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Medical Applications of Solid Nitrosyl Complexes

Phoebe K. Allan and Russell E. Morris

Abstract Solid nitrosyl compounds are under investigation as ways of delivering nitric oxide for medical applications. This contribution discusses the role of nitric oxide in biology and the need for solids that can be used to store and deliver the gas in biologically relevant amounts. The types of solid that make suitable gas storage media are discussed, as is the relationship between nitric oxide storage and other areas of gas storage research. The particular materials that show most promise for nitric oxide delivery are discussed in detail, including their preliminary medical applications on humans. Finally, a forward look is described as to how current nitric oxide technology is informing other potential gas delivery applications in medicine.

Keywords Gas adsorption · Medical applications · Metal–organic frameworks · Nitric oxide

Contents

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Abbreviations

BET	Brunauer, Emmett, and Teller
btc	Benzenetricarboxylic acid
btt	1,3,5-Benzenetristetrazolate
CBS	Cystathionine-β-synthase
cGC	Cytosolic guanylate cyclase
cGMP	Cyclic guanosine-3,5-monophosphate
CO	Carbon monoxide
CORM	Carbon monoxide-releasing molecule
CSE	Cystathionine-γ-lyase
CUS	Coordinatively unsaturated sites
FAD	Flavin adenine dinucleotide
FMN	Flavin mononucleotide
GTP	Guanosine-5-triphosphate
H_2S	Hydrogen sulfide
Hb	Hemoglobin
HbCo	Carboxy-hemoglobin
HO	Heme oxygenase
MIL	Material of the Institute Lavoisier
mmol	Millimole
MOF	Metal–organic framework
NADP	Nicotinamide adenine dinucleotide phosphate
NO	Nitric oxide
NOS	Nitric oxide synthase
OxHb	Oxyhemoglobin
PBS	Phosphate buffer solution
PDF	Pair-distribution function
ppm	Parts per million
PTFE	Polytetrafluoroethylene
ROS	Radical oxygenating species
SBU	Secondary building unit
STP	Standard temperature and pressure

1 Nitric Oxide in Biology

Cells signal to each other in order to coordinate cellular actions. This intercellular signaling takes place through the use of neurotransmitters. Chemicals traditionally recognized as neurotransmitters are compounds produced by neurons and stored in vesicles until stimulation of the neurons trigger their release (Fig. 1, top). They bind to specific membrane receptors in a neighboring cell to produce a physiological effect. "Gasotransmitters" are a group of small gaseous molecules that exhibit a similar signaling function in the body but through a different mechanism. They function without receptors because they are freely permeable to cell membranes (Fig. 1, bottom) [1]. The term gasotransmitter was first used in a paper by Rui Wang [2], in order to distinguish the receptor-independent signaling nature of these molecules from that of traditional neurotransmitters. Wang suggested that for a molecule to be considered a gasotransmitter, a number of criteria must be met (Table 1) [1]. Most importantly, the molecule must be produced endogenously (within the body) for a specific biological function. The term gasotransmitter additionally serves to recognize the similarities between signaling methods employed by each of the gasotransmitter molecules and to group the molecules together.

To date, three gasotransmitter molecules have been proposed: nitric oxide, carbon monoxide, and hydrogen sulfide. Ironically, considering this biological role, the reputation of all of these gases is for being detrimental to health; inhalation of high concentrations of any of the three can be lethal. Nitric oxide is best known for being an atmospheric pollutant as part of NO_x, a component of smog. Carbon monoxide is a common household hazard produced by incomplete combustion of fossil fuels, and is undetectable by the human senses making it known as the "silent killer." Hydrogen sulfide has a toxicity of similar potency to cyanide and is responsible for the characteristic smell of rotten eggs.

However dangerous large doses of these gases are, it has been shown that small amounts of all three gases are actually vital to human health. In fact, the body produces a small but biologically significant amount of all three gases and they are known to modulate cellular functions by influencing a range of intercellular signaling processes. The significance of this discovery was reflected in the award of the 1998 Nobel Prize for physiology to the three American scientists, Murad, Furchgott, and Ignarro for the discovery of the endogenous production of NO. In addition to the three accepted gasotransmitter molecules, recent reports suggest that the small gaseous sulfur dioxide molecule also plays a gasotransmitter role within the body [3, 4], and other gases such as carbonyl sulfide [5] and nitrous oxide [6] have been suggested for investigation.

Here, we consider the endogenous production and biological effects of nitric oxide before outlining the work done toward using exogenous dosage of nitric

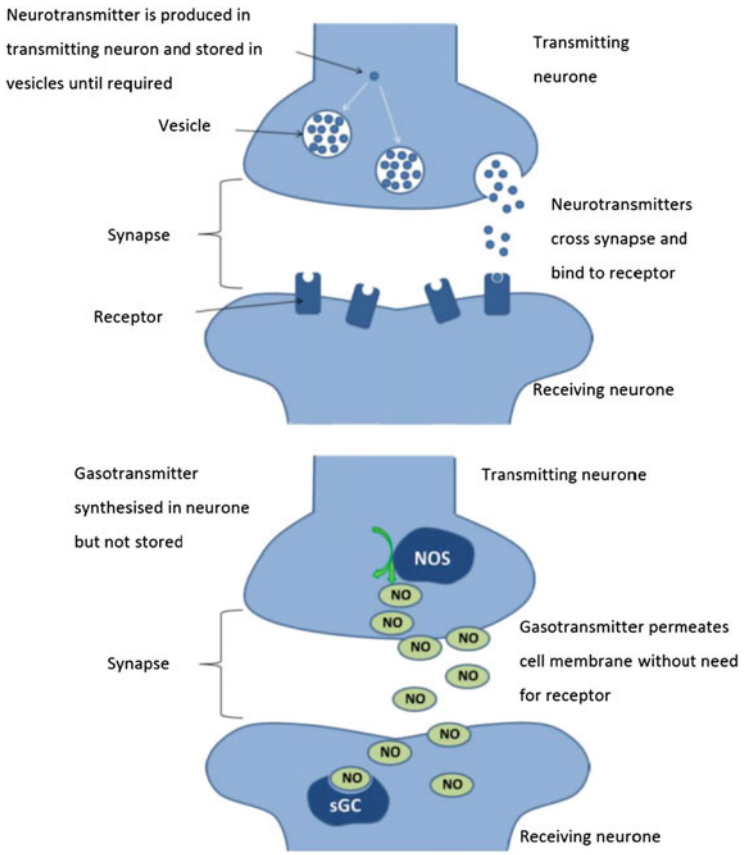

Fig. 1 Schematics of mechanism of neurotransmitter (1-1a, *top*) and gasotransmitter (1-1b, *bottom*) action

Table 1 Criteria for gasotransmitters

1. They are small, gaseous molecules
2. They are freely permeable to cell membranes
3. They are endogenously and enzymatically produced and regulated
4. They have specific well-defined biological roles at specific concentrations

oxide as a medical device. We summarize work done using chemical donors – polymers, porous materials, particularly zeolites and metal–organic frameworks (MOFs) – as delivery vessels for this gas. Finally, we briefly consider the role that the other gasotransmitters could play and the in vivo interactions of the gases.

1.1 Endogenous Production of Nitric Oxide

Endogenous production of nitric oxide was suggested in 1987 when reports from the groups of Louis Ignarro and Salvador Moncada suggested that nitric oxide was responsible for the relaxation of endothelial cells[1] in blood vessels [7, 8]. Direct evidence that endogenous nitric oxide production was responsible for this effect was given shortly thereafter by the use of isotopic labeling of nitrogen in arginine in endothelium cell cultures [9].

It is now well established that the bulk of endogenous nitric oxide is formed by the reaction of the amino acid L-arginine (which provides the nitrogen of the NO) with oxygen gas to form citrulline and nitric oxide. The reaction is shown in Fig. 2. This reaction is catalyzed by the family of enzymes called nitric oxide synthase (NOS). There are several isoforms of NOS: the constitutive forms, eNOS and nNOS, which are expressed within tissues in all physiological conditions, and an inducible form, iNOS, which only exists when induced by the switching on of a central gene. All forms involve a central metal ion such as zinc, copper, or iron within a heme moiety.

The mechanism by which nitric oxide is formed is similar for all types of NOS [10]. Electrons are required for the conversion and these are provided by the chemical nicotinamide adenine dinucleotide phosphate (NADPH) which, while not part of the NOS enzyme itself, is essential to the enzyme activity. NOS has two distinct domains which take part in the conversion of L-arginine: reductase and oxygenase. The reductase domain contains two cofactors,[2] flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD), which receive the electrons from the NADPH and pass them, via calmodulin, to the oxygenase domain. The oxygenase domain contains, in addition to the NADPH, two cofactors: heme, where the substrate oxygen binds to the iron before reacting with the L-arginine, and BH_4, whose role is currently unknown. The electrons from the reductase domain activate the oxygen attached to the heme moiety and facilitate attack of the arginine. While most nitric oxide is produced by the method above, other sources of nitric oxide within the body are also known, such as *S*-nitrosothiols.

The endogenous concentration of nitric oxide has been estimated to be in the nanomolar concentration range [11], which is quite low for something to show significant biological activity. However, as NO is reactive and its lifetime in the body is thought to be a few seconds at the most, there would not be much free nitric oxide in tissues to be detected [7].

[1] In blood vessels, endothelial cells exist in the endothelium, which is the single-layer of cells between the hole through the middle of blood vessels where blood flows (the lumen) and the exterior wall of the blood vessel (smooth muscle layer). Relaxation of the muscle layer increases the size of the lumen and allows more blood to flow through the vessel, which is called dilation of the blood vessel (vasodilation).

[2] Cofactors are "helper molecules" for enzymes – chemical compounds which are not part of the enzyme itself but are required for the enzyme to catalyze biochemical processes.

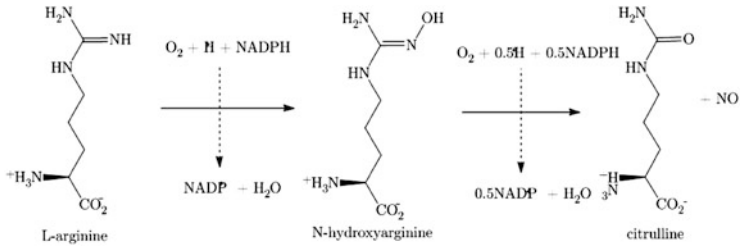

Fig. 2 Nitric oxide production via the conversion of L-arginine to citrulline

1.2 Toxicity and Biological Activity of Nitric Oxide

The direct toxicity of nitric oxide is modest, but is greatly enhanced by it reacting with superoxide to form peroxynitrite (ONOO-) [12]. The generation of excess $ONOO^{-}$ leads to oxidative injury and lung damage culminating, at high dosages, in pulmonary edema. On contact with oxygen, NO spontaneously produces NO_2 which is considerably more toxic than nitric oxide itself.

The biological effects of nitric oxide appear to be ubiquitously present in the body. Research is only in its infancy, and in many areas there is not a clear consensus of the role NO performs, with many contradictory accounts of effects being reported. Part of the reason for this is that endogenous levels of the gases must strike a very fine balance; for example, nitric oxide deficiency can cause unwanted effects such as hypertension, thrombosis, and a reduced ability to fight infection and heal wounds [13] while overproduction of NO has been linked to conditions such as septic shock and inflammation [14].

NO produced in the endothelium prevents platelet aggregation in healthy blood vessels through a cGC-derived mechanism, implicating NO in wound healing and thrombosis [15]. When the endothelium of a blood vessel is damaged, the level of NO produced is lowered and platelet aggregation is no longer prevented. This leads to platelet aggregation clotting and healing of the vessel. NO is known to regulate the growth of new blood vessels and may regulate the production of new skin cells during wound healing [16]. This, coupled with the roles NO plays in fighting infection and in clotting, means that the endogenous dosage of nitric oxide has been suggested to improve wound healing, particularly in situations where the body's wound healing mechanisms are lowered (such as in diabetic ulcers). There are growing reports that H_2S, like nitric oxide, has therapeutic potential in the angiogenesis/wound healing area; in vitro studies demonstrate that hydrogen sulfide induces angiogenesis and stimulates gastric ulcer healing in rodent models [17–19].

In cases where platelet aggregation is not associated with a wound, there is a danger of clots which can prevent blood flow to key organs. This danger is increased when foreign matter, which does not produce NO, is inserted into the blood vessels, as is the case when stents are used to alleviate stenosis. Stenosis, the narrowing of the blood vessels by fatty lipid deposits, is a very dangerous condition which can increase blood pressure and strain on the heart. A stent at the end of a

catheter is inserted into the vessel and a balloon is inflated to increase the size of the lumen and increase blood flow. This procedure can damage the endothelium, lowering NO levels and increasing risk of clots on the surface of the stent, forming a thrombosis. Using stent materials which produce NO to mimic endothelial action could have a role in preventing thrombosis.

NO is a known antibacterial agent. Macrophages, which are scavenger cells and part of the immune system, protect the body from infection by killing and digesting microbes via the production of toxic chemicals to destroy the microbe cells. These chemicals are quickly removed from the body by enzymes, preventing them from damaging cells of the host tissue. NO is known to be one of the chemicals produced by macrophages and is involved in cell death, both necrosis[3] and apoptosis,[4] in its produced form and via conversion to peroxynitrite and nitrate [20]. NO-induced necrosis has also been suggested as the mechanism by which nitric oxide attacks tumor cells, although the role of nitric oxide in cancer is neither simple nor well understood at present [21].

The role of nitric oxide in inflammation is complex, and is both tissue- and concentration-dependent. Nitric oxide is generally labeled as pro-inflammatory, and the overproduction of NO by the inducible form of NOS (iNOS) has been implicated in pro-inflammatory conditions such as rheumatoid arthritis. Despite being pro-inflammatory, NO produced by eNOS is essential to wound repair and the growth of new blood vessels in the area affected by inflammation, meaning that therapies involving the inhibition of all NO production would not necessarily improve inflammatory conditions. Drugs which down-regulate iNOS-induced nitric oxide production without stopping production of eNOS-NO may possibly improve inflammatory conditions, and the subtle structural differences between the enzymes may mean that this level of selectivity is possible [22].

1.3 Potential of Gasotransmitters as Therapeutics

NO is an exciting potential therapeutic and the required concentrations of the gas for particular biological applications are starting to be realized. It is thought, for example, that for antiplatelet action very low concentrations of nitric oxide, of the order of nano- to pico-molar, are required [23]. For antibacterial action, much higher concentrations (millimolar) are needed. The biological effects are highly dependent on the concentration of the nitric oxide, meaning that potential therapies

[3] Necrosis is cell death caused by factors external to the cell or tissue, such as infection, toxins, or trauma. It is generally "messy" leaving behind debris in the body, and is normally detrimental to tissue.

[4] Apoptosis is programmed cell death. It results in cell fragments which can be engulfed and removed from the body before the contents of the cell can spill out onto surrounding cells and cause damage.

require a method that allows delivery of the exact amount of gas appropriate to the therapy at the desired rate.

There are number of difficulties with the dosage of nitric oxide; NO is a gas at room temperature and pressure. Secondly, it is lethal in high doses, meaning that the use of gas cylinders would have to be very tightly controlled and dosing an appropriately small amount would be awkward and difficult. Additionally, any exposure to oxygen causes immediate conversion to the extremely toxic NO_2. Inhalation of NO has been used extensively in biological experiments and, in fact, has met with some success in the treatment of infants with respiratory failure [24]. Recently, a delivery system specifically for dosing inhaled carbon monoxide (CO), NO's biologically signaling counterpart, has been developed by Ikaria to provide quantitative delivery of pharmaceutical-grade CO for inhalation in proportion to the subject's body weight [25].

The short lifetimes in vivo of NO mean that systemic delivery may not be able to dose the gas to the correct areas. Particularly for applications such as wound healing, direct delivery of the gas to a targeted area is desirable, and this would further avoid unwanted side effects of the gas's action in other parts of the body.

Outside of inhalation, chemical compounds which release the gas when exposed to a specific stimulus are the most widely researched source of gasotransmitters. NO donors are a growing area of research. Exogenous sources of NO have unwittingly been used as therapies for centuries; there are reports of potassium nitrate, which is broken down by NOS to produce NO, being used to treat the discomfort and pain associated with angina as early as 800 AD [20]. Glyceryl trinitrate, which is thought to be metabolized to form nitric oxide is the most common treatment for angina [26].[5] Diazeniumdiolate compounds (NONOates) release nitric oxide in a first order, proton-mediated reaction, and the rate of gas release from compounds can be chemically controlled [27]. The drug Viagra works by prolonging the effect of NO in the penis, where the gas acts to relax the vessels, thereby enhancing blood flow [28]. *S*-nitrosothiols, when used as NO donor drugs, break down to form NO.

Some uses such as wound healing applications require topical delivery of the gas. Topical delivery of nitric oxide has received the most attention. Acidified nitrite creams have improved the wound healing time in both normal and diabetic mice, but there is some concern with regard to skin inflammation. Dressings with NO-releasing materials improved the wound healing time in diabetic mice [29]. Coatings for stents and catheters which release nitric oxide and better mimic endothelial nitric oxide production have been shown to decrease thrombosis formation [30–33]. This technology also requires materials which can release nitric oxide at a rate which mimics endogenous production.

[5] Angina is a condition caused by constriction of the arteries supplying the heart, putting increased strain on the heart to maintain the same level of blood flow. Its symptoms are chest pain and choking.

2 Delivery of Nitric Oxide from Nitrosyl Complexes and Clusters

Some NO complexes of transition metals (metal nitrosyls) are photosensitive, that is, they release NO upon exposure to light. If NO release is of appropriate quantity and rate, these complexes could deliver NO in a site specific manner to malignant locations for applications such as apoptosis in tumor cells. Two main concerns for these complexes are a low quantum yield meaning that long exposures of UV light are required to release nitric oxide, which is harmful to tissues and low stability in aqueous media, limiting their implementation in real applications. Several groups have been active in the design of nitrosyl complexes which release nitric oxide exclusively on exposure to light [34, 35].

Choice of metal-oxidation state, spin configuration, and the spectator ligands in a complex can promote the release of nitric oxide and tailor the wavelength at which this nitric oxide is released as well as the stability of the complex in various media [35]. To increase the sensitivity of such compounds to visible light dyes have been added to the molecules or directly ligating a light-harvesting chromophore to the ruthenium center [36–38]. Initial work on iron and manganese complexes of the type $(PaPy_3)M(NO)(BF_4)_2$ where $PaPy_3$ is the pentadentate ligand *N*,*N*-bis(2-pyridylmethyl)amine-*N*-ethyl-2-pyridine-2-carboxamide showed release exclusively on exposure to visible light with reasonable quantum yield, but both iron and manganese complexes are unstable in aqueous buffers when NO converts to NO_2. The ruthenium complex $[(PaPy_3)Ru(NO)](BF_4)_2$ showed much better stability but showed a lower quantum yield [38].

Recently, the photoactive manganese nitrosyl complex $Mn(PaPy_3)(NO)](ClO_4)$ releases nitric oxide on exposure to visible light and is fairly stable to aqueous media [39]. Sensitivity of these compounds to wavelength can be adjusted by ligand replacement; in the case of $[Mn(PaPy_3)(NO)](ClO_4)$ pyridine ring of the $PaPy_3$– ligand frame with a quinoline moiety results in sensitivity in the near infrared region [40].

Photolytic delivery of nitric oxide in biological applications was actually implemented during the initial period when the role of nitric oxide in biology was emerging. Commercially available photolytic donors of nitric oxide were used as NO donors in biological experiments. For example, $[Ru(NO)(Cl)_5]^{2-}$ releases nitric oxide when exposed to light causing vasodilation in aortic rings, but NO release also occurs spontaneously from these compounds meaning that careful controls are required in any biological experiments [38]. In another example, clusters of $[Fe_4S_4(NO)_4]$ irradiated with visible laser light were able to release NO both in solution and when contained in the endothelium. This nitric oxide was able to dilate rat arteries dependent of the length of exposure and wavelength of light used [41].

NO transfer to several proteins including hemoglobin, cytochrome *c* oxidase from $[(PaPy_3)Ru(NO)](BF_4)_2$ within milliseconds of laser-pulse activation has been reported, as well as the activation of soluble granulate cyclase [35]. These materials require incorporation into release platforms to be used in real applications. NO released from photoactive nitrosyls has antibacterial action from a number of delivery platforms [34, 42–44]. $Mn(PaPy_3)(NO)](ClO_4)$ can be incorporated into a sol−gel

matrix with a polyurethane coating and still shows a linear release of nitric oxide, which was further shown to have antibacterial actions against *Pseudomonas aeruginosa*, *Escherichia coli*, *Staphylococcus aureus*, and methicillin-resistant *S. aureus* [44, 45]. When incorporated into aluminosilicate MCM-41 the system has been reported to release micromolar concentrations of NO rapidly from the entrapped nitrosyl while the photoproducts are retained in the host structure [42]. Authors observed clearing of both drug-sensitive and drug-resistant strains of *A. baumannii*, showing antibacterial properties of the released nitric oxide. A layered delivery system using polydimethylsiloxane (PDMS) and Pluronic (R) F127 gel impregnated with, $[Mn(PaPy3)(NO)]ClO_4$ has recently been proposed for use in bandages [44].

In addition to reduction and photolysis, a method of NO release from ruthenium complexes using the body's mitochondria cells has recently been proposed. Mitochondria are able to facilitate the release of NO from nitrosyl ruthenium complexes because they are sources of reducing agents such as NADH, and this indicates that the role of nitric oxide in site specific cell death could occur in mitochondria-mediated processes and could find use in the treatment of tumors and skin cancers [46].

2.1 Gas Storage in Porous Materials

Gas storage is a topical issue; with the projected exhaustion of fossil fuels, the urgency of our search for new energy sources has increased, and porous materials have been highlighted as a possible storage medium. Gas storage in zeolites has been studied extensively, especially in those materials with extra-framework ions which can interact with guest species [47]. Some MOFs have large surface areas and high porosity and this means that they have the potential to store significant amounts of gas in their pores. Most work to date has concentrated on gas storage for environmental applications, and this can be broadly split into adsorption of potential fuel gases, hydrogen and methane [48–52], and the capture of carbon dioxide and other hazardous gases [53, 54].

There are several potential advantages of using MOFs for gas storage compared to gas cylinders. Firstly, there can be an increased storage density when compared with gas cylinders, zeolites, and activated carbons [50]. Secondly, in applications where only a small amount of gas is required, it could be easier to handle the gas in the form of solid pellets with adsorbed gas whose capacity can be tailored for application. Lastly, it might be safer to handle a gas when it is adsorbed in a solid, especially if higher pressures can be avoided. This is particularly applicable in the case of biological gases, where very controlled delivery of the gas is required.

Storage of a gas in a MOF requires large enough pore windows to allow the gas molecules to diffuse into the material and an ability to keep the molecule in the material through the interaction of the gas and the framework's internal surface. Storage implies that the gas can be removed when required, meaning the ability to trigger the release of the gas from the material is necessary. Gas adsorption capacity is generally reported as

adsorption isotherms, which quantify the amount of gas that a material adsorbs as a function of partial pressure of the gas. In general, few gas release experiments are performed, meaning that in reality if the delivery of gas is incomplete, the deliverable storage capacity may be less than the adsorption values reported.

2.2 Methods of Gas Storage

When gas molecules enter the material, they can bind to sites on its internal surface. This is adsorption. Adsorption is loosely divided into physical adsorption, or physisorption, and chemical adsorption, or chemisorption. Physisorption is generally weak, is due to induced or permanent dipoles and is generally observed at low temperatures with reduced capacity at higher temperature. Chemisorption involves the exchange of electrons (formation of chemical bonds) between adsorbate and adsorbant and is a much stronger interaction. While physisorption tends to be completely reversible on the decrease in partial pressure, species chemisorbed to a surface are likely to need an extra driving force such as heat for their removal.

For an uncharged gas molecule, the main interaction with the framework surface is via physisorption. Because of this, uptake is generally correlated with higher surface area, though this is not necessarily the only factor. The strength of interactions between the framework and gases can be reflected by isosteric heats of adsorption, Q_{st} [55]. When van der Waals interactions dominate, Q_{st} values are generally small; for hydrogen gas, for example, the Q_{st} for interaction with frameworks is typically in the range of 4–7 kJ mol^{-1} [56]. For larger molecules such as methane, the Columbic portion of the interaction is larger, meaning that the gas is more "sticky." The relatively weak interaction between the framework and the gas molecules is often the limiting factor with regard to gas adsorption capacity, but there are a number of ways in which this interaction energy can be increased through functionalization of the framework surface.

Unlike in zeolites, where metal ions exchanged into the framework sit extra- to the framework and are readily available for interaction with guest species, the metal ions within MOFs are an integral part of the structure. This means that in many cases their coordination sphere is made up entirely of strong ligand bonds and so they are unable to interact with guest species without breakdown of the framework. However, in some cases where one or more coordination site is taken up by solvent molecules from the synthesis, their removal leaves the structure with metals which are not coordinatively saturated. These metals with empty sites in their coordination spheres are named coordinatively unsaturated sites (CUS), or open metal sites. They can be very reactive with a high affinity for guest molecules and can become involved in chemisorption processes. CUS have been shown to enhance gas storage in a number of systems [48]. The Cu-framework HKUST-1 ($[Cu_3(btc)_2(H_2O)_3]$) shown at the bottom of Fig. 3 was the first example of functionalizable CUS. The aqua ligands from the Cu-site can be removed upon heating, and replaced by other groups such as pyridine [57]. The Mn-framework $Mn_3[(Mn_4Cl)_3(BTT)_8]_2$ (BTT = 1,3,5-benzenetristetrazolate) was reported by Dinca et al. to contain open Mn^{2+} coordination sites. Interaction with D_2

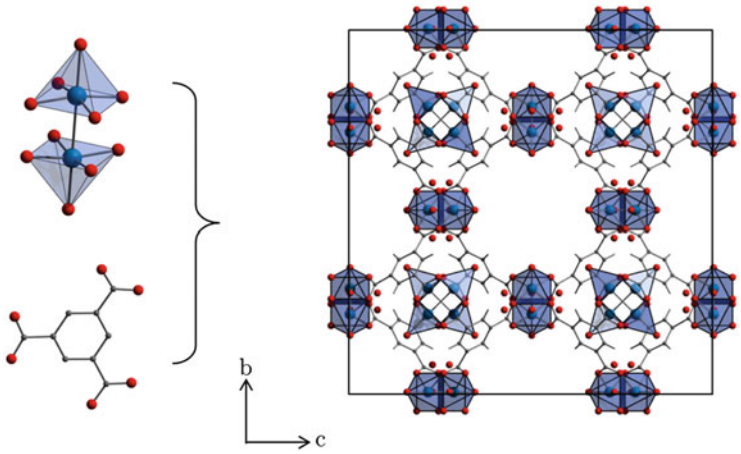

Fig. 3 $M_3(btc)_2$ framework topology

gives a Q_{st} value of 10.1 kJ mol^{-1} at zero coverage at 77 K, with a Mn–D_2 bond length (2.27 Å) much shorter than would be expected for physisorption [58]. Similarly, the interaction of H_2 with the open Ni-sites in Ni-CPO-27 was shown to give $Q_{st} = 13$ kJ mol^{-1} at low coverages, the highest framework-H_2 interaction energy to date [59].

Interaction of a guest with the ligand can also increase the energy of adsorption. The higher methane capacity of IRMOF-6 compared to the other IRMOFs was ascribed to interaction with the cyclobutyl 1,4-benzenedicarboxylate ligand [60]. PCN-14, which combines both copper open metal sites and additional adsorption sites interacting with the anthracene ligand, shows the highest interaction energy and adsorption capacity for methane to date [61, 62]. Use of amine-based ligands has been shown to greatly increase the interaction of CO_2 with the framework. Interaction with organic groups can be increased further by grafting pendant functionalities onto the surface; this strategy to introduce alkylamine functionality onto bridging ligands or onto open metal sites can result in the increased uptake of carbon dioxide [54].

Gas storage by framework flexibility has been reported for several frameworks [63–69]. These transformations can include stretching, "breathing" and rotation and in some cases the selective induction of framework transitions can lead to selective gas adsorption properties through size selectivity or thermodynamic effects.

2.3 Metal–Organic Frameworks

MOFs, also known as coordination polymers, are extended materials which consist of metal ions or clusters which act as polyhedral "nodes," connected by multidentate ligand molecules acting as linkers. Frameworks are formed by coordinate

bonds into infinite arrays, sometimes forming crystalline solids. The first MOF crystal structure was reported in 1959 [70], although significant research into the science and applications of MOFs started in the 1990s. To date, several thousand MOFs have been synthesized, usually via hydrothermal and solvothermal methods (Sect. 2.1) but increasingly using other techniques such as microwaves and electrochemistry [23].

2.4 Synthesis and General Features

MOFs can exist as one-dimensional chains, two-dimensional sheets or three-dimensional frameworks. 2D and 3D structures can exhibit pores or channels running through them which are usually filled with solvent molecules from the synthesis. Many frameworks have fairly low thermal stability, but those which show higher stability can have guest molecules removed from pores by exposing the material to a vacuum or to heat. This results in materials with large pore volumes and high surface areas of thousands of square meters per gram. This compares favorably with several hundred square meters per gram for the most porous zeolites (the maximum surface area is zeolite Y, at 904 $m^2\ g^{-1}$) and activated carbons which have a theoretical maximum surface area of 2,630 $m^2\ g^{-1}$ [63]. The highest reported MOF surface area (BET) to date is 6,240 $m^2\ g^{-1}$, shown by MIL-200 [71].

The connectivities and topologies of MOF structures are dependent on coordination preferences of the synthetic conditions. Metals provide coordination sites for linkers and the geometry of the metal caused by oxidation states and coordination numbers determines the shape of the node and therefore the geometry of the framework. Linkers have multiple functional groups in order to act as a bridge between metal centers. The most common linker atoms are oxygen and nitrogen – carboxylates, phenol, pyridine, and imidazole donors are by far the most common donor groups reported, though the use of more "exotic" functional groups such as sulfonates, nitrates, and phosphonates are becoming increasingly common as the search for new frameworks continues. Rigid linkers, where the movement of the lone pair is restricted, increase the predictability of reactions and act as rods between metal nodes which can lead to robust frameworks with permanent porosity. Linkers with flexible binding modes have the potential to act as hemi-labile ligands and can lead to coordinative flexibility in the framework. Counter anions from reagents and solvents can act as reactants; both can take an active part in the framework, or act as template ions. Reaction conditions are also known to have a determining effect on the structure.

The range of metals and organic linkers available and the ability to change experimental conditions gives potential for a seemingly infinite number of framework topologies. However, in practice, the chemistry of these systems favor the in situ generation of particular polyatomic metal units, meaning that the same so-called "secondary building units" (SBUs) are seen over and over again

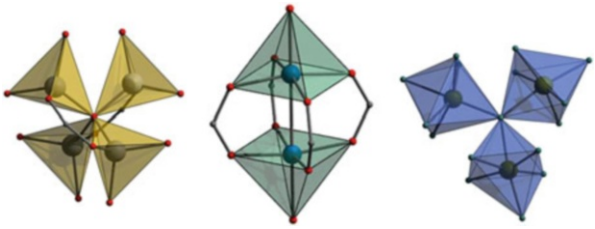

Fig. 4 Common secondary building units for MOFs: Zn_4O-cluster used in MOF-5 and IRMOFs (*left*); Cu-paddlewheel dimer seen in HKUST-1 (*middle*); Cr-trimer found in MIL-101 (*right*)

[72]. This is analogous to aluminosilicate zeolite chemistry, where a description of the structure can be given in terms of nine SBUs based on tetrahedral AlO_4 and SiO_4 primary building units [47]. Some common secondary building units – the Zn_4O-cluster, the copper paddlewheel dimer, and $Cr_3(OH)$-trimer – are shown in Fig. 4.

It is possible to tailor the structure and properties of a framework. Firstly, knowledge of SBU formation can be applied in order to design frameworks with the same topology but utilizing different ligands, resulting in different pore sizes and surface areas. The best known example of this "isoreticular synthesis" is the IRMOFs reported by Yaghi and co-workers which use the same Zn_4O-cluster with different linkers to form a series of frameworks based on the same cubic topology but with different pore sizes and chemical functionality and thus varying gas adsorption properties [60, 73]. In a similar manner, the same framework topology can be created with different metals, as demonstrated by the M-CPO-27 framework where metals (Ni, Co, Zn, Mn, Mg, Fe) are linked by 2,5,-dihydroxyterephthalic acid into a 3-D honeycomb framework, and the $[M_3(btc)_2]$ framework, based on M_2-paddle-wheel units linked by benzenetricarboxylic acid (btc) which can be synthesized with M = Cu (where it is commonly called HKUST-1) Fe, Cr, Mo (Fig. 3) [57, 74–76].

In addition to the range of frameworks which can be synthesized directly, it is also possible to modify the framework after the initial synthesis. This strategy of post-synthetic modification is frequently used to introduce functionalities to the pores and channels of the material required for specific purposes [77]. Post-synthetic modification can take several forms; removal of guest solvent molecules through the application of heat could be described as the most simple of post-synthetic modification procedures. Others include carrying out organic reactions on functional groups within the framework, grafting functional groups either onto the linker group or onto open metal sites in the material, or adding metal ions, clusters, or other species into the pores in order to enhance a particular characteristic of the material.

This ability to tailor a MOF's structure to specific needs and requirements makes them exciting for a range of applications. Initially, the high porosity of the materials focused attention onto gas adsorption (see Sect. 2.2), but MOFs have since been suggested for potential applications in areas such as gas separation [78, 79], catalysis [80–82], luminescence and sensing [83, 84], magnetism [85], and medicine.

2.5 MOFs for Biological Applications

In recent years a growing area of research has involved MOFs for biological applications [23]. The use of MOFs for biomedical purposes is attractive for a number of reasons. MOFs are generally quite biodegradable because of the relatively labile nature of the coordination linkages holding the materials together, and this feature can be modified by the careful choice of metal and linker. Additionally, there is a wide range of MOFs available including those which use nontoxic components. This range lends itself to the idea that a MOF could be tailored for a specific therapeutic purpose.

Several ways in which MOFs could be used for biological applications have been suggested and this literature reviewed by Horcajada et al. [23]. Firstly, MOFs could be used as a container to store and deliver biologically active guests. Alternatively, the MOFs themselves could be biologically active or could be used as a diagnostic for applications such as imaging within the body.

2.6 Porous Materials for Storage and Delivery of Nitric Oxide

The exogenous dosage of gasotransmitter molecules has been shown to have beneficial medical effects. Unlike with gas storage and release for energy applications, it is not the amount of the gas stored but the release amounts and rate which are key [49].

Both zeolites and MOFs have been shown to store and release NO. There are two ways of storing NO in a structure (Fig. 5). The first is through the formation of diazeniumdiolate (or NONOates), which can deliver nitric oxide on exposure to water, and the second is by coordination of nitric oxide to a metal. The interaction of NO with zeolite materials is well characterized due to their use as deNO_x catalysts to remove the NO and NO_2 molecules from car exhaust fumes. Some of the NO is bound weakly by physisorption and some binds to the metal site making a strong, chemisorption interaction. The chemisorbed nitric oxide is not released from the material even at low pressures, making the adsorption irreversible. Both single-crystal experiments [86] and IR studies indicate that this chemisorption component involves the interaction of nitric oxide with the metal sites in the zeolite [86–88].

The different structures of zeolites give some measure of control over the kinetics of release. Work by Wheatley et al. [89, 90] probed the effect that zeolite topology and extra-framework cations had on NO adsorption and release, and concluded that the most effective framework topology was LTA. Different metal cations within the same zeolite framework topology (LTA) gave rise to differing adsorption capacities and rates of release, with cobalt showing the best characteristics – adsorption of 1.7 mmol g^{-1} of nitric oxide at 1 atm. of NO and at room temperature.

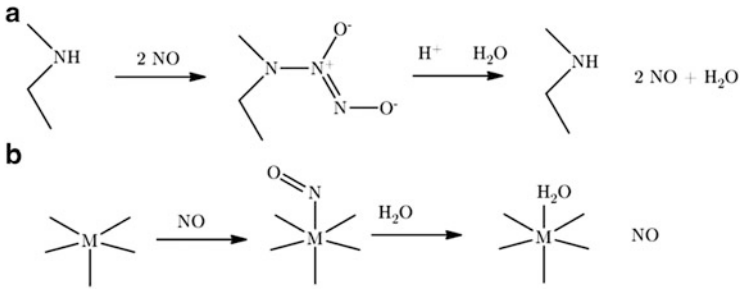

Fig. 5 Methods of storing nitric oxide in a zeolite or MOF. (**a**) Formation of diazeniumdiolates; (**b**) coordination to a metal ion

On the reduction of pressure, the weakly held physisorbed nitric oxide was removed leaving the irreversible chemisorbed content within the material. Upon exposure to moisture, water replaces the NO on the extra cation site and the nitric oxide is released. The zeolites show release of NO that is comparable in quantity to the adsorption process, although the total amount which is adsorbed is not released. The toxic nature of cobalt makes it unsuitable for some applications, so the much less toxic zinc framework, despite showing less ideal adsorption and desorption characteristics, has been used in several biological experiments.

NO-releasing zeolites show the expected biological activity. Wheatley et al. demonstrated anti-thrombosis activity on human platelet-rich plasma where a NO-loaded Co-exchanged zeolite-A sample completely inhibited platelet aggregation. When a NO scavenger was introduced to remove the NO from the system this inhibitory effect was removed, confirming the central role for NO in the inhibitory process and excluding the possibility that the effects of the NO−zeolite were merely cytotoxic. A sample of the Co-exchanged zeolite that has not been loaded with NO failed to inhibit aggregation. Figure 6 shows large platelet aggregants (PA) on the surface of the untreated zeolite which are no observed on the nitric oxide treated zeolite [89].

The well characterized low toxicity of zeolites makes them ideal for use in dermatological applications, and the sensitive nature of the delivery method compared favorably to other nitric oxide donors. Mowbray and co-workers have completed studies on human skin that show no significant inflammation of the skin on application of NO-releasing zeolites (Fig. 7), in contrast to chemically produced NO (from acidified nitrite creams), which is a competitor to gas storage materials for topical delivery [89].

Nitric oxide-loaded zeolite has also been shown to have antibacterial properties. A study by Fox et al. demonstrates the antibacterial properties of a NO-loaded Zn^{2+}-exchanged zeolite material at a 50 wt.% composition in a polytetrafluoroethylene polymer against clinically relevant strains of bacteria, namely Gram-negative *P. aeruginosa* and Gram-positive methicillin-sensitive and methicillin-resistant *S. aureus* and *Clostridium difficile* [91]. NO-loaded zeolite treatments significantly reduced bacterial numbers compared to control NO-free zeolite control disks did not significantly reduce bacterial numbers in any of the samples measured. Wei

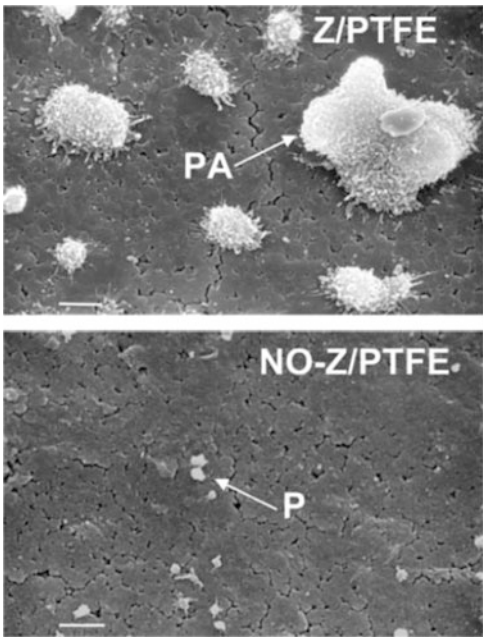

Fig. 6 Scanning electron micrographs of the surface of untreated Co-zeolite-A/PTFE disks (Z/PTFE) (*top*) and of NO-loaded Co-zeolite-A/PTFE disks (*bottom*). The *top* figure shows large platelet aggregants (PA) on the surface of the untreated zeolite/PTFE disk, while the bottom shows only a few, isolated platelets (P) on the surface of the NO-treated zeolite-PTFE disk. The scale bar is 10 μm. Reprinted with permission from J Am Chem Soc, 2006, 128 (2), pp 502–509. Copyright 2006 American Chemical Society

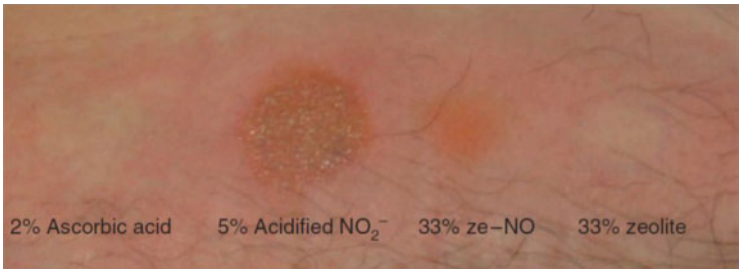

Fig. 7 Clinically visible cutaneous inflammation following topical acidified NO_2, but not Ze–NO application. Reprinted with permission from Mowbray et al., J Investig Dermatol (2008) 128, 352

et al. recently demonstrated nitric oxide delivery from saturated zeolites as part of a multi-functional material which captured nitrosamine by alumina-modified zeolite samples in the gastric juice mimic [92].

Work by Wheatley et al. [89, 90] probed the effect that zeolite topology and extra-framework cations had on NO adsorption and release, and concluded that the

most effective framework topology was LTA. Different metal cations within the same zeolite framework topology (LTA) gave rise to differing adsorption capacities and rates of release, with cobalt showing the best characteristics – adsorption of 1.7 mmol g^{-1} of nitric oxide at 1 atm. of NO and at room temperature.

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The toxic nature of cobalt makes it unsuitable for some applications, so the much less toxic zinc framework, despite showing less ideal adsorption and desorption characteristics, has been used in several biological experiments. The nitric oxide released from these materials has been shown to have antithrombotic effects [89]. The well characterized low toxicity of zeolites makes them ideal for use in dermatological applications, and the sensitive nature of the delivery method compared favorably to other nitric oxide donors; nitric oxide from a zeolite showed increased blood flow to the skin (due to the vasodilatory effect) without the redness from irritation found from acidified nitrate [93].

Several framework materials have been studied for nitric oxide adsorption and release. The storage of nitric oxide in MOFs can take place via either mechanism shown in Fig. 5. MOFs with open metal sites have shown much stronger adsorption of nitric oxide than those without [94]. This can be proven both structurally using X-ray diffraction or by infrared spectroscopy. Every MOF with open metal sites appears to store nitric oxide to some degree due to interaction of the gas molecule with the open metal site. The first studied MOF for NO adsorption, HKUST-1, adsorbs around 3 mmol g^{-1} of nitric oxide at room temperature and pressure [95].

The behavior of the CPO-27 isostructural series of frameworks for nitric oxide adsorption and release has been extensively studied [94]. McKinlay et al. report that both Ni-CPO-27 and Co-CPO-27 store considerable amounts of nitric oxide, with up to 8 mmol g^{-1} via coordination of the nitric oxide to the metal site resulting in octahedral geometry.

Other materials, such as the Fe-MIL-88 [64], Fe-MIL-100 [96], and Fe-MIL-101 also show good uptake of NO [97], and are of particular interest because of the redox chemistry that occurs on activation of the solids, with changes in activation energy that strongly affect the interaction of the NO with the open metal sites in the structure.

Storage of NO via the formation of diethylenetriamines, or NONOates was reported by Rosseinsky et al. who used post-synthetic modification of the open metal site of HKUST-1 [98]. However, on immersion in water, nitric oxide was released, but the amines were also leeched from the metal sites. Cohen and co-workers use a similar method for functionalizing MOFs with NONOates by conversion of secondary amines from the functionalized ligands in MOFs rather than the open metal sites, thus improving the stability of the grafted amine species [99].

For biological applications, the release of nitric oxide is very important. In structures which chemisorb nitric oxide, reduction in gas pressure is not enough to induce release of the nitric oxide molecule. Nitric oxide can be released on heating the material, or photolytically, but the most common method of release is exposure to water. If the framework-nitrosyl compound is susceptible to water, water replaces the nitric oxide on the framework binding site and the nitric oxide is released. The amount of nitric oxide released is dependent on how susceptible the framework is to moisture. For example, HKUST-1, which chemisorbs 3 mmol g^{-1} of NO at room temperature, releases only a tiny fraction because the nitrosyl complex is too stable [90].

Both Ni-CPO-27 and Co-CPO-27 show exceptional release capabilities and the full adsorbed capacity is released on exposure to water [100]. Here, water replaced nitric oxide on the metal site in the structure, forcing the nitric oxide out of the structure to be released. The other members (Zn-CPO-27, Mn-CPO-27, and Mg-CPO-27) of the series also store and release nitric oxide but without the same exceptional release capacities [94]. The release capacities of these materials appear to be in some way correlated with the ease of dehydration and the stability of the open metal sites [23]. Between the two extremes of HKUST-1 and CPO-27 lie other MOFs with open metal sites which release a portion of their adsorbed amounts of nitric oxide.

Harding et al. recently reported the generation of nitric oxide via the MOF-catalyzed reaction of *S*-nitrosocysteine. At the peak of nitric oxide production, 200 picomolar concentrations were released whereas control experiments without the MOF present did not yield appreciable NO generation [101].

The use of MOF-nitrosyl complex released nitric oxide has concentrated on three areas: anti-thrombosis, antibacterial, and vasodilatory experiments. Each application requires a different release profile for the nitric oxide; antibacterial actions require a much larger dose of nitric oxide than the slow picomole dosage required for antiplatelet action. HKUST-1, which releases only a tiny percentage of the adsorbed nitric oxide, presumably because of the high stability of the copper-nitrosyl complex, was shown to be active in completely inhibiting the aggregation of platelets in human platelet-rich plasma (PRP). Aggregation was initiated using an exogenous agent, and after a short induction period no aggregation could be seen in the NO-loaded MOFs, whereas the MOF tested without NO loading showed no antiplatelet activity.

An investigation of NO-loaded MOF Zn-CPO-27 against methicillin-resistant *S. aureus*, *P. aeruginosa*, and *C. difficile* all showed significant bactericidal effects indicating that NO delivered in this way is very much a potential method of developing new technologies in this increasingly important field [46].

Vasodilatory actions of MOF-released nitric oxide were reported by McKinlay et al. [100]. Here, placement of pellets a distance of 2 mm from the vessel in the 10 mL organ bath resulted in rapid 100% relaxation of the vessel. The pellet could be seen to generate bubbles of gas for 10 min of submersion, although the relaxation remained maximal for >1 h. This effect was not observed when the pellet without nitric oxide loaded was placed in the same position.

Nitric oxide delivery from open framework sites has been developed further in an exciting strategy utilizing the tri-functionality of frameworks, where the fast release of nitric oxide from metal center on exposure to moisture can be combined with slower release of antibacterial drugs which fill up the space in the pores unoccupied by metal-bound nitric oxide. The third functionality is realized through using a bioactive metal such as zinc which is leached very slowly from the framework in buffer solution.

2.7 *Structural and Mechanistic Studies of Nitric Oxide Adsorption and Release*

The formation of stable nitrosyl complexes within active frameworks make these compounds ideal for studying mechanisms of gas adsorption, particularly selective adsorption. Ultraselectivity in frameworks can be tailored by the functional group present. In the case of the MOF Cu-SIP-3 [102], the dehydration process which activates the material toward gas adsorption takes place via a single-crystal to single-crystal thermally activated transition which goes via an amorphous intermediate and results in an essentially nonporous MOF. This material does not adsorb any of the common gases tried such as hydrogen or carbon dioxide but above a gate-opening pressure, nitric oxide can interact strongly enough with the framework to reverse the phase transition. Thus the material is effectively ultraselective toward NO showing a 2.2 mmol g^{-1} uptake at 1 atm. of pressure. The nitric oxide uptake of this material was characterized by single-crystal and pair-distribution function analysis, which allowed probing of the ordered and disordered regions, respectively, and determine the order of atomic movements during the dehydration period. This, combined with in situ gas loading experiments using the two techniques was able to postulate that the formation of copper-nitrosyl complexes above the gate-opening pressure was responsible for the uptake and release of nitric oxide from the material [103, 104]. In another example of selectivity, a zinc-TCNQ MOF structure prepared by Kitagawa and co-workers displays nitric oxide selectivity over O_2 adsorption because of their ability to undergo electron transfer with the framework ligand [105].

In addition, the strong interaction of NO with some frameworks makes it useful as a selective probe molecule, especially for flexible frameworks where it can be used to induce changes in some parts of the framework. A prime example of this is in STAM-1, a copper-based MOF with two different channels: one pore lined only by organic groups rendering it hydrophobic while the other is hydrophilic and lined by potential open metal sites [106]. Which channel is accessible can actually be controlled by changing the activation conditions and the adsorption between the two channels can be switched. Here, the nitric oxide can interact relatively strongly with both types of surface, so is an excellent probe for such switchable adsorption. NO adsorption can be used to probe which pore is open as the strong interaction due

to the formation of nitrosyl at the open metal sites that are available leads to a steep increase in uptake at low pressure compared to that in the hydrophobic channel, which has no open metal sites.

3 Looking Ahead: Other Gasotransmitter Molecules

In addition to nitric oxide, there is increasing interest in carbon monoxide and hydrogen sulfide, two other accepted gaseous biological signaling molecules, and their role in biology. Like nitric oxide, the endogenous production mechanism of both gases has been discovered. In fact, the endogenous carbon monoxide production was postulated by Saint-Martin and Nicloux in 1898 [107], though the first experimental evidence was published in two papers by Sjostrand in 1949 and 1951 [108, 109]. It has also been known since the 1950s that breakdown of heme results in the production of carbon monoxide in the body, and in 1968 these facts were linked by the discovery of the enzyme heme oxygenase (HO), the main source of endogenous carbon monoxide, accounting for over 80% of endogenous production [110]. Carbon monoxide production is visible to anyone who has ever had a bruise. This process is illustrated in Fig. 8. Injury to a tissue results in free heme being released from hemoglobin forming a dark red patch (oxyhemoglobin). Free heme does not occur in healthy tissue and is toxic, so it is broken down by the body. HO catalyzes the oxidation of heme, producing first biliverdin (green) and then bilirubin (yellow) and carbon monoxide. This carbon monoxide coordinates to heme to give a bright red color. The blue color seen as the bruise develops is deoxygenated venous blood as the degradation of each heme requires three equivalents of dioxygen.

Most endogenous CO is part of the bloodstream, meaning that in the absence of significant ambient CO, blood Hb–CO levels are around 0.4–1% of the total Hb content [111]. The stability of carbon monoxide means that elimination of CO from the bodies of mammals occurs strictly through exhalation from the lungs with no further metabolism.

Hydrogen sulfide is produced within the body by both enzymatic and nonenzymatic pathways [112]. There are four enzymatic pathways which are known to produce hydrogen sulfide from cysteine derivatives. Of these, the bulk of endogenous H_2S is produced by the enzymes cystathionine-β-synthase (CBS) and cystathionine-γ-lyase (CSE) [113]. L-Cysteine is hydrolyzed by CBS to produce equimolar amounts of H_2S and L-serine. CBS is responsible for the bulk of H_2S production in the brain and central nervous system, whereas CSE is expressed largely in endothelial and smooth muscle cells in the cardiovascular system.

Several estimates of endogenous hydrogen sulfide levels have been made. Many of these show relatively high levels of hydrogen sulfide (50–160 μM concentrations in brain tissue [114]), but figures should be approached with caution as their measurement involves an assay which is also sensitive to HS^- and S^{2-} [115, 116]. Recent estimates of H_2S put levels much lower, for example in a mouse brain the concentration is thought to be 15 nM [115, 117]. As for NO, these low

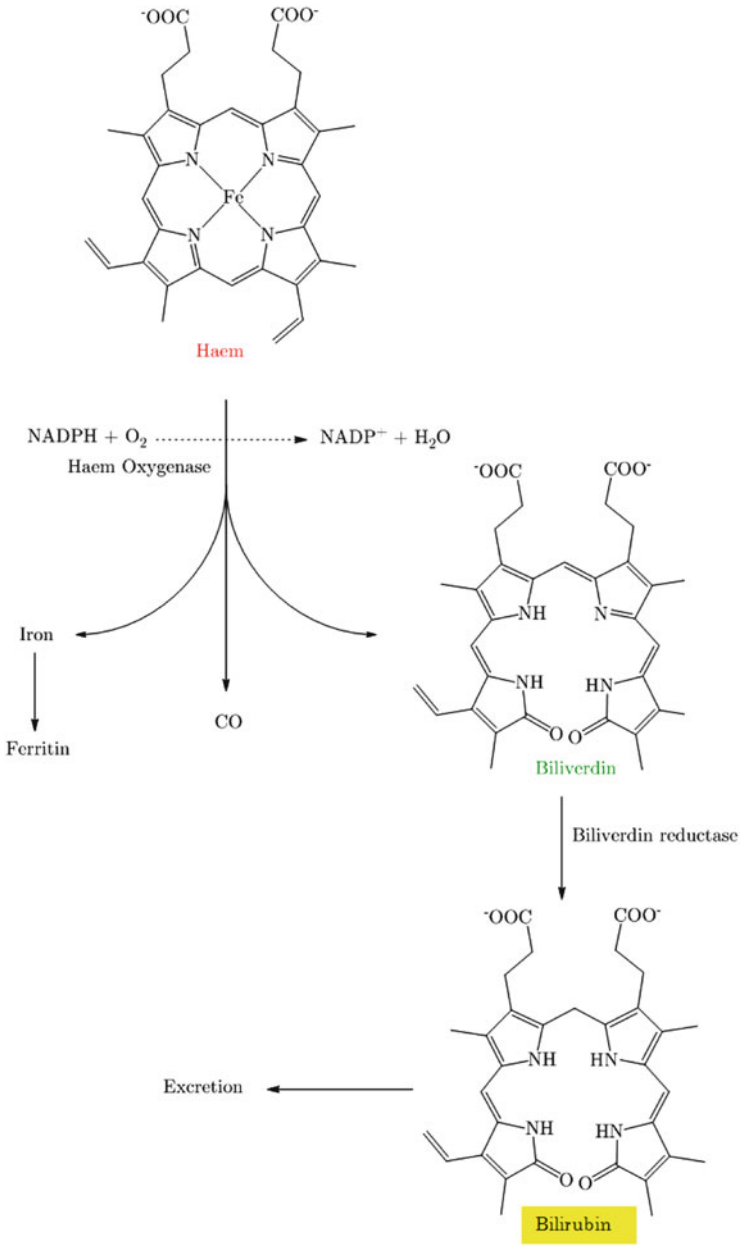

Fig. 8 Oxidation of heme to produce carbon monoxide as a by-product

levels are not necessarily a marker of biological inactivity, but are more of an indication that biological activity takes place rapidly upon production of the H_2S [7]. More accurate methods of measuring endogenous H_2S production is an area of current research [118].

Once produced, hydrogen sulfide is quickly metabolized by a number of pathways meaning that its lifetime in the body is fairly short with a half-life of the order of minutes [18]. Metabolism takes place mainly in the kidneys through oxidation by mitochondria yielding thiosulfate ($S_2O_3^{2-}$), sulfite (SO_3^{2-}), and sulfate (SO_4^{2-}), by methylation to dimethyl sulfide, or by reaction with metallo- or disulfide-containing molecules [2, 119]. One of these metalloproteins – the interaction with hemoglobin – is of particular interest, as this molecule is a common sink for both NO and CO. Interaction of H_2S with porphyrin forms the green sulfhemoglobin, and its formation could significantly alter the binding capacity for other gases [2].

3.1 Carbon Monoxide and Organ Transplantation

Organ transplantation is used routinely as a treatment for end-stage organ disease. A major challenge associated with the process of cold storage and warm reperfusion is ischemia/reperfusion injury[6] (I/R injury) which affects the short-term and long-term outcomes of transplants. Lack of oxygen to the tissue leads to increased expression of anaerobic mediators which, when combined with reoxygenated blood can lead to an excess of oxygen and radical oxygenating species (ROS).[7] This causes damage to the organ [120, 121] leading to chronic deterioration of the graft, infection and ultimately graft rejection [120–122]. A shortage of suitable donors leads to the use of more "marginal" organs [122] which are more susceptible to I/R injury and chronic deterioration, and makes patients more likely to suffer post-transplant complications.

The heme oxygenase system has been shown to have cytoprotective effects in transplantation using a number of disease models, and several papers have postulated that it is carbon monoxide generation which underlies this cytoprotective effect [122–124]. Transplants of organs from patients who have died from carbon monoxide poisoning have been successful and have shown reduced susceptibility to I/R injury [125]. Exogenous dosage of carbon monoxide has been shown to have a protective effect against I/R injury in many transplant models, including liver, intestinal, kidney, heart, and lung grafts. Increased survival rates in CO-dosed animals have been reported, indicating that carbon monoxide could be an exciting potential therapeutic in this area [122, 124, 126–129]. More recently, hydrogen sulfide has been suggested to have a similar role in I/R injury models [130, 131].

[6] Ischemia is a state of tissue oxygen deprivation through loss of blood flow to an organ. Reperfusion is the restoration of blood flow to an ischemic tissue.

[7] Reactive oxygenating species are intermediates formed by the incomplete one-electron reduction of molecular oxygen and include singlet oxygen, superoxides, peroxides, and hydroxyl radicals. They have crucial roles in oxidative stress, signal transduction, regulation of gene expression, and host defense.

3.2 Hydrogen Sulfide and Suspended Animation

Hydrogen sulfide has been shown to have an effect on metabolism and help survival in very low oxygen conditions. Administration of low levels (80 ppm) of hydrogen sulfide to mice led to a suspended animation or "H_2S hibernation" state where the body maintains a baseline metabolism that protects the vital organs from damage until energy supply levels and the heart rate returns to normal [132, 133]. These results indicate that H_2S may be able to protect against some of the effects of hypoxia,[8] but experiments using larger animals such as sheep [134, 135] and piglets [136] have not seen the same effect, and whether H_2S could induce a hibernation-like state in humans is unknown.

3.3 Interactions of the Gasotransmitters

As more research appears in the literature it is becoming clearer that NO, CO, and H_2S all interact with each other and, to some extent, mediate the function of one another at many different levels [112]. There are at least two common sites of action for the three gases involving interaction with heme moieties; all three gases are known to bind to iron in hemoglobin and both CO and NO are known to interact with cGC, an enzyme involved in vasodilation. There are reports that the presence of more than one gasotransmitter has different effects to each gasotransmitter alone, depending on the location and conditions. Each gas appears to be able to regulate the expression of the other two gases, and the best known of these currently is that NO donors up-regulate HO-1, increasing the synthesis of carbon monoxide in blood vessels. The activity of CBS, an H_2S producing enzyme, can be directly inhibited by both nitric oxide and carbon monoxide [18]. H_2S can also induce an up-regulation of anti-inflammatory and cytoprotective genes including heme oxygenase. The interactions of the three gases are likely to be complex and highly dependent on the tissue and the absolute and relative concentrations of the gases involved.

There is less literature describing the interaction of carbon monoxide and hydrogen sulfide releasing media that for nitric oxide, and this reflects the less advanced stage at which biological research has reached to date. However, reports of carbon monoxide-releasing molecules (CORMs) based on transition metal carbonyl complexes, as well as the binding of carbon monoxide to metal centers in zeolites means that progress is being made in this area. The storage of hydrogen sulfide via coordination to the metal center in Ni-CPO-27 and Zn-CPO-27 has been reported crystallographically, and while there is not the exceptional release behavior observed for nitric oxide, the hydrogen sulfide which is released showed the

[8] Hypoxia is a state when a tissue has an inadequate oxygen supply to allow normal cellular processes to take place.

expected vasodilatory actions [137]. Reports of hydrogen sulfide binding to other MOFs have been reported [138, 139], meaning that these frameworks are a real possibility of release method in this area.

4 General Implications and Future Directions

Since the discovery of the biological significance of NO in the body, the development of NO biology has been remarkable. The development of drug molecules that act as NO donors has perhaps been a little disappointing. However, the targeted delivery of NO from solids has the advantage of potentially avoiding the pitfalls associated with the systemic delivery of such a highly active molecule. However, there are still many challenges. Controlling the rate of release is the key to the development of real applications of solid nitrosyls – whether they are in the form of metal-containing polymers, MOFs or zeolites. Matching the rate and profile of the release to the required biological activity is by no means easy, and getting this right will be pivotal in achieving the desired efficacy of any therapy. However, controlling the release rate, either by changing the materials itself or by altering its formulation, is at least possible, and so there seems great promise that this approach may well in the medium term lead to successful products.

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