Photocontrol of NO, H₂S, and HNO Release in Biological Systems by Using Specific Caged Compounds

Hidehiko Nakagawa

Graduate School of Pharmaceutical Sciences, Nagoya City University; 3–1 Tanabe-dori, Mizuho-ku, Nagoya 467–8603, Japan.
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Nitric oxide (NO) is a gas that plays various roles in physiological signal transduction, for example, in vasodilation, neural transmission, and biodefence. Recently, other gaseous signal mediators such as carbon monoxide (CO) and hydrogen sulfide (H₂S) have also been found to have important biological activities. Since experimental studies with gaseous mediators are difficult, chemicals that enable controlled release of these gases are indispensable. We have developed a range of photocontrollable releasers that generate NO, H₂S, and related species with fine spatiotemporal control, and we have also employed these caged compounds in various applications. This paper briefly reviews our work on photocontrollable NO, H₂S, and HNO releasers, and presents some typical applications illustrating the suitability of our compounds for controlled release of these biologically active species in cellular and tissue systems. These compounds also appear to have potential for future therapeutic applications.

Key words caged compound; nitric oxide; hydrogen sulfide; two-photon excitation; photochemistry; spatiotemporal control

1. Introduction

Nitric oxide (NO) has a simple structure, but a complex chemistry, and it is well established as a gaseous cellular signal mediator with pleiotropic roles in physiological signal transduction, e.g., in vasodilation, modulation of neural transmission, and biodefence. Subsequent studies have uncovered additional gaseous signal mediators, such as carbon monoxide (CO) and hydrogen sulfide (H₂S), with unique biological activities and chemical properties. 1–3) Studies of the biological properties of these compounds are hampered by their gaseous nature and potential toxicity, and therefore many kinds of releasing agents for these mediators have been investigated and developed. Among them, controllable releasers are most useful for providing precisely controlled release in various experimental settings. This is important, because endogenous NO, CO and H₂S are believed to be produced under strict control of biological signaling systems in vivo, so spatiotemporally well-controlled release of these mediators is essential for studies of their biological functions. For this purpose, the use of caged compounds that release the desired species in a photoirradiation-dependent manner is expected to be an effective strategy. Indeed, various kinds of photocontrollable NO releasers have been reported,4–7) though so far, few of them are applicable to cellular systems and tissues. On the other hand, work is less advanced on photocontrollable CO8) and H₂S9–11) releasers.

We have been working on photocontrollable releasers of NO, H₂S, and related species during the past decade, and we have developed a range of useful compounds. This paper briefly reviews our work on photocontrollable NO, H₂S, and HNO releasers, together with some typical applications.

2. Photocontrollable NO Releasers (Caged NO)

As mentioned above, various types of photocontrollable NO releasers have been developed. We focused on two mechanisms for photo-dependent NO release, i.e., photoinduced isomerization of a dimethylnitrobenzene (DNB) moiety conjugated with a π-electron system, and intramolecular photoinduced electron transfer (PeT) of a moderately electron-rich N-nitroso aminophenol moiety linked with an antenna dye moiety.

2.1 DNB-Type Photocontrollable NO Releasers

In the course of investigation of the carcinogenicity of benzo[a]-pyrene, Fukuhara et al. found that 6-nitrobenzo[a]pyrene can release NO upon photoirradiation. The reaction is considered to proceed by homolytic cleavage of aryl nitrite ester generated by photoinduced isomerization of the nitroarene structure. A key feature of this reaction seems to be the twisted conformation of the nitro group due to steric hindrance by hydrogen atoms at the peri-positions.12) Although intense shorter-wavelength UV irradiation was reported to induce isomerization of simple nitrobenzenes,13) Suzuki and colleagues in our group assumed that a twisted conformation induced by introduction of a bulky moiety, such as ortho-dimethyl groups, would facilitate the isomerization reaction. Therefore, we designed and developed compounds bearing a 2,6-dimethylnitrobenzene (DNB) moiety, in which the nitro group is considered to be twisted due to the presence of the two vicinal methyl groups.

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groups at ortho-positions. We confirmed that these compounds released NO upon photoirradiation in the UVA range (330–380 nm), which corresponds to the absorption band of the compounds. We next developed Flu-DNB (Fig. 1, 1) as a cell-applicable DNB-type NO releaser, and we showed that Flu-DNB is distributed into cells, and releases NO within the cells upon UVA irradiation\(^{15,16}\) (Fig. 2). Flu-DNB was applicable to in vivo experiments in combination with two-photon excitation by means of femtosecond (fs)-pulse laser technology. Flu-DNB was introduced into anesthetized mouse brain in artificial cerebrospinal fluid (ACSF) through a small hole made in the skull and dura, and we used two-photon fluorescence microscopy to observe the response of mouse brain vessels to a near-infrared (735 nm) pulse laser at the regions where Flu-DNB was distributed. The near-infrared region is more favorable than UV or visible light, as it penetrates deeper into tissues. In this experiment, an increase of the vessel diameter was observed only during the irradiation, and was confined to the irradiated area\(^{15}\) (Fig. 3). This indicated that Flu-DNB released NO in vivo, and induced physiological responses under the control of the near-infrared laser. It is possible that a combination of DNB-type NO releasers with pulse laser technology could be used for site-specific therapy for infarction in the future.

We also set out to develop another DNB-type NO releaser responsive to visible light from conventional light sources. This would be useful, because it would not require expensive and complex pulse laser systems. We explored other DNB-type structures and designed a novel NO releaser, Rol-DNB (Fig. 1, 2), in which the linker region between the dye and dimethylnitrobenzene moieties was shortened. Rol-DNB showed absorption at around 550 nm, as expected, due to the rhodamine moiety, but unexpectedly released NO in response to visible light (550 nm) irradiation. Rol-DNB was found to localize to mitochondria in cultured cells, and released NO inside the cells. Interestingly, mitochondria were fragmented in Rol-DNB-treated cells upon visible light (550 nm) irradiation\(^{17}\) (Fig. 4). It is known that a cytosolic protein Drp-1 is involved in mitochondrial fission, and is activated by nitrosylation of a specific cysteine residue. We considered that NO released from Rol-DNB in response to the irradiation would activate Drp-1 and facilitate mitochondrial fission. When the cells were pretreated with Midi-1, a Drp-1 inhibitor, the mitochondrial fragmentation induced by Rol-DNB combined with irradiation was attenuated. Thus, Rol-DNB should be also a useful research tool for investigating NO signaling in cellular signal transduction.

We also tried another modification of Flu-DNB. In Flu-DNB, photosorption and NO release are considered to depend on the stilbene moiety, so we expanded the electron conjugation in this region to the adjacent benzene moiety.

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Hidehiko Nakagawa is currently a Professor at Graduate School of Pharmaceutical Sciences, Nagoya City University. He was born in Kanagawa, Japan, in 1966, and received the B.S. in 1990 from the Faculty of Pharmaceutical Sciences, the University of Tokyo, and the M.S. in 1992 and the Ph.D. in 1995 from Graduate School of Pharmaceutical Sciences, the University of Tokyo (Supervisor: Masaki Hirobe). During 1995–2004, he was a Scientist at National Institute of Radiological Sciences, Japan. During 1999–2001, he was also a visiting scientist in Johns Hopkins University School of Medicine, U.S.A. (Ted and Valina Dawson’s Lab). In 2004, he became an Associate Professor at Nagoya City University, and was promoted to Professor at the same university in 2013. He received the Pharmaceutical Society of Japan Award for Divisional Scientific Promotions in 2016. His research interests are in the development of methodology for photo-control of bioactive molecules by integrating organic chemistry, and adopting them to manipulate physiological functions.
of fluorescein by using an olefin linker instead of the amide linker, affording Flu-DNB-DB (Fig. 1, 3). It was found the absorption maximum was shifted to 359 nm, whereas that of Flu-DNB was at 322 nm, as expected. We also found that Flu-DNB-DB released NO upon photoirradiation at 450–480 nm, and even upon irradiation with a fs-pulse laser at 950 nm (in the near-infrared range). The two-photon decomposition cross-section ($\delta u$ value), or efficiency of photodecomposition of Flu-DNB-DB, was found to be about 8 times higher than that of Flu-DNB ($\delta u = 0.98$; Flu-DNB, $\delta u = 0.12$). It was also confirmed that Flu-DNB-DB released NO efficiently in HCT116 cancer cells with fine spatiotemporal resolution in response to pulse laser irradiation.\(^{16}\)

2.2 Intracellular Photoinduced Electron Transfer (PeT)-Type Photocontrollable NO Releasers

To exploit another type of NO-releasing mechanism, we investigated the NO release reaction of BNN-5\(^5\) (Fig. 1, 4), a previously reported photocontrollable NO releaser, from which two NO molecules are released upon photoirradiation. The first is considered to be released via photoinduced homolytic dissociation of the N–NO bond, and then release of the second is facilitated by formation of a stable quinonimine from the radical intermediate remaining after the first NO dissociation. We focused on the release mechanism of the second NO molecule in BNN5, and set out to produce an unstable intermediate radical species via intramolecular photoinduced electron transfer reac-

![Fig. 2. Photoinduced NO Release from Flu-DNB in Cells](image)

Flu-DNB was loaded into HCT116 cells with DAR 4M AM as a fluorescent NO probe. Irradiation with UVA light induced an increase of fluorescence intensity in the cells, indicating intracellular NO production from Flu-DNB upon photoirradiation; a, c) before photoirradiation, b, d) after photoirradiation, a) Flu-DNB-loaded cells, c) DMSO-treated cells as controls.\(^{15}\) Adapted from ACS Chem. Biol., 8, 2493–2500 (2013) American Chemical Society.

![Fig. 3. Two-Photon Fluorescence Images of Vessels in Mouse Brain Treated with Flu-DNB](image)

Mouse brain treated with Flu-DNB or fluorescein was irradiated with a pulse laser (735 nm) at the ROI indicated by red lines. Two-photon images were obtained simultaneously by scanning with the acquisition pulse laser (950 nm). The observed fluorescence is due to Flu-DNB or fluorescein. Representative images are shown in panels a–d: a, b) Two-photon fluorescence images of a vessel in mouse brain treated with Flu-DNB immediately before (a) and during (b) the uncaging pulse irradiation; c, d) images of mouse brain without Flu-DNB immediately before (c) and during (d) the uncaging pulse irradiation. The vessel diameter before irradiation is shown by a yellow scale bar in each pair of images.\(^{15}\) Adapted from ACS Chem. Biol., 8, 2493–2500 (2013) American Chemical Society.

![Fig. 4. Mitochondrial Fragmentation Induced by Photoirradiation of Rol-DNB-Loaded Cells](image)

HEK293 cells in which mitochondria were labeled with green fluorescent protein (GFP) were treated with Rol-DNB-pyr (1 $\mu$M), and subjected to confocal fluorescence microscopy. Photoirradiation was then performed at 530–590 nm (300 W Xe lamp, 10–40 mW/cm$^2$) for 3 min. Green: Mitochondria-GFP, A: before irradiation, B: 60 min after irradiation.\(^{17}\) Adapted from ACS Chem. Biol., DOI: 10.1021/acschembio.5b00962 (2016) American Chemical Society.

![Fig. 5. Changes in Tension of Rat Aorta ex Vivo Induced by Blue-Light-Mediated NO Release from NOBL-1](image)

Rat aorta was treated with L-NAME (10 $\mu$M) and noradrenaline (10 $\mu$M), followed by NOBL-1 (1 $\mu$M), in Magnus tubes. The tubes were irradiated (470–500 nm, 14.5 mW/cm$^2$) for 1, 2, and 3 min as indicated by colored thick lines.\(^{18}\) Adapted from J. Am. Chem. Soc., 136, 7085–7091 (2015) American Chemical Society.

Flu-DNB was at 322 nm, as expected. We also found that Flu-DNB-DB released NO upon photoirradiation at 450–480 nm, and even upon irradiation with a fs-pulse laser at 950 nm (in the near-infrared range). The two-photon decomposition cross-section ($\delta u$ value), or efficiency of photodecomposition of Flu-DNB-DB, was found to be about 8 times higher than that of Flu-DNB (Flu-DNB-DB, $\delta u = 0.98$; Flu-DNB, $\delta u = 0.12$). It was also confirmed that Flu-DNB-DB released NO efficiently in HCT116 cancer cells with fine spatiotemporal resolution in response to pulse laser irradiation.\(^{16}\)

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to achieve this, we designed and synthesized an \(N\)-nitrosoaminophenol derivative linked to a visible-light absorbing dye moiety, NOBL-1 (Fig. 1, 5). NOBL-1 contains a borondipyrromethene (BODIPY) structure with absorption around 500 nm. When NOBL-1 was photoirradiated in aqueous solution, NO release was observed by means of an ESR spin trapping method, as well as with a fluorogenic NO-specific probe, DAR-4M. NOBL-1 was found to be applicable for cellular experiments, and the release of NO could be controlled by blue light irradiation with fine spatiotemporal resolution.\(^{18}\) It was also applicable for \textit{ex vivo} experiments. In a Magnus model using rat aorta strips, the specimen was treated first with \(L\)-\(N\)-nitro-arginine methyl ester (\(L\)-NAME) and noradrenaline to exclude endogenous NO and induce tension, respectively, and then treated with NOBL-1 in reperfusion buffer. Upon irradiation at 530–580 nm with a Xe lamp, relaxation of the aorta was observed in a photoirradiation-dependent manner (Fig. 5). The relaxation response was completely abolished in the presence of ODQ, a soluble guanylyl cyclase inhibitor, indicating that the relaxation induced by NOBL-1 and photoirradiation occurred through a physiological vasodilatory pathway. This observation suggested that NOBL-1, in combination with photoirradiation, is able to modulate physiological NO signaling. We are now examining practical application of NOBL-1 for vasodilation to treat erectile dysfunction.

3. **Photocontrollable HNO Releasers (Caged HNO)**

In the course of the development of NO releasers, we were also interested in NO-related species, one of which is HNO. This is a one-electron-reduced form of NO, and interestingly, has a positive isotope effect different from that of NO.\(^{19}\) It also activates calcium signaling through SERCA (sarcoplasmic reticulum \(Ca\^{2+}\)-ATPase)\(^{20}\) and RyR (ryanodine receptor).\(^{21,22}\) Functional alterations of these proteins are considered to be associated with cardiac diseases. It has also been reported that HNO has a cardioprotective activity owing to a preconditioning-like effect.\(^{23}\) These properties of HNO imply that it would be a good candidate for examining calcium signaling in cardiovascular systems, and may also be a candidate for the pharmacological treatment of heart failure. However, HNO itself is a very unstable and dimerizes to form \(N_2O\), so controllable HNO releasers would be indispensable. In biological experiments, Angelis’s salt (\(Na_2N_2O_4\)) is often used as an HNO releaser, even though it is not a controllable releaser but a spontaneous releaser, depending on decomposition in aqueous solution.\(^{24,25}\) To achieve photocontrol of HNO release, we focused on the work of King and colleagues,\(^{26}\) in which they reported hetero Diels–Alder cycloadducts of acylnitroso compounds with 9,10-dimethylanthracene, and described thermal decomposition of the adduct followed by hydrolysis of acylnitroso derivatives to form HNO, carbon dioxide, and amines. We hypothesized that the thermal decomposition of Diels–Alder adducts may be induced \textit{via} photoirradiation-dependent excitation, even though photodynamic \(4+2\) electro cyclic reactions are known to be prohibited.

We designed a hetero Diels–Alder-type acylnitroso derivative of 9,10-dialkylated anthracene. The alkyl group at the 9 and 10 positions of anthracene served to stabilize the Diels–Alder adduct thermally, and we added the nitroaryl group to an acylnitroso moiety to facilitate absorption in the UVA region. Based on this molecular design, we synthesized a candidate HNO releaser, NiP-DAC-DA\(^{27,28}\) (Fig. 1, 6).

When NiP-DAC-DA was dissolved in an aqueous solution containing 10\% dimethyl sulfoxide (DMSO) as a cosolvent, we observed HNO formation in response to photoirradiation in the UVA range (330–380 nm). Further, \(N\),\(O\), the dimerized product of HNO, was detected by means of GC-MS analysis in a photoirradiation-dependent manner. The anthracene derivative was also concomitantly produced, as determined by monitoring the 402 nm absorption of the anthracene moiety.\(^{27}\) These results indicated that the compound decomposed to produce HNO as expected, and the HNO immediately dimerized to afford \(N_2O\) (Chart 1). NiP-DAC-DA was also shown to be applicable for cellular experiments.\(^{28}\) For example, in several cell lines, such as A549, HNO induces calctinin gene-related peptide, CGRP, a neuropeptide that exhibits vasodilatory, ionotropic and chronotropic activities \textit{via} induction of cAMP.\(^{19}\) We then examined whether CGRP was induced in A549 cells treated with NiP-DAC-DA upon photoirradiation, by means of enzyme immunoassay (EIA). As expected, CGRP induction was observed in A549 cells after treatment with 50 \(\mu\)M NiP-DAC-DA and exposure to UVA photoirradiation (330–380 nm) for 10 min (Fig. 6). This is an important result, indicating that photo-controlled intracellular formation of HNO can induce a cellular response related to cardiac function. The compound, however, needs to be further improved, because it is unstable under ambient conditions and gradually decomposes to release HNO even in the dark. The hetero Diels–Alder adduct-type structure might be hard to stabilize thermodynamically, so it may be better to seek another caging
method for acylnitroso compounds.

4. Photocontrollable \( \text{H}_2\text{S} \) Releasers

Hydrogen sulfide (\( \text{H}_2\text{S} \)) is another biologically active, endogenous signaling molecule, like NO. The biological actions of \( \text{H}_2\text{S} \) appear to be closely related to those of NO, so it would be very interesting to control \( \text{H}_2\text{S} \) formation in biological systems for studies of signaling mechanisms and potential therapeutic applications, as in the case of NO. Therefore, we focused on the design of photocontrollable \( \text{H}_2\text{S} \) releasers by protecting, or caging, the sulfur atom in \( \text{H}_2\text{S} \) with photolabile protecting groups. For efficient and specific \( \text{H}_2\text{S} \) release, it is important to avoid substantial production of intermediate alkyl thiol, which might have different biological activities from those of \( \text{H}_2\text{S} \) itself. The key property of a suitable protecting group is rapid and efficient deprotection reaction upon photoirradiation. For this purpose, we employed a ketoprofen-type photolabile protecting group, and developed SPD-1 and SPD-2 (Fig. 1, 7, 8). As another type of photo-activatable \( \text{H}_2\text{S} \), secondary geminal dithiols protected with an ortho-nitrobenzyl group, a typical caging group, were also reported. However, \( \text{H}_2\text{S} \) releasers of this type depend on the hydrolysis of the geminal thiols as the rate-determining step for \( \text{H}_2\text{S} \) release, while our compounds can release \( \text{H}_2\text{S} \) directly via the photoinduced deprotection reaction (Chart 2). We confirmed \( \text{H}_2\text{S} \) release from SPD-2 in a photoirradiation intensity- and duration-dependent manner by means of the methylene blue method (Fig. 7) and by using a fluorogenic \( \text{H}_2\text{S} \) probe, HSip-1 (Fig. 8), and we also confirmed the absence of substantial production of intermediate thiol compounds by means
of HPLC analysis. SPD-2 is a photocontrollable H$_2$S releaser bearing a xanthonylpropanate moiety instead of the ketoprofen moiety (Fig. 1, 9); this absorbs light in the UVA region (330–380 nm), leading to release of H$_2$S. It is considered that UVA is less harmful than shorter-wavelength UV light, so SPD-2 should be available for use in cellular systems, as long as the irradiation time is relatively short. To allow SPD-2 to permeate into the cells, it was necessary to synthesize a prodrug form, SPD-2 AM, in which the carboxylic acid moieties are protected with an intracellular enzyme-cleavable acetoxymethyl ester (AM ester). When SPD-2 AM was applied to cultured cells (HEK293) concomitantly loaded with HSip-1 DA, a cell-permeable H$_2$S probe, we found that H$_2$S was released upon photoirradiation with UVA, as fluorescence signals were observed only within the irradiated cell (Fig. 9). This result also indicated that cells could be treated with H$_2$S in a spatiotemporally controlled manner by the use of SPD-2 AM and photoirradiation. The physiological signaling interactions between H$_2$S and NO are increasingly being discussed in connection with oxidative stress responses and related diseases, so our H$_2$S-releasing compounds should be valuable tools for precise investigation of this topic.

5. Conclusion

In conclusion, we have developed photocontrollable NO releasers based on two different types of reaction, i.e., photoinduced isomerization of a sterically hindered nitro group on a benzene ring, and photoinduced electron transfer reaction followed by homolytic dissociation. The obtained NO releasers were found to be available in cellular systems and even in vivo, in mouse brain. We also developed efficient H$_2$S releasers. Our compounds enable precise spatiotemporal control of the release of these unstable gaseous signaling molecules, and will be valuable tools for biological studies. They also have potential for therapeutic use. Our HNO releaser should be useful for investigating the role of HNO in cardiac function, although further improvements are needed to obtain more practical HNO releasers. Overall, photocontrollable releasers of gaseous mediators and related species are expected to be widely useful for studies to establish the physiological functions of these mediators, and may also find therapeutic applications in due course.

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Conflict of Interest

The author declares no conflict of interest.

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