Luminescent Metal-Organic Frameworks Development and Applications

Catherine Amaya, Amherst College, 2014, Fall 2013, CHEM 371

Nitric Oxide sensing, porous metal-organic frameworks, luminescent imaging

ABSTRACT:
Nitric Oxide (NO) is a critical part of many biological processes and functions. NO reacts with many radical species and metal-containing proteins, posing a difficult challenge for scientists working towards developing methods to detect it in biological systems. The paper of interest proposes a solution to this challenge with two porous metal-organic frameworks (PMOFs), made of either copper or europium and several linkers that are selective to NO and fluoresce when NO binds. The authors provide data for their selective and sensitive PMOFs. In physiologically relevant solutions, the authors have determined that incorporation of a triphenylamine moiety as a bright blue emitter results in an effective NO chemosensor. The concepts of molecular orbital interactions between copper and NO and electron excitation in the context of this complex will be discussed. (Need figure!!!)

Introduction

The Importance of Nitric Oxide

Nitric Oxide plays a crucial role in several biological processes. The relaxation of smooth muscle depends on guanylate cyclase activation accompanied by guanosine triphosphate (GTP) converting into cyclic guanosine monophosphate (cGMP). Nitric oxide is one of the key activators of guanylate cyclase. [1] (Figure 1)

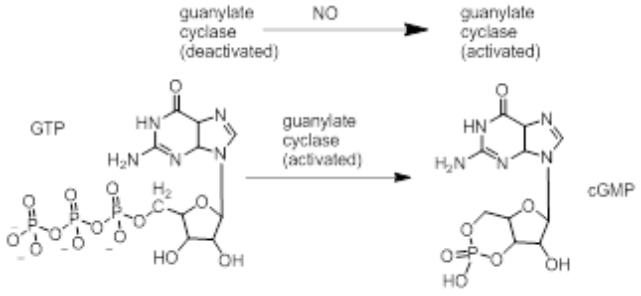

Figure 1. NO is an activator of guanylate cyclase, which in turn catalyzes the reaction that converts GTP into cGMP.

NO-donating compounds are able to increase blood flow by delivering NO directly to the muscle cells in the artery walls. NO also prevents platelet aggregation and adhesion, which could otherwise cause heart attacks. NO also has two important functions in our central nervous system and brain. Its first function is as part of a feedback loop that strengthens the connection between the cells on either side of a synapse. The second function of NO is to act as a normal neurotransmitter as it acts upon nerve cells. NO is involved in a variety of processes in different locations in the human body. The ability to detect NO in the body would allow for a measurement of the efficiency of NO delivery drugs. Porous metal-organic frameworks provide a solution for delivering and detecting NO.

Porous Metal-Organic Frameworks Development

Porous Metal-Organic Frameworks (PMOFs) are a recent development in the field of inorganic chemistry. The first goal was tuning the pore size and functionality. The purpose was to achieve specific and unique molecular recognition between a PMOF and the guest substrate. The strategy is to construct simple cubic nets from paddle-wheel clusters and two types of organic linkers, dicarboxylic acid and pillar bidentate organic linkers (Figure 2).

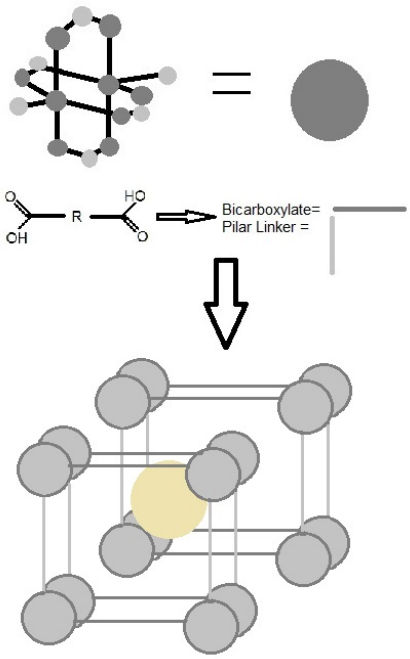

Figure 2. Basic paddle wheel cluster forming a primitive cubic network. The distances can be tuned by varying the sizes of the bicarboxylate and pilar linkers employed.

The pores of these 3D cubic PMOFs are determined by the different lengths of linkers used, adjusting the height and width according to the target molecule. Since most of the interactions between a framework and the guest substrate occur through van der Waals interactions, these interactions can be strengthened by incorporating metal ions. Such PMOFs have been developed to store gases like acetylene and selectively interact with H_2. [2] One biologically relevant gas the paper of interest is concerned with is NO.

NO delivery by PMOFs

Because PMOFs have been optimized to selectively sense a specific gas, the next development in the field was to develop PMOFs as a delivery vehicle of biologically relevant gases. The ideal PMOF for biological applications should have strong interactions with the gas so as not to separate when stored but that will also allow for release when required [4]. Delivery of NO had previously been achieved through complexes called zeolites and silica nanoparticles, but these complexes caused carcinogenic or pro-inflammatory side products. Therefore, the PMOF needs to also be stable enough after it delivers the gas so the remaining products can be dealt with by the body [5]. PMOFs are a viable solution because they can deliver pure NO. There are no significant amounts of by-products or other oxides of nitrogen after they deliver NO. The amount of PMOF needed and the rate of delivery of a gas it provides can also be tailored as necessary. Two coordination polymers have been reported to deliver NO (Figure 3).

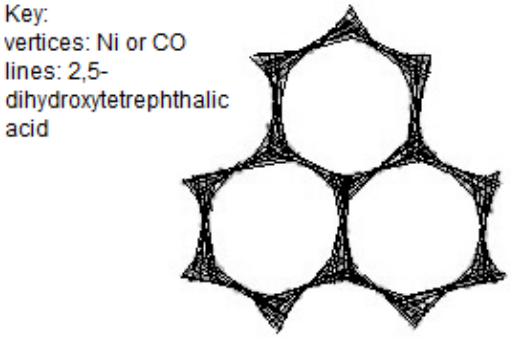

Figure 3. The structure of part of one PMOF that successfully and selective binds nitric oxide. This motif repeats itself creating a larger framework.

The two PMOFs that deliver NO are stable in a biological system for over four days, which is much longer than such a complex needs to deliver the NO and leave the body [4].

Incorporation of Luminescence in PMOFs

Since tuning the pore size had been achieved, employing these PMOFs as sensing agents was the next development. In 2007, Chen reported a rare example of microporous Eu(benzenetricarbonyl), Eu(BTC), which employs luminescence to sense small molecules. BTC organic linkers were incorporated to form a 3D rod-packing structure that bridges europium atoms. Eu has fluorescent properties in different which were investigated. It was found that the complex had the greatest intensity of fluorescence in DMF and the lowest in acetone [3]. Although this may not be biologically relevant, it was crucial to discover that these PMOFs can be made to fluoresce and therefore, move in the right direction to develop small molecules for gas sensing purposes.

The question of imaging NO binding complexes still remained a challenge. A Gd^{III}-based nanoscale PMOF took advantage of Gd(III) paramagnetic quality to produce a possible imaging solution. However, the toxicity of this element results in a complex too toxic to be biologically relevant [4]. The necessary nanoparticle needs to be small enough to avoid tissue damage, avoid embolism (blood clots), and remain stable in various aqueous mediums while not aggregating or precipitating [6]. Wu et al took advantage of all the developments so far to instead design a PMOF that is luminescent when bound to NO. Their novel idea was to incorporate a triphenylamine moiety to get efficient luminescence. They chose Cu^{+2} as the metal ion because its paramagnetic character would be quenched when NO is not present, resulting in no emission. When NO coordinates to the metal ion, though, Cu^{+2} would be reduced to Cu^{+} and the luminescence property would be available [6]. The authors were able to characterize an absorption band as assignable to the $\pi - \pi^*$ transition of the phenylamine group.

How Luminescence works

The reason for creating a Cu-TCA complex was to achieve imaging in a biological system. Imaging was possible in this case because the electron in the highest π bond between Cu and NO is excitable by blue light, which corresponds to a certain wavelength range. Blue light is of the right wavelength, 350 nm, to excite the electron when shone on the complex. This allows the electron to jump to the LUMO orbital. In this complex, the LUMO is an anti-bonding π orbital. Once it gets to this excited state, it soon relaxes and goes back to the lower energy π orbital because too much energy is required to stay in the excited state. As the electron relaxes, it emits light of specific wavelength in the visible range, so bio-imaging becomes possible. The Cu-TCA complex emitted light at 430 nm when bound to NO, which was also blue, and therefore visible.

Molecular Orbital Interactions and electron excitation

It is important to know what the molecular orbital diagram between copper, TCA, and NO looks like to facilitate understanding that a $\pi - \pi^*$ transition is occurring. TCA and NO are sigma-donators and pi-acceptor ligands respectively. If the angular overlap model is used to create a representation of this complex, the d_{xy} d_{xz}, and d_{yz} orbitals are stabilized because of the pi-acceptor interaction, and the d_{x2} and d_{x2-y2} are destabilized due to the sigma-donating interactions. The highest energy electron occupies a pi-bonding orbital. If this electron were to be excited, it would be promoted to a π anti-bonding orbital (Figure 4). This corresponds to the transition seen by Wu et al [6].

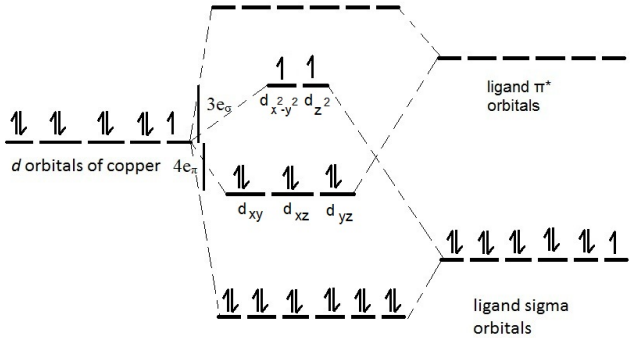

Figure 4. Molecular Orbital diagram of copper-NO interaction.

Using an angular overlap model allows the fact that the electron in the HOMO will be promoted to an anti-boding orbital when excited.

Results

The selectivity of the complex for NO was tested by screening several possible competitive reactive oxygen and nitrogen species in up to five-fold excess compared to NO (Figure 5). As hoped for, NO bound and fluoresced at a 700-fold increase compared to the competitors.

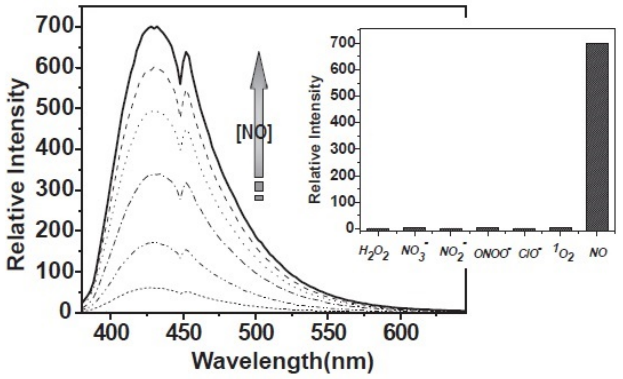

Figure 5. The left graph shows the Cu-TCA emission spectra as the NO concentration was increased in the following mM concentrations: 0.0, 0.3, 0.5, 0.6, 0.7, 0.8, 1.0. The bar graph shows the luminescence intensities of Cu-TCA treated with various gases. NO, 1 mM, all other gases were used at 5 mM. This figure is from reference 6.

Crystal structures of the Cu-TCA complex confirmed that its dimensions are on the nanometer scale, as is needed. The complex was also tested in living cells to see if imaging was possible. Live cells were stained with a suspension of the Cu-TCA complex and washed three times with Tris buffer. After incubation for twenty minutes, bright-field measurement confirmed that imaging NO was possible (Figure 6). Panel (a) shows no evidence of luminescence, which is expected since no NO is present; this means Cu-TCA is not reacting with any other gases present in living cells. Panel (d) shows the incubated cells excited by blue light, in which luminescence occurs. This provides the most evidence of the how biologically significant this development is. This is the first success in synthesizing a PMOF that has biological relevancy in both sensing and imaging.

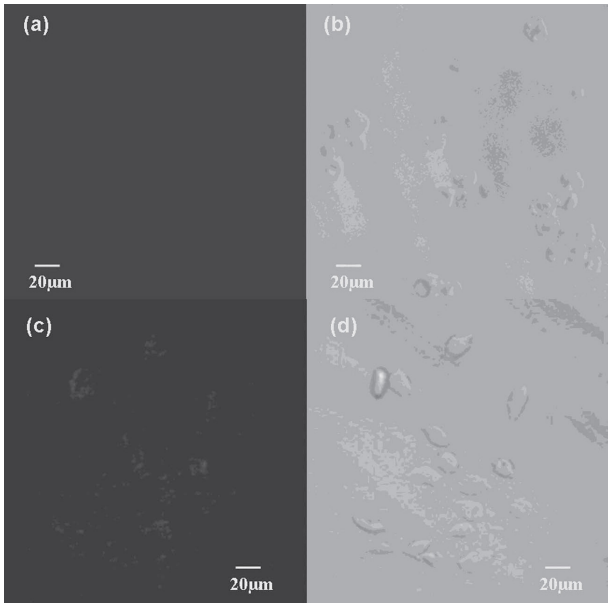

Figure 6. Fluorescence imaging response of Cu-TCA induced by sodium nitroprusside (2.0 mM). a) Fluorescence image of MCF-7 cells incubated with Cu-TCA. b) Brightfiled image of cells shown in panel (a). c) Cells incubated with sodium nitroprusside. d) Brightfield image of cells shown in panel (c) excited with blue light. This figure is taken from reference 6.

The other complex Wu et al synthesized was a Eu-TCA complex. This complex was also selective to NO and fluoresced when NO bound. Unfortunately, the fluorescence property was quenched in the presence of water, making this complex biologically irrelevant.

Conclusion and Further Developments

This finding was doubly exciting because it combined the ability of PMOFs that selectively sense nitric oxide with biological imaging applications. The Cu-TCA complex utilized the ability to selectively sense a small gas molecule based on previous developments that allowed the size of PMOF to be tunable. The Cu-TCA exploited the fact that an PMOF could be fluorescent. These two qualities allowed them to synthesize the first biologically relevant complex the binds only NO and fluoresces once NO is bound. The authors provided sufficient information to prove the efficient and biological relevance of their development. This complex could be used for several medical applications in conjunction with NO delivery drugs. Such a Cu-TCA complex would allow a visible representation of the efficiency of NO delivery drugs or the lack thereof.

Recently, PMOFs that incorporate lanthanide metals have been investigated due to the intense luminescence that is a result of f-f or f-d energy transfers. Based on the colors and wavelengths at which the light was emitted, the authors were able to assign spectra peaks to specific orbital transitions. Due to their toxicity, these PMOFs were designed with the aim to detect environmental pollutants, such as formaldehyde and acetonitrile [7]. Due to the colors produced, it may be feasible to determine if the pollutant is present quite easily by a human eye.

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