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Theoretical approach to design new effective chelators for iron-containing enzymes

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Iron homeostasis affects energy metabolism, DNA replication, inflammatory processes, etc. *In vivo* and *in vitro* models provide evidence that the administration of iron chelators is effective in fighting cancer, possibly because of their involvement in destabilizing iron-dependent enzymes such as aconitase and ribonucleotide reductase. However, the experimental work in this field requires a huge amount of time to synthesize and characterize chelators, and also for the experiments with real biological objects. In this case, preliminary calculations make it possible to predict the effectiveness of a particular ligand in the processes of iron binding in biological systems.

In the present work, the thermodynamic characteristics of the scavenging of iron from transferrin (TF) and ribonucleotide reductase (RNR) by desferrioxamine (DFO) and its different derivatives were calculated using DFT (Gaussian 16; B3LYP, 6-31G(d,p), PCM model). The RNR and the TF active sites, containing 72 and 86 atoms, respectively, were taken from X-ray structures. The thermodynamic data for these active centers were calculated without geometry optimization. All other structures were fully optimized, and energy minima were verified by analytical calculation of normal vibration frequencies. The efficiency of chelation is determined by the equilibrium constant of the following process:

$$Fe(RNR/TF) + DFO \rightleftharpoons RNR/TF + Fe(DFO)$$

The lnK values for calculated processes for DFO and its different derivatives are given in Table 1. Although the absolute values of the equilibrium constants are apparently quite far from the real ones, nevertheless, their relative values allow us to make a conclusion about the effectiveness of DFO and its derivatives as chelators. Thus, in the case of RNR, the most effective chelating ligand is DFCAF, and for the iron chelation from TF it is DFO-SS02. These calculations are confirmed by available experimental data on the iron chelation from TF with DFO and DFO-SS02. [1]. Experimental studies for the remaining chelators are still being carried out.

Thus, an effective method has been developed for pre-experimental assessment of the iron chelation efficiency from the enzymes' active sites and can be applied to similar systems as well.

Table 1. Calculated lnK values for chelating processes.

Chelator	DFO	DFCAF	DFOQUN	ALA-DFO	GABA-DFO	DFO-SS02
RNR	416	433	414	410	398	426
TF	352	393	360	500	486	515

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References

[1] R. Y. P. Alta *et al*., PLoS ONE, **12(2)**, e0171729 (2017).