PPIX and the Imidazole ligand were chosen due to its presence in the active site of many heme enzymes involved in the biophysics of NO. The different coordination modes of the nitrosyl molecule as well as its different oxidation states are explored. The effects of the different metallic center (Fe^{2+} and Ru^{2+}) on the nature of the Metal–NO interaction is discussed. It is important to mention that several theoretical studies on the nature of the M–NO bond in numerous compounds with potential pharmacological use have been performed [31–35]. However, the systematic study of the nature of the metal–NO bond in metalloporphyrins that mimic the active site of several enzymes involved in the biochemistry of NO, analyzing the different coordination modes, oxydation state of nitrosyl and different metallic ions, as far as we know, is been performed for the first time. As we shall see the replacement of Fe^{2+} by Ru^{2+} generates a compound that interacts with NO stronger than the heme group and, the NO molecule in this compound can be released by photochemical stimulus in the visible region of the spectrum.

2. Computational details

Full unconstrained geometry optimizations and frequency calculations for the complexes [**M**(Im)(PPIX)(**L**)]^q, where **M** = Fe^{2+} and Ru^{2+}, q is the overall charge of the complex and **L** = NO^+, NO and NO^- were carried out at the DFT level of theory with the B3LYP exchange–correlation functional [46]. For all complexes, the inner shell electrons of ruthenium ($1s^2 2s^2 2p^6 3s^2 3p^6 3d^{10}$) and iron ($1s^2 2s^2 2p^6$)were described by the SBKJC effective core potential and its associated VDZ basis set was used for the valence electrons ($4s^2 4p^6 5s^2 4d^6$) and ($3s^2 3p^6 4s^2 3d^6$), respectively [47]. The other atoms of the ligands were treated with the full electrons 6-31G(d) basis set [48,49]. For all complexes, the ruthenium and iron atoms were treated assuming its low spin configuration, giving rise to $S = 1/2$ for the neutral $NO^{\cdot}$ complex, which has an unpaired electron. Since the metal ions have +2 charge, the overall charges of the complexes, q, assumes the values of +1, 0 and −1 for L = NO^+, $NO^{\cdot}$ and NO^-, respectively, since PPIX is doubly deprotonated. The calculations were performed at the spin restricted level, except for the $NO^{\cdot}$ complexes ($S = 1/2$) which were treated at the spin unrestricted level. All structures reported here have been checked to be energy minima on the potential energy surface. The geometry optimization and frequency calculations were done with the GAUSSIAN 09 program [50].

For the bonding analysis, uncontracted Slater type orbitals (STOs) [51], with triple-ζ-quality in the valence region and double-ζ-quality in the core region, augmented by one set of polarization functions (TZP) were used as basis functions for the SCF calculations, with the B3LYP functional. Scalar relativistic effects have been considered for the transition metals using the zero order