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Review

Metal complex strategies for photo-uncaging the small molecule bioregulators nitric oxide and carbon monoxide

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ABSTRACT

Photochemical release (uncaging) of small molecule bioregulators (SMBs) such as nitric oxide (NO) or carbon monoxide (CO) at physiological sites offers exquisite control of timing, location and dosage. However, photo-uncaging faces two major problems that challenge its therapeutic applications: the relatively poor transmision of visible light through tissue and the need to deliver the appropriate precursors to the desired targets. In this brief review are discussed research activities that address these issues of spatial-temporal control.

Contents

Abbreviations: bpy, 2,2′-bipyridine; CORM, carbon monoxide releasing moiety; CrONO, *trans*-Cr^{III}(cyclam)$(ONO)_2^+$; CW, continuous wave; cyclam, 1,4,8,11 tetraazacyclotetradecane; DAF-FM DA, 4-amino-5-methylamino-2′,7′-difluorofluorescein diacetate; DFT, density functional theory; DMSO, dimethylsulfoxide; $dpaq^{NO2}$, 2-[*N*,*N*-bis(pyridin-2-ylmethyl)]-amino-*N*′-5-nitro-quinolin-8-yl-acetamido); DSPE-PEG, phospholipid-functionalized poly(ethylene glycol); ES, excited state; Fluor, fluorescein; FRET, Förster resonance energy transfer; gly^-, glycinato; GM, Goeppert-Mayer unit for two photon absorption; GSH, glutathione; HGN, hollow gold nanosphere; HO, heme oxygenase; I_i, incident light intensity; I_{abs}, intensity of light absorbed; IR, infrared; LF, ligand field; Mb, myoglobin; MLCT, metal to ligand charge transfer; NIR, near infrared; NMR, nuclear magnetic resonance; NOA, Sievers nitric oxide analyzer; NP, nanoparticle; PDMS, polydimethylsiloxane; PEG, polyethylene glycol; PetA, 5,12-dimethyl-7,14-diphenyl-1,4,8,11-tetra-aza-cyclotetradecane; phen, 1,10-phenanthroline; photoCORM, photo-activated CO releasing moiety; photoNORM, photo-activated NO releasing moiety; PL, photoluminescence; PLGA, poly(D,L-lactic-co-glycolic) acid; Por, porphyrin; PPIX, protoporphyrin-IX; py, pyridine; QD, quantum dot; R_i, photochemical rate; RBS, Roussin's black salts; RRS, Roussin's red salt; RSE, Roussin's red ester; Salen, *N*,*N*′-ethylenebis(salicylideneiminato)dianion; Salophen, *N*,*N*′-1,2-phenylenebis(salicylideneiminato)dianion; TCF, thiol functionalized derivative of cupferron; TD-DFT, time-dependent density functional theory; TMOS, tetramethylorthosilicate; TPE, two-photon excitation; TPPTS, tris(sulfonatophenyl)phosphine trianion; UCNP, upconverting nanoparticle; UV, ultraviolet; Φ, quantum yield; λ_{irr}, irradiation wavelength; β, two-photon absorption cross section.

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1. Introduction

This review discusses innovative strategies for the photochemical release (uncaging) of the small molecule bioregulators nitric oxide (NO, aka nitrogen monoxide) and carbon monoxide (CO) at specific physiological sites. Localized delivery of these moieties is of interest for potential therapeutic applications. Key concerns include the roles of NO in the cardiovascular system, in antibacterial applications and in cancer therapy [1–4] as well as the roles of CO in suppressing inflammation, wound healing and anti-bacterial activity [5–7]. Precise spatial-temporal control is essential, since, for example, NO delivered systemically can induce precipitous blood pressure decline; indeed, this is a cause of toxic shock. Dosage control is also important, since high levels of NO can kill tissue by inducing cell apoptosis, but low levels may instead be proliferative [8,9].

The revolutionary discoveries in the late 1980s that nitric oxide is synthesized endogenously and that such a simple molecule plays a plethora of roles in mammalian physiology led to the remarkable outpouring of research relevant to the chemical biology and biomedicine of NO. A key issue that emerged was what techniques could be used to deliver exogenous NO to specific targets. As a result, a number of compounds capable of the thermal release of NO were developed [10]. The story of carbon monoxide as a small molecule bioregulator (SMB) is similar. Although it has been known for decades that CO is generated endogenously by constitutive and inducible forms of the enzyme heme oxygenase [11], its bioregulatory and potentially therapeutic aspects were only more recently recognized. Several compounds called CORMs (CO releasing moieties) have been developed that are effective for the thermochemical CO release at physiological targets [6,12]. Interestingly, most of these CORMs are transition metal carbonyls, the ruthenium complex $Ru(CO)_3(gly)Cl$ (CORM-3, gly^- = glycinato) being an example [13]. The foci of the present discussion are photochemical methodologies for the targeted release of these small molecule bioregulators (SMBs).

If the SMB in the form of a photochemical precursor is benign, it is defined as "caged". Electronic excitation releases or transforms it into an active or "uncaged" form. The external signal (light) determines the location and timing of SMB release, while the quantity of light absorbed controls the extent of photoreaction (i.e., dosage). Thus, photo-uncaging defines the *location*, *timing* and *dosage* of SMB delivery and has value both as an investigative tool and in the potential therapy of specific disease states [14–16]. An example of a therapeutic application would be the uncaging of a radiation sensitizer during radiotherapy. Hypoxic regions of malignant tumors are more γ-radiation resistant than are normoxic tissue; therefore, one could reduce the collateral damage from such treatments by increasing the sensitivity of the targeted site [17]. NO is both a radiation sensitizer [18] and an exceptionally potent vasodilator [1,19], so releasing even nanomolar concentrations of NO at a targeted site synchronously with γ-radiation treatment [20] would enhance the efficacy of radiotherapy [21].

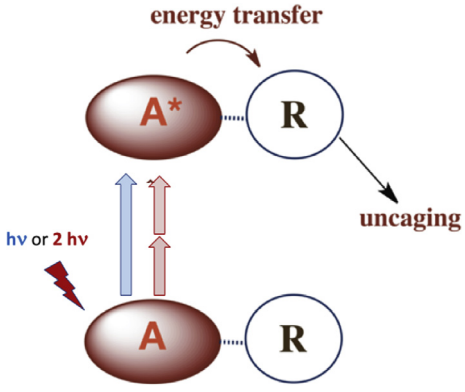
Developing such applications requires elucidating the fundamental photochemistry and photophysics of effective SMB precursors as well as defining the mechanisms for transporting these species to the physiological sites of interest. The photo-uncaging of NO has been an active research topic in this laboratory [20,22–33] and others [34–43] for several decades, while the photo-uncaging of CO has drawn growing attention for the past decade [44–54]. These two topics were the subject of a several comprehensive reviews over the past several years [5,55], so the present article will not duplicate those efforts. Instead, we focus on presenting an overview of different photo-uncaging strategies for these two SMBs with an emphasis on studies from this laboratory, but also drawing attention to newer reports from other researchers. We will use the term "photoCORM" (photo-activated CO releasing moiety), which we coined several years ago for caged carbon monoxide [44], and for consistency the parallel term "photoNORM" (photo-activated NO releasing moiety) for caged nitric oxide [55a].

2. Key issues in photo-uncaging

Notably, different bioregulatory tasks require different net or steady state quantities of SMB release. Since small molecules can defuse away from a targeted site and/or are consumed by various physiological processes, the rate of the photo-uncaging process is of critical importance. This rate is defined for single photon excitation by the product of the quantum yield (Φ_i) for the photoreaction of interest times the intensity of light absorbed (I_{abs}) by the photochemical precursor (Eq. (1)),

$$R_i = \Phi_i \times I_{abs} \quad (1)$$

where R_i is the rate of the particular photochemical process of interest and Φ_I is the efficiency by which excited states once formed decay along that specific pathway. (Φ_I is unit-less.) I_{abs} is a function both of the incident light intensity I_i and of the absorbance Abs(λ) by the photochemical precursor at the irradiation wavelength(s) λ_{irr}. (See the Appendix where the relationship between I_{abs} and photochemical rates are discussed in greater detail). Thus, one approach to enhancing uncaging rates is to increase the molecular absorbance by designing conjugate systems with strongly absorbing antennas (Scheme 1). However, it is important to recognize that such an



Scheme 1. **A** is the antenna, **R** is a precursor of a SMB that is uncaged once **R** is photosensitized by one- or two-photon excitation.