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CO IN BIOINORGANIC CHEMISTRY

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This essay is an attempt to explore the multifaceted nature of carbon monoxide, with emphasis on bioinorganic implications.

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Millions of years ago, in an extremely hostile environment, the first life forms on planet Earth had to make use of their advantage of certain conditions from the outside world in order to survive and thrive, while from others they had to run away fast. This is how and why chemotaxis came about, the movement of microorganisms according to the chemical gradients in the environment.

It would be a perfectly legitimate question to ask why would something, suppose you've already hinted where we were heading, go where carbon monoxide takes it? In those times, microorganisms used carbon monoxide in order to synthesize larger biomolecules required for growth, reproduction and communication. While carbon dioxide, to which we all are more familiar to, is also a good precursor for such carpentry business, within carbon monoxide the carbon atom, essential for the large skeleton of molecules, is closer to the reduced state in which it is usually found in organic substances. One particular enzyme that can perform this feat of integration and construction is acetylcoenzyme A synthase, an enzyme that is endowed with a metal center that CO so openly loves, a nickel ion (Bertini et al., 2001).

In order to do the whole job efficiently, without all the bureaucracy characteristic of newer times, some microorganisms had and still have some complex enzymatic equipment that contains both a sensor for carbon monoxide, as the building block, as well as an RNA-polymerase, an enzyme involved in the syntheses of proteins. When triggered by the presence of CO, this machinery can immediately begin the mechanism of its incorporation into larger structures (Bertini et al., 2001).

How do such sensors even work? In some instances they can contain an iron center, which in the inactive state is in the ferric form, i.e. a state difficult to convince to bind to carbon monoxide, except, always the exception, when encountering reducing conditions. If such is the case, then changing the oxidation state would also lead to a change in the ligands, since different ligands are comfortable with different ranges of electronic densities (Bertini et al., 2001). This change is sensed deep within the sensor, and then whispered on to someone with a more entrepreneurial nature in order for the required action to be commenced.

As organisms began to evolve, carbon monoxide itself started to play a more complex role, that of an angel as well as the demon, that of a toxin and also a messenger, according to the dose of exposure. For instance, in the presence of carbon monoxide, the hemoglobin in our blood can no longer deliver oxygen in an efficient and sufficient manner, due to the fact that the monoxide binds to it instead of oxygen in a much stronger manner – and related proteins involved in oxygen usage fail in a similar manner (Bertini et al., 2001; Silaghi-Dumitrescu, 2010). As a consequence, the victim asphyxiates from the cellular level up, bound to an invisible halter.

When it comes to this competition between oxygen and carbon monoxide for the love of iron, the triangle would not be complete if one didn't take into consideration another character, hydrogen, much like in a screwball comedy. It seems that in some metalloenzymes, such as hydrogenases, whose job description contains both producing a proton gradient and molecular hydrogen from acids, carbon monoxide shows politeness and gets out of the way in order for hydrogen to accommodate between the two metal centers (Bertini et al., 2001; Silaghi-Dumitrescu, 2010). Would you warm up the bed in order that someone else benefit from it? Not such a bad guy, after all, this carbon monoxide.

To make the matters even more thrilling and tangled, precisely the hemoglobin, the one that wants to serve the higher good of the body by supplying it with fresh oxygen, happens to also produce carbon monoxide, upon its degradation by heme oxygenases (Bertini et al., 2001). There is a catch though: this time, the freed carbon monoxide embarks on various signaling routes, activating different cellular messengers, all with protective roles (Wu, Wang, 2006; Boczkowski et al., 2006).

Just as one can see the birth of a new day in the purple of dawn, so one can witness the birth of CO when bruises appear, heme degradation being one of the most visible enzymatic reactions to be found. Nature would not have made its birth as noticeable as it is if CO was not of significant importance to life. It is both released as a consequence of damage, of oxidative stress to be more precise, in order to counteract it, and also as part of business as usual, required for maintenance (Metzler-Nolte, Schatzschneider, 2009). Even the superstars that make splashy headlines have daily chores, you know.

The paradoxical nature of CO in living organisms can be seen once more in the roles it plays in oxidative stress. By binding to cytochromes *c* and P450, enzymes involved in the processes of mitochondrial respiration and xenobiotic metabolism respectively, it may disrupt their natural course of action, and therefore modulate production of a number of reactive oxygen species, which can and will cause damage (Wu, Wang, 2006; Boczkowski et al., 2006). On the other hand, CO is precisely the one that protects the kidneys from the oxidative damage brought upon by drugs and also protects from ischemia the tissues and organs that were stored at freezing temperatures (Wu, Wang, 2006; Boczkowski et al., 2006).

Not such a long time ago, people used to view carbon monoxide simply as an invisible enemy, some sort of malefic spirit, who, on the contrary of what we might expect from the "Tales of 1001 Nights", didn't use to come out only from petrol lamps, but also from stoves or gas pipes. People eventually realized that throwing sheets up in the air didn't reveal its presence as it was accustomed in ghost stories; modern gas detectors are therefore a must nowadays and perhaps related to this is also the story of the obnoxiously-smelling mercaptane, added in trace amounts to another odorless dangerous gas, methane, again for safety reasons.

Although we used to fight against it in a blind-folded fashion, CO has its own principles of belonging, by always trying to go back and attach to where it first came from, heme proteins. CO does not behave in an indiscriminate way, such as radicals use to do, but then again, CO is not even a radical. It is stable and, without a trace of the restlessness that describes the characters in 3000-episode soap operas, only becomes highly reactive when bound to other molecules. Another principle it obeys? Mould accordingly to the company you keep. It preferentially seeks heme proteins and binds only to transitional metals, iron being one of its favorite companions – although it does not shy away even from copper or nickel (Boczkowski et al., 2006).

What to make of all of this? Oxygen may be crowned as the substance of life – from our humanly narrow point of view of course, because there are other organisms that can do just fine without it, but with each breath we take, oxygen leaves some traces behind, some scars that accumulate over time. CO may sometimes impede the globin proteins to effectively transport or store oxygen, but in other sites and circumstances, it is the CO who stays late to clean oxygen's mess.

While it is true that CO is a significant pollutant, being released in the environment whenever incomplete combustion takes place, and it is also true that CO becomes dangerous when it exceeds certain limits within the body; ultimately, too much of everything might kill you. Just think about water: essential, yes, but then again except Noah, his arch and a bunch of animals, no one was quite happy with the Great Deluge. Or consider light, mandatory for life, well-being, but too much and you're sunburned or prone to cancer.

There's no need for despair, though, as nowadays carbon monoxide has almost been tamed to work for mankind as well, and not just in direct competition, the same way things happened with the much feared wolves that became our playful pets. CO is currently being used as a probe ligand to elucidate various reaction mechanisms, their distinctive intermediates and also interesting substances that resist to other tools of investigation. For instance, certain metal centers in proteins that remain silent in many spectroscopic investigation techniques in the laboratory, may be brought into a more spectroscopically-amenable form by incorporating CO as a ligand: CO's unique spectroscopic signature can then be used as a reporter giving clues about the otherwise very complex interior of the metalloprotein.

Speaking of taming, we may also mention CO's use as an alternative energy source. It seems that the byproduct of the microbial metabolism mentioned in the beginning of this text, that makes use of CO as a building block, is precisely molecular hydrogen, a highly sought after, clean and green fuel. The enzyme carbonmonoxide dehydrogenase, CODH by its stage name, has a key role in this chain of reactions (Bertini et al., 2001). Therefore, if oxygen is one prerequisite for energy so that our brains can be *put* to work, CO could from now on provide us with the energy to *drive* them to work.

There are other types of bacteria that not only make use of the resources at hand, but also modify the environment so that it suits them in the short term. Indeed, *Helicobacter pylori* is a bacterium from our digestive system that does not particularly like acidic conditions found in the stomach, and therefore tries to raise the alkalinity by secreting urease, an enzyme that releases the alkali ammonia (Bertini et al., 2001; Silaghi-Dumitrescu, 2010).

After finding out what an important messenger CO really is, a true gasotransmitter alongside NO and H_2S, and that most tissues in our body possess the enzymes necessary for its production when needed, be it liver, brain, heart, ears, eyes or nose, stomach or pancreas, scientists began searching for pharmacological applications for it (Wu, Wang, 2006; Boczkowski et al., 2006).

But how to prescribe or administer it, since CO is a gas? Surprisingly, it seems that even inhalation – the one exposure route we so intensely fear – at small and clockwork-precise doses, can work. But why not take advantage of its long history in binding to metals? Water-soluble solid metal-carbonyls have become household names with respect to their therapeutic potential (Metzler-Nolte, Schatzschneider, 2009). But since CO is also produced endogenously, it is also possible to enhance its production through various triggers, such as hemins, substances that resemble and therefore mimic an excess of free hemes in the body (Wu, Wang, 2006; Boczkowski et al., 2006). CO has therefore found its way to being used as a remedy for hypertension, because it has a modulatory effect on the contractility of muscle tissue, leading to the dilation of blood vessels. It is even being used as a tremendous aid during transplant procedures, as it protects both the transplanting organs from the cold damage during their storage, and also the receiving patient, by reducing the inflammation that ensues and suppressing the immune system that so eagerly tries to discard the foreign tissue (Wu, Wang, 2006; Boczkowski et al., 2006).

Whenever you see again someone deeply fascinated with the world of bacteria, handling their Petri dishes with the greatest of delicacy, and wonder why won't they get a real job instead, remember that many of the challenges our society is facing have already been solved successfully by tiny microorganisms a good while ago, and that all we have to do is take the time to ask them politely about their accomplishments.

After all, CO may be more than a messenger within living systems; its long history might just provide us with a message across time as well. How else can you explain its effect upon genes in our body that keep track of the time elapsed for each of us (Boczkowski et al., 2006)? Although we're facing accelerations in terms of pollution, in our quest for alternative energy sources, as well as in terms of the expanding knowledge in fundamental physiology, could it be that the message we're hearing is not that our time is running out, but one of hope and encouragement? The lesson that we ought to take with us from this odyssey of CO and the other molecules is that it is alright to live a low-key life, cleaning the mess after big spenders, recycling the carriers for big players, doing some apparently mundane chores if it serves a higher good; it is alright to be 'misunderstood', to have an undeserved bad reputation, because someday you might just prove yourself to be the missing link to a plethora of grand solutions.

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