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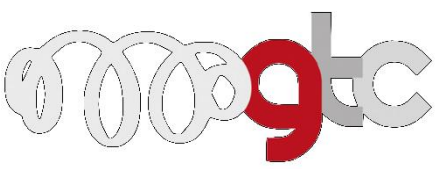

Deferoxamine as Zr(IV) Chelator: the *K* to Understanding.

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Due to its own emission properties, cyclotron preparation of ^{89}Zr was saluted as a major breakthrough for PET imaging. Much of the initial success of this radionuclide was due to the quick recognition of Deferoxamine (DFO) as an effective chelator: a true godsend. Among the advantages it provided there is the huge shortcut offered by using a long-time FDA approved drug, not to mention the fact that this ligand is considerably cheap to manufacture, needing only a few chemists, if any, to supervise the peaceful synthetic work of Streptomyces bacteria.

Concerning the Zr(IV)-DFO system, most of chemists' remarks were misunderstood by part of the Bio-Medical community. When somebody asserted that expected stability constants for complexes of 4+ ions are higher than those for 3+ ones (read Fe^{3+}, the ion DFO was approved for) [1], or that they exceed impressive values (e.g. 10^{31}, meaning only that they could not be determined) [2], or that pM values are extremely low (yet estimated within a 3 orders of magnitude indetermination) [3], or even that "water further stabilize the Zr-DFO complex" (2 water molecules appear to be needed to complete Zr(IV) coordination environment according to DFT calculations) [4], the take home message was understood by non-chemists as: Zr(IV)-DFO complex is more stable than Fe(III)-DFO complex; since everything is fine for Fe(III), and FDA has our backs on that, then everything is going to work even better for Zr(IV) [5]. Problem solved.

Fallacies leads to false expectations, and their delusion leads to titles like "Alternative chelator for ^{89}Zr Radiopharmaceuticals" [6], with more and more people involved in the effort of surpassing DFO limitations. But what is the nature of such limitations? In the best-case scenario, we read concepts like: "[…] Data have led us to conclude that a ligand designed specifically with the chemistry of Zr^{4+} in mind may demonstrate improved stability upon complexation with Zr^{4+}. Furthermore […], a more stable complex should be less prone to demetalation in vivo, resulting in […] a safer and more efficient ^{89}Zr-based PET tracer [6]." Now, having the chemistry of Zr^{4+} in mind and obtaining more stable complexes than those of DFO is quite a harsh task when no (zero, 0, Ø) equilibrium constants have been determined.

The pursuit for clarity prompted us to go back to the few data available for complex formation with the Zr^{4+} ion, dating back to some of the most eminent papers on the topic. Among them, a 1964 paper by Martell et al. [7] provided a reliable ground for the EDTA-Zr(IV) system. EDTA complexes, partially owing to their solubility in water, have historically been widely studied and well-characterized systems, oftentimes providing the key to the determination of stability constants of more troublesome ligands, providing a solid background for competition experiments. Most of the observations of Martell and coworkers have been found to be quantitatively accurate, yet we were able to overcome several limitations of their work, providing numerical solutions accounting for multiple simultaneous equilibria which were beyond the possibilities of the computing power of the '60s. Full speciation of Zr(IV)-EDTA systems is now available, including a detailed description of

polynuclear Zr(IV)-EDTA complexes, an already observed phenomenon [7] which was in need of a proper quantification.

Unluckily, knowledge of Zr(IV)-EDTA complexes stability has been proved of no use for the determination of the binding constants for the Zr(IV)-DFO system, due to the higher stability of DFO complex (5-6 orders of magnitude, vide infra) compared to EDTA one.

A sufficiently strong competing ligand was recognized in the OH^- anion. It is well known that Zr(IV) forms very stable hydroxide complexes, which can and have been previously characterized. According to literature information, some of Zr(IV) hydroxo species may be from quite to very insoluble [8]. However, it remains unclear whether such insolubility is real (i.e. intrinsic) or due to the polymerization process tied to the olation of the cation. Re-determined hydrolysis constants of monomeric soluble species are found fully congruent with those published by Baes and Mesmer in their cornerstone handbook for Inorganic Chemistry [9], confirming that solubility issues do not prevent their determination.

Owing to the high stability of the Zr(IV)-DFO complex, it is possible to conduct experiments where such hydroxo complexes are non-existent in solution below pH 7-8 and titrations can be prosecuted in alkaline media until a significant percentage of the cation is present as $Zr(OH)_4$. Establishment of such equilibrium, which has been studied for several metal:ligand ratios, allows the determination of the Zr(IV)-DFO stability constant and the backward complete speciation of the Zr(IV)-DFO system.

Turns out that, similarly to what observed by Martell for EDTA complexes [7] and quite reasonably according to the unsaturated coordination sphere of Zr(IV) in the DFT model of its DFO complex [4], the most abundant species at physiological pH is not a 1:1 complex, but its 2:2 dimer! On this basis, with the complete speciation of the system at hand, we anticipate not only a long-term blooming of the research field in producing more fit ligands, but also a short term major revision of clinical protocols for the preparation of DFO-based Zr(IV) PET agents.

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