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Comment on the section: "Antioxidant measurements and hydroxyl radical scavenging activity" in synthesis, characterization, DNA binding, and antioxidant activities of four copper(II) complexes containing N-(3-hydroxybenzyl)-amino amide ligands, by Zhi Li-Hua, Wu Wei-Na, Wang Yuan, Sun Guang, *J. Coord. Chem.*, 66, 227 (2013)

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SHORT COMMUNICATION

Comment on the section: “Antioxidant measurements and hydroxyl radical scavenging activity” in synthesis, characterization, DNA binding, and antioxidant activities of four copper(II) complexes containing N-(3-hydroxybenzyl)-amino amide ligands, by Zhi Li-Hua, Wu Wei-Na, Wang Yuan, Sun Guang, *J. Coord. Chem.*, 66, 227 (2013)

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This comment, though addressed to a given paper [1], relates to the general approach for determining the antioxidant activity of various compounds by measuring their reactivity towards hydroxyl radicals. Two points are addressed:

- (1) Do antioxidants added to living biological samples scavenge hydroxyl radicals?
- (2) Do the assays used to determine hydroxyl radical scavenging by different antioxidants measure indeed this property?

As to the first question: hydroxyl radicals are known as the most active and, therefore, the most dangerous Reactive Oxygen Species (ROS). Hydroxyl radicals react with rate constants approaching the diffusion-controlled limit, $k > 1 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$, with all alcohols of the type RCH_2OH and $\text{R}^1\text{R}^2\text{CHOH}$, except methanol (e.g. with all sugars); with all ethers of the type $\text{R}^1\text{R}^2\text{CHOCR}^3\text{R}^4\text{R}^5$ and esters of the type $\text{R}^1\text{R}^2\text{CHOC(O)CR}^3\text{R}^4\text{R}^5$ (e.g. with all phospholipids); with all R^1SH groups (e.g. with glutathione and cysteine); with all amines of the type $\text{R}^1\text{R}^2\text{CHNR}^3\text{R}^4$; (where $\text{R}^i = \text{H}$ or substituted alkyl) with all alkenes (e.g. with all unsaturated acids); and with all aromatic compounds (e.g. with all nucleic acids and with the residues of the amino acids phenylalanine, tyrosine, tryptophan, and histidine) [2]. Therefore, due to the high concentrations of these compounds in biological systems, one cannot add any antioxidant to a living biological system at concentrations that will enable it to inhibit the reactions of hydroxyl radicals with the natural components of the cells.

If so, how do antioxidants inhibit oxidative stress?

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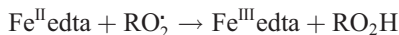
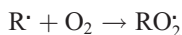
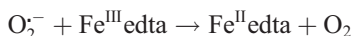
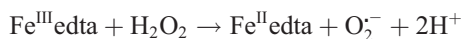
- (1) They inhibit the formation of hydroxyl radicals by reacting with their precursors, e.g. with H_2O_2 or ONOO^- , or by inhibiting the redox recycling of various transition metals, e.g. Fe(III/II) ; Cu(II/I) , thus inhibiting the formation of hydroxyl radicals [3, 4].
- (2) They react with the secondary radicals $\text{R}^1\text{R}^2\text{R}^3\text{C}\cdot$ formed in the reactions of the hydroxyl radicals with the different components of the cells. In aerated systems, as in most biological systems, these radicals react with O_2 to form the $\text{R}^1\text{R}^2\text{R}^3\text{CO}_2\cdot$ radicals. The $\text{R}^1\text{R}^2\text{R}^3\text{C}\cdot$ and $\text{R}^1\text{R}^2\text{R}^3\text{CO}_2\cdot$ radicals are considerably less reactive than the hydroxyl radicals and, therefore, react more selectively with the different components of the cells. The scavenging of these radicals by the antioxidants inhibits the latter reactions and often terminates the radical chain processes.

As to the second question, does the assay used [1] to determine “hydroxyl radical scavenging” indeed measure this property? The answer is clearly no! Due to the following reasons:

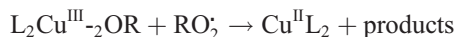
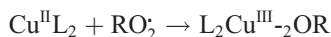
- (1) Clearly, Fe(II)edta does not exist in aerated solutions as it is oxidized in a fast reaction by O_2 .
- (2) As $k(\text{OH} + \text{DMF}) = 1.7 \times 10^9 \text{ M}^{-1}\text{s}^{-1}$ [2] and CuL_2 complexes were dissolved in DMF; clearly, hydroxyl radicals reacted with the DMF and not with the complexes.
- (3) In the assay solution $[\text{H}_2\text{O}_2] > 1000[\text{Fe}^{\text{III/II}}\text{edta}]$, i.e. the catalyst produces many radicals via the sequence:



or



The antioxidant activities of copper complexes are due to their role in shortening this chain process. The detailed mechanism of the role of the copper complexes is unclear, but it probably involves:



The role of the ligands in such mechanisms is to inhibit the reduction of Cu(II) to Cu(I), as do Fe(III) ligands used in medicine [3, 4].

The main conclusion of this comment is that many hydroxyl radical scavenging assays really do not measure “hydroxyl scavenging” as claimed but shorten the radical chain reaction.

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