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ScienceDirect
Coordination Chemistry Reviews 252 (2008) 2093–2114
COORDINATION CHEMISTRY REVIEWS
www.elsevier.com/locate/ccr

Review

Photoactive ruthenium nitrosyls: Effects of light and potential application as NO donors

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Received 6 September 2007; accepted 11 November 2007
Available online 19 November 2007

Contents

Abstract

In recent years, various exogenous nitric oxide (NO) donors have been synthesized to modulate NO concentrations in cellular environments and control physiological processes that are regulated by NO. Transition metal complexes of NO (metal nitrosyls) are one such class of NO donors. Since complexes of ruthenium are in general more stable, a variety of ruthenium nitrosyls have been isolated and studied in detail in terms of their NO donating capacities. A large number of $\{Ru–NO\}^6$ type of nitrosyls release NO upon exposure to UV light. Several research groups have studied their photochemistry to evaluate their potential as NO donors under the control of light. In general, the nitrosyls with non-porphyrin ligands (such as amines, Schiff bases, thiolates and ligands with carboxamide groups) readily release NO upon illumination and generate Ru(III) photoproducts. In contrast, NO photorelease from ruthenium nitrosyls derived from porphyrins remains limited due to rapid recombination. In some cases, the $\{Ru–NO\}^6$ nitrosyls are photochemically converted to nitrite species (especially in water at neutral pH) while a few afford Ru(II)

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0010-8545/$ – see front matter
doi:10.1016/j.ccr.2007.11.011

photoproducts. UV irradiation of selected ruthenium nitrosyls in the solid state results in NO linkage isomerism. To date, notable progress has been made in the area of nitrosyl-polymer hybrids that could be used for site-specific delivery of NO. Various strategies have also been developed to make these nitrosyls release NO under the influence of visible and/or near IR light. Although some ruthenium nitrosyls are stable under physiological conditions and are capable to NO delivery to proteins such as myoglobin and cytochrome c oxidase, so far success has been limited in using these nitrosyls as light-activated NO donors in cellular and tissue models. In this review, the effects of light on ruthenium nitrosyls derived from a wide variety of ligands (reported so far) have been summarized and their utility as NO donors have been discussed.

Keywords: Nitric oxide; Ruthenium nitrosyl; Photoactivity; NO photorelease; NO delivery to biological targets

1. Introduction

During the past three decades, nitric oxide (NO) has been shown to be an important signaling molecule in a wide variety of physiological processes, including blood pressure control, neurotransmission, immune response, and cell death [1–11]. Since these discoveries, research efforts have been directed towards development of exogenous NO donors that can deliver NO to biological targets to elicit desired responses [12–15]. Various NO donors have been developed in this regard, including organic nitrites and nitrates [16], nitrosothiols [17], diazeniumdiolates (NONOates) [18,19], and lastly transition metal-based NO donors such as sodium nitroprusside [20,21]. Organic NO donors such as glyceryl trinitrate and isosorbide dinitrate have been successfully used to treat hypertension and episodes of angina pectoris. Nitrosothiols have shown some promise in regulating immune response, while selected NONOates were shown to improve neurotransmission. Use of exogenous NO donors as potential anti-cancer agents has also been explored [22–25]. Indeed, NO has been shown to induce both apoptosis (programmed cell death) and cell destruction at elevated concentrations (mM range) [26–31]. Precise targeting of malignant sites versus healthy tissues however remains as a challenge in the use of systemic NO donors in anticancer therapy. Most NO donors in current use are non-specific in that they release NO spontaneously, although in some cases the rate of NO release can be modulated by ubiquitous stimuli such as temperature, pH or enzymes. Controlled (favorably triggered) release of NO at a selected site is the key for successful employment of an NO donor in the treatment of tumors and localized malignancy.

With the advent of photodynamic therapy (PDT) [32,33] as a common treatment for certain (especially skin) cancers [34–38], light-activated NO donors have gained much attention. The site-specificity provided by laser treatment allows for more precise targeting than systemic drugs alone. Early on, it was recognized that NO complexes of transition metals (metal nitrosyls) could release NO when exposed to light. For example, several iron-based nitrosyls including sodium nitroprusside (SNP, $Na_2[Fe(NO)(CN)_5]$) [39–44] and Roussin's salts [20,41,45–48] were found to release NO when exposed to light. However, these complexes also release NO spontaneously (i.e. in the dark), and often changes in pH and temperature also induce loss of NO, rendering them non-specific for PDT. Additionally, side effects from labile ancillary cyanide ligands often limit the use of SNP [49–51]. Chelating ligands provide some relief from these problems. For example, the iron complex $[(PaPy_3)Fe(NO)](ClO_4)_2$ was the first of many NO donors to be studied by Mascharak and co-workers [52–54]. This nitrosyl is derived from a tightly coordinating, pentadentate ligand that imparts high stability in donor solvents like MeCN or DMF, and it was shown to cleanly release NO when exposed to low-intensity visible light. Unfortunately, like many other iron nitrosyls, $[(PaPy_3)Fe(NO)](ClO_4)_2$ exhibits unpredictable stability under biological conditions. In general, iron nitrosyls like Roussin's salts and $[(PaPy_3)Fe(NO)](ClO_4)_2$ undergo hydrolytic decomposition in aqueous solutions under physiological conditions (pH ~7, presence of oxygen) [55–58] and problems like NO_x disproportionation [59–64] or ferric hydroxide (or oxide) precipitation limit the use of such iron-based NO donors. Several NO-releasing complexes of chromium [65–67] and manganese [68,69] have also been described, but are limited by similar effects. The only exception is the manganese nitrosyl $[(PaPy_3)Mn(NO)](BF_4)$ [70–72]. This photoactive NO donor has been used to deliver NO to biological targets like myoglobin, cytochrome c oxidase, and papain [73,74]. Clearly, the number of metal nitrosyls that release NO *exclusively* when triggered by light and exhibit stability under physiological conditions is very limited. Researchers have therefore looked into more stable transition metal analogues, such as ruthenium nitrosyls to achieve these goals during the past several years. The results of such studies are included in this review.

Much like other complexes of ruthenium, the ruthenium nitrosyls are substitutionally inert at room temperature. However, some of these nitrosyls release NO when exposed to light. For example, nitrosyls of simple compositions such as $K_2[Ru(NO)(Cl)_5]$ readily release NO when exposed to UV light. This property of ruthenium nitrosyls has been known for some time. One must note at this point that many coordination complexes of ruthenium (without NO) are also sensitive to light and undergo light-driven substitution reactions [75–78]. Typically, upon exposure to light, one coordinated ligand (L) is replaced by a solvent molecule, as indicated in Eq. (1):

$$\text{Ru–(L)} + h\nu \rightarrow \text{Ru–(solv)} + \text{L} \quad (1)$$

Sauvage and co-workers have studied the photochemistry of such ligand replacement reactions quite extensively [75]. The reaction is usually driven by ultraviolet (UV) light in the region of 200–450 nm and the photosensitivity stems from accessibility to substitutionally active excited states with UV irradiation. The oxidation state of the metal center is crucial for such photoactivity. Only complexes with Ru(II) centers experience photosubstitution reactions. Also, photosubstitution reactions occur only with a select group of ligands, primarily neu-