Lipid peroxidation processes involving thiosemicarbozones

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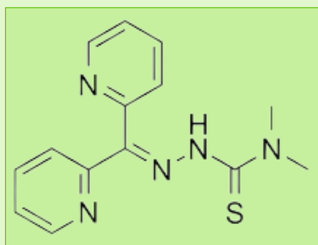
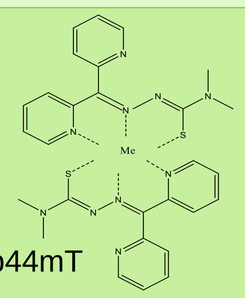


Dp44mT



Me(II)-Dp44mT

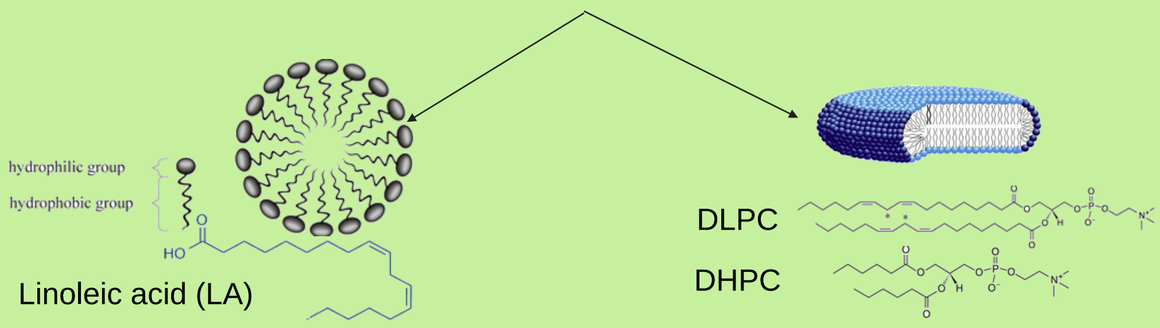
The interaction of Dp44mT-metal complexes with the lipid bilayer and their role in the reaction of lipid peroxidation was studied on model systems by ^{1}H NMR and optical spectroscopy.

Motivation

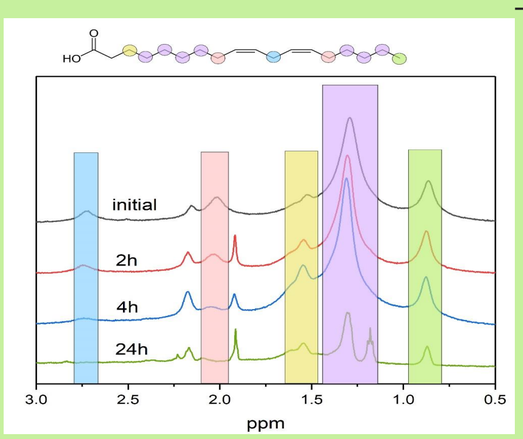
Lipid peroxidation is oxidative damage under conditions of oxidative stress caused by an imbalance of pro-oxidants and antioxidants in the cell. The study of the process of lipid peroxidation makes practical sense, since controlled oxidative stress can potentially be used in anticancer therapy.

Our task was to investigate the processes of lipid peroxidation involving chelate complexes with iron and copper ions using the thiosemicarbazones di-2-pyridylketone-4,4-dimethyl-3-thiosemicarbazone (Dp44mT), di-2-pyridylketone 4-cyclohexyl-4-methyl-3-thiosemicarbazone (DpC) and novel thiosemicarbazones AOBP and AODP as examples.

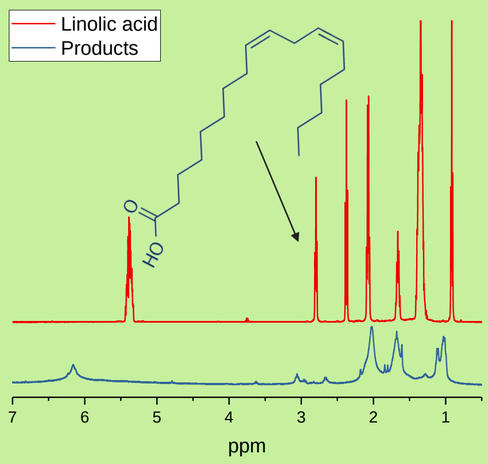
Reactions in organized environments



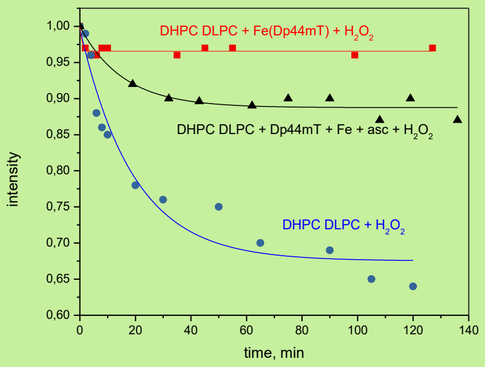
^{1}H NMR spectra of linoleic acid and products



^{1}H NMR spectrum of the reaction mixture
(LA 3.5 мМ, $FeSO_4$ 0.1 мМ, H_2O_2 0.5M, PBS, pH=7.4)

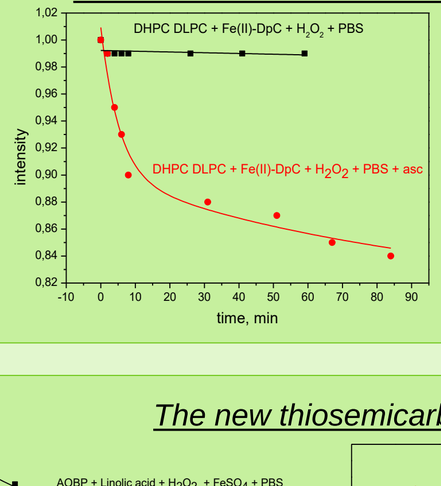


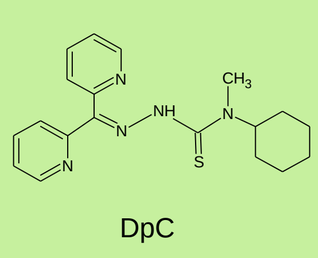
Reactions are completely inhibited



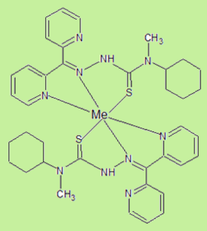
Sample	Reaction rate constant
DHPC/DLPC + $Fe(Dp44mT)_2$	$k=(0.16\pm0.15)*10^{-5}$ s^{-1}
DHPC/DLPC + $Fe(Dp44mT)_2$ +asc	$k=(106\pm30)*10^{-5}$ s^{-1}
DHPC/DLPC + Fe^{2+}	$k=(86\pm18)*10^{-5}$ s^{-1}

Ascorbic acid launches reactions



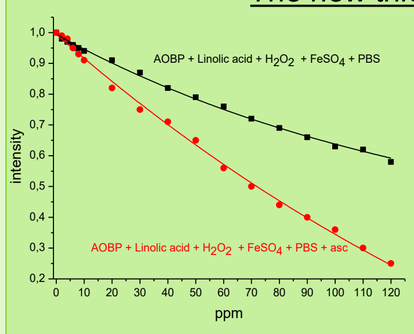


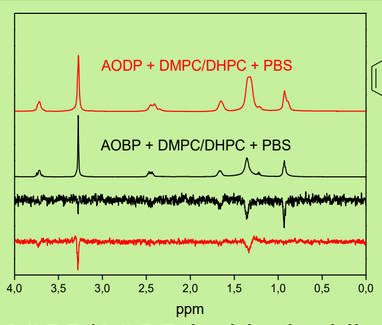
DpC

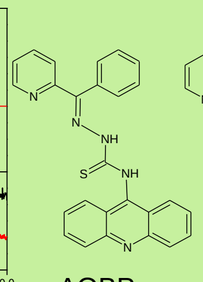


Me-DpC

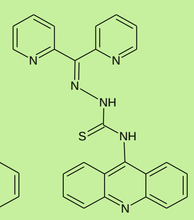
The new thiosemicarbazones were tried out







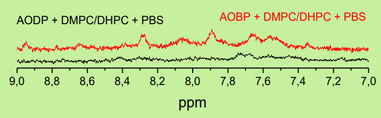
AOBP



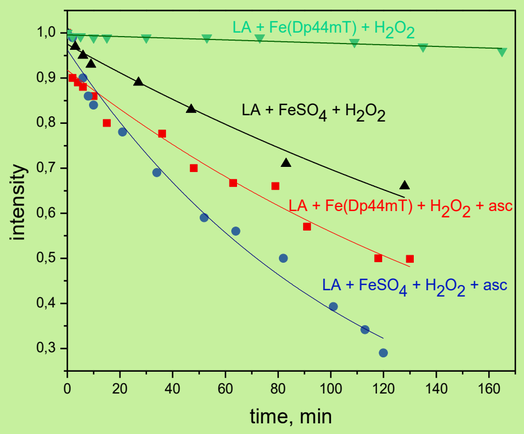
AODP

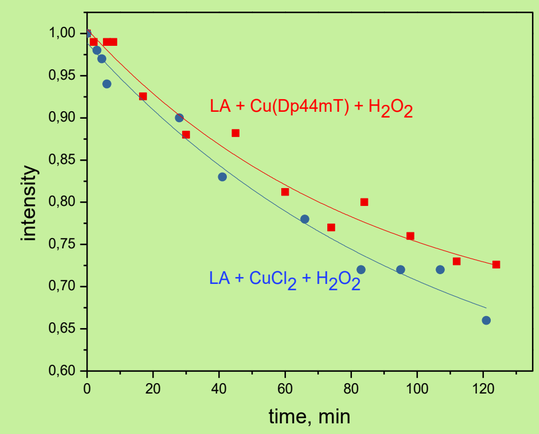
AOBP/AODP inside the bilayer

Sample	Reaction rate constant
LA + AOBP	$k=(7\pm0.6)*10^{-5}$ s^{-1}
LA + AOBP +asc	$k=(17\pm1.2)*10^{-5}$ s^{-1}



Complexes with copper exhibit oxidative activity, but complexes with iron do not





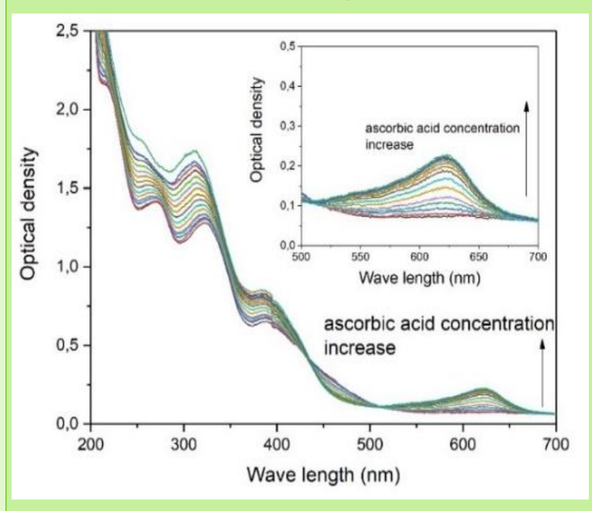
The initiation rate of lipid peroxidation was studied using the decay of intensity of the signal of the bis-allylic proton. The line broadening of the products signal indicates that the main product of the peroxidation is polymer. Similar results were observed for phospholipid bicelles.

Sample	Reaction rate constant
LA + Fe^{2+}	$k=(5.6\pm0.4)*10^{-5}$ s^{-1}
LA + $Fe(Dp44mT)_2$	$k=(0.3\pm0.04)*10^{-5}$ s^{-1}
LA + Fe^{2+} + asc	$k=(15\pm0.7)*10^{-5}$ s^{-1}
LA + $Fe(Dp44mT)_2$ + asc	$k=(8\pm0.6)*10^{-5}$ s^{-1}
LA + Cu^{2+}	$k=(16\pm5.6)*10^{-5}$ s^{-1}
LA + $Cu(Dp44mT)_2$	$k=(20\pm6)*10^{-5}$ s^{-1}

Concentrations:
- 3.5 mM of LA
- 0.1 mM of TSC
- 2.5 mM of ascorbic acid
- DLPC:DHPC ratio 1:2,

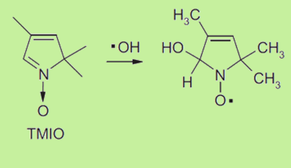
total lipid concentration 12 mM

There is an additional peak at 620 nm

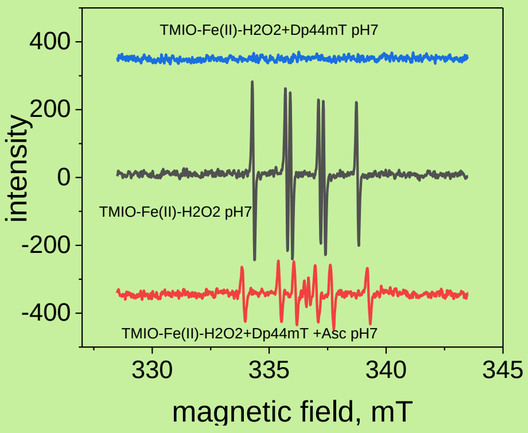


$$[Fe^{II}(Dp44mT)_2] + O_2 \xrightarrow{k_{ox}} [Fe^{III}(Dp44mT)_2]^{+} + O_2^{-\cdot}$$

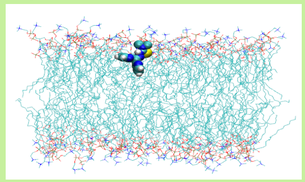
$$AscH^{-} + [Fe^{III}(Dp44mT)_2] \xrightarrow{-H+} Asc^{\bullet -} + [Fe^{II}(Dp44mT)_2]$$

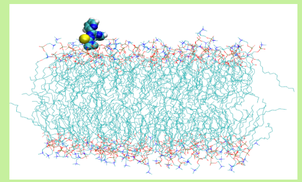


TMIO (2,2,4-trimethyl-2H-imidazole-1-oxide) spin trap



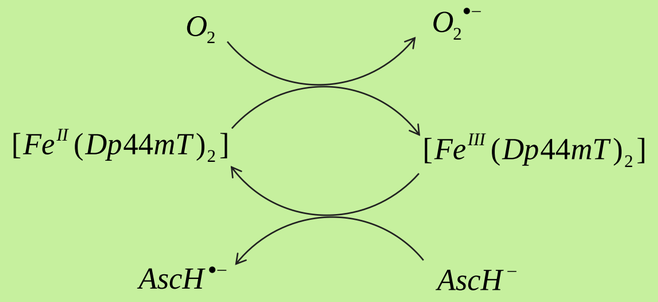
Dp44mT is located on the surface of the lipid bilayer





Conclusion

- *Complexation with iron almost completely inhibits the peroxidation reaction, while complexes with copper retain their oxidative activity. In the presence of ascorbic acid, the Dp44mT complexes with iron demonstrates pro-oxidant activity.*
- *Dp44mT molecule is located on the surface of the lipid bilayer, while AOBP and AODP molecules could penetrate inside the bilayer. AODP molecule is located closer to the bilayer surface than AOBP*
- *Fe-DpC complex is inactive, but ascorbic acid initiates peroxidation reaction*
- *Fe-AOBP complex is active, and ascorbic acid accelerates lipid peroxidation reaction*



Redox reaction of Fe-Dp44mT complex with ascorbic acid