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Review

Reaction mechanisms relevant to the formation of iron and ruthenium nitric oxide complexes

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Submitted in honor of Professor Henry Taube, mentor and friend

Contents

Abstract

Presented here is a review of recent mechanistic work related to the formation of iron and ruthenium nitrosyl complexes. Given the importance of NO as a biological molecule and that the targets for NO in vivo are metal centers, knowledge of the mechanisms by which metal nitrosyls are formed is fundamental for understanding the diverse roles that NO plays in biology. The kinetics of metal nitrosyl formation from the reactions of free NO with metal complex precursors are dominated by the lability of the complexes. The free radical character of NO however, asserts itself especially if the precursors are relatively substitution inert or are coordinatively unsaturated.

Keywords: Nitric oxide; Reaction mechanisms; Ruthenium; Iron; Kinetics

Abbreviations: Cat, catalase; CytII, ferro-cytochrome *c*; CytIII, ferri-cytochrome *c*; edta, ethylenediaminetetraacetic acid; Hb, hemoglobin; MCPH, protohemin 3-(1-imadazoyl) propylamide stearyl ester; metMb, metmyoglobin; NOS, nitric oxide synthase; NP, nitroprusside; NPn, nitrophorin; nta, nitriloacetic acid; OEP, octaethylporphyrin; Por, porphyrin; PPIX, protoporphyrin IX; pz, pyrazine; RBS, Roussin's black salt; salen, *N*,*N*′-bis(salicylidene)ethylenediamine dianion; SCE, standard calomel electrode; sGC, soluble guanylyl cyclase; Sol, solvent; tBu_4salen, *N*,*N*′-ethylenebis(3,5-di-*t*-butlysalicylideneiminato) dianion; tBu_4salophen, *N*,*N*′-1,2-phenylenediamine-bis(3-*t*-butlysalicylideneiminato) dianion; TMPS, tetramesitylporphinato; TmTP, tetra(*meta*-tolyl)porphyrin; TPP, tetraphenylporphyrin; TPPS, tetra(4-sulfonato-phenyl)porphinato

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1. Introduction

Nitric oxide (nitrogen monoxide) is important to a wide variety of mammalian physiological processes [1,2], including blood pressure control, neurotransmission and immune response. Numerous disease states involving NO imbalances have been reported, although it is not always evident whether such imbalances are causal or symptomatic [2,3]. In this context, the reactions of NO with metal complexes are of particular interest since metal centers such as hemes are well established as targets for NO reactions in mammalian biology. Here, we present an overview of more recent developments involving the reactions leading to the formation of selected metal nitrosyl complexes.

NO is a stable free radical, and this feature is understandably a dominant theme in its chemistry and biochemistry. It reacts rapidly with other free radicals and with substitution labile, redox active metals, but it is not a strong one-electron oxidant or reductant. Its solubility and transport properties are similar to those of dioxygen [4,5]. Notably, its solubility in aqueous solution (1.9 mM atm^{-1} at 298 K and 1.4 mM atm^{-1} at 310 K [4]) is considerably less than in organic solvents (for example, 15.0 mM atm^{-1} in cyclohexane at 298 K). Thus in a heterogeneous environment such as a cell, NO would be expected to partition preferentially into hydrophobic regions.

The focus of this article will be the formation of metal nitrosyl complexes by the direct reaction of metal complexes with NO itself (Eq. (1)). However, it should be noted that metal nitrosyl bonds can also form by reaction with a nitric oxide precursor such as nitrite ion, alkyl nitrites or *S*-nitrosothiols [6] with a species such as HNO [7].

$$ML_nX + NO \underset{k_{off}}{\overset{k_{on}}{\rightleftharpoons}} ML_n(NO) + X \quad (1)$$

Coordinated NO can range in character (formally) from a nitrosyl cation (NO^+) to a nitroxyl anion (NO^-). The former is isoelectronic to CO with nearly linear M–N–O bonds and involves considerable charge transfer to the metal center. With the latter, charge transfer is in the opposite direction and a bond angle approaching 120° would be predicted. Between these two extremes would be the situation where NO binds to a 16 electron complex such as $Ru(H)(Cl)(CO)(NO)(PR_3)_2$. In this case it was concluded that NO is acting as a $2e^-$ donor with the unpaired e^- localized on the nitrosyl nitrogen [8]. The bonding of NO to metals was the subject of a generalized description by Feltham and Enemark [9]. These researchers proposed the $\{MNO\}^n$ formulation (where *n* is the sum of metal d-electrons and nitrosyl π* electrons) and used Walsh-type diagrams to predict M–N–O bond angles of ground state complexes. It should be noted that metastable complexes generated photochemically in low temperature solids display oxygen coordinated η^1-NO and η^2-NO structures [10,11]. Certain polynuclear complexes display bridging nitrosyls [12].

A key question to be asked when exploring formation of metal nitrosyl complexes is whether the free radical nature of NO leads to different substitution mechanisms than for other small diatomic ligands such as CO. Should the reactivity pattern be different from other small Lewis bases, given that the odd electron of NO resides in the π* orbital and may not be strongly involved until the M–NO bond is largely formed? As we will discuss in subsequent sections, there are examples where the kinetics of the bimolecular substitution (Eq. (1)) are dominated by the lability of ML_nX thus the nature of the incoming ligand is largely irrelevant. However, when considering the rates of metal–ligand bond formation from geminate pairs $\{ML_n,AB\}$, the situation is different. When such a species is formed, for example, by flash photolysis of a L_nM–AB complex, there are often significant reactivity differences between NO and CO. Furthermore, as described immediately below, kinetics data suggest that the radical nature of NO leads to associative substitution with the $4d^5$ ruthenium(III) ammine complex $Ru(NH_3)_6^{3+}$. Thus, there is a range of answers to the question posed above.

Nitric oxide is active as a diffusible signaling agent in blood pressure regulation and in nervous tissue. The concentrations present in the endothelial cells have been reported to be as high as 400 nM [13]; however, recent studies suggest that values as much as two orders of magnitude lower (4 nM) may represent true physiological conditions in tissue [13b]. In contrast, NO concentrations are much higher during episodes of immune response to pathogen invasions. Under these conditions other reactive nitrogen species such as peroxynitrite ($OONO^-$) and N_2O_3 may play important roles. The primary targets for NO in bioregulatory functions are metal centers, chiefly iron heme proteins [14]. The biological relevance of the "on" reaction in Eq. (1) is highlighted by noting that the activation of the ferro-heme enzyme soluble guanylyl cyclase (sGC), involves the formation of a nitrosyl complex where ML_nX is a Fe^{II}(PPIX) moiety (PPIX: protoporphyrin IX) [15]. Additional reports describe NO as an inhibitor for other metalloenzmes such as cytochrome P450 [16], cytochrome oxidase [17], catalase [18] and nitrile hydratase [19]. NO has also been shown to be a substrate for several peroxidase enzymes [20] and is responsible for the vasodilator properties of nitrophorins, which are salivary ferri-heme proteins found in certain blood sucking insects [21].

Fast reaction with its biological targets would be necessary for NO to serve as an effective regulatory agent at the sub-micromolar concentrations found in vivo. This is indeed the case for the reaction of NO with sGC for which $k_{on} = 1.4 \times 10^8\ M^{-1}\ s^{-1}$ (277 K) was measured [22]. Developing insight into the mechanisms of NO substitution reactions is key to understanding the diverse chemical biology of this seemingly simple molecule. For example, the low reactivity of ferro- and ferri-cytochrome *c* (Cyt^{II}, Cyt^{III}) toward NO can be attributed to occupation of the heme axial coordination sites by protein bound ligands [23]. As will be discussed below, NO requires a vacant or labile coordination