Influence of metal ions on the radical yield in photochemical reactions involving quinone-chelators

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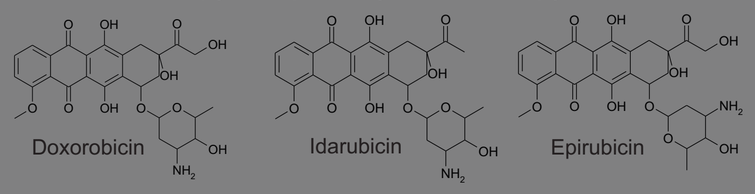
Introduction

Study object: anthracycline quinones - widely used in medicine as highly effective cytotoxic agents in chemotherapy and photodynamic therapy of tumors.

Examples:



Mechanisms of action: DNA intercalation, Topoisomerase II poison, DNA adduct formation, reactive oxygen species (ROS)

ROS are produced in the presence of ox/red enzymes such as cytochrome P450 reductase, NADH dehydrogenase and xanthine oxidase. As a result free radicals are generated which react with oxygen to generate superoxides, hydroxyl radicals and peroxides.The excessive ROS that cannot be detoxified results in oxidative stress, DNA damage, and lipid peroxidation thereby triggering apoptosis.

General goal: increase the efficiency of the drug by increasing its cytotoxic activity (ROS production)

Possible solution: chelate complexes of anthracycline quinones

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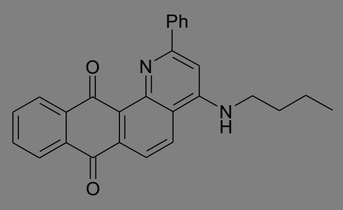
Goal of the present study: Check the possibility of increasing the ROS production in the reaction of photoinduced electron transfer between chelate complexes of model anthracycline quinone (Qc) and reduction agents (such as ascorbic acid, substituted dihydropyridine and etc.)

Qc =

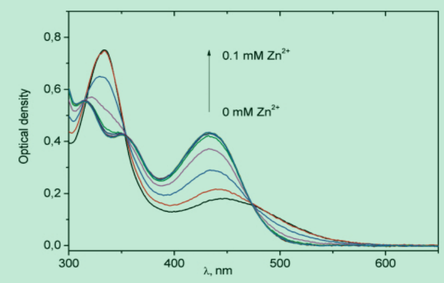


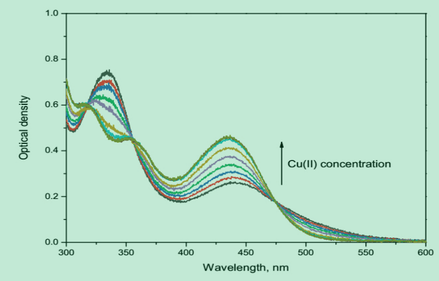
Photoinduced electron transfer:

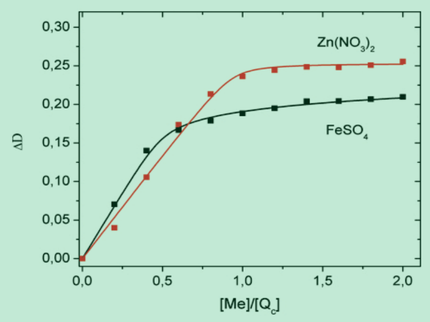
$\Delta G_{et}=E^{1/2}(ox)-E^{1/2}(red)-E_T+\Delta E_{coul}$

The highlighted term is prone to changes upon chelate formation

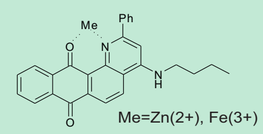
Chelate complexes of Qc with metal ions



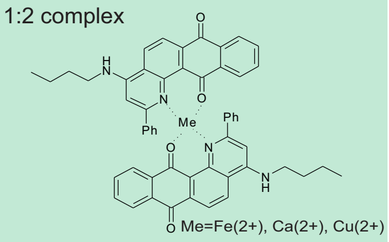


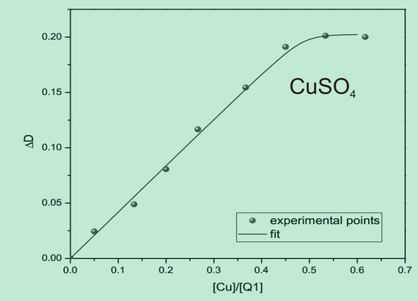


1:1 complex



1:2 complex



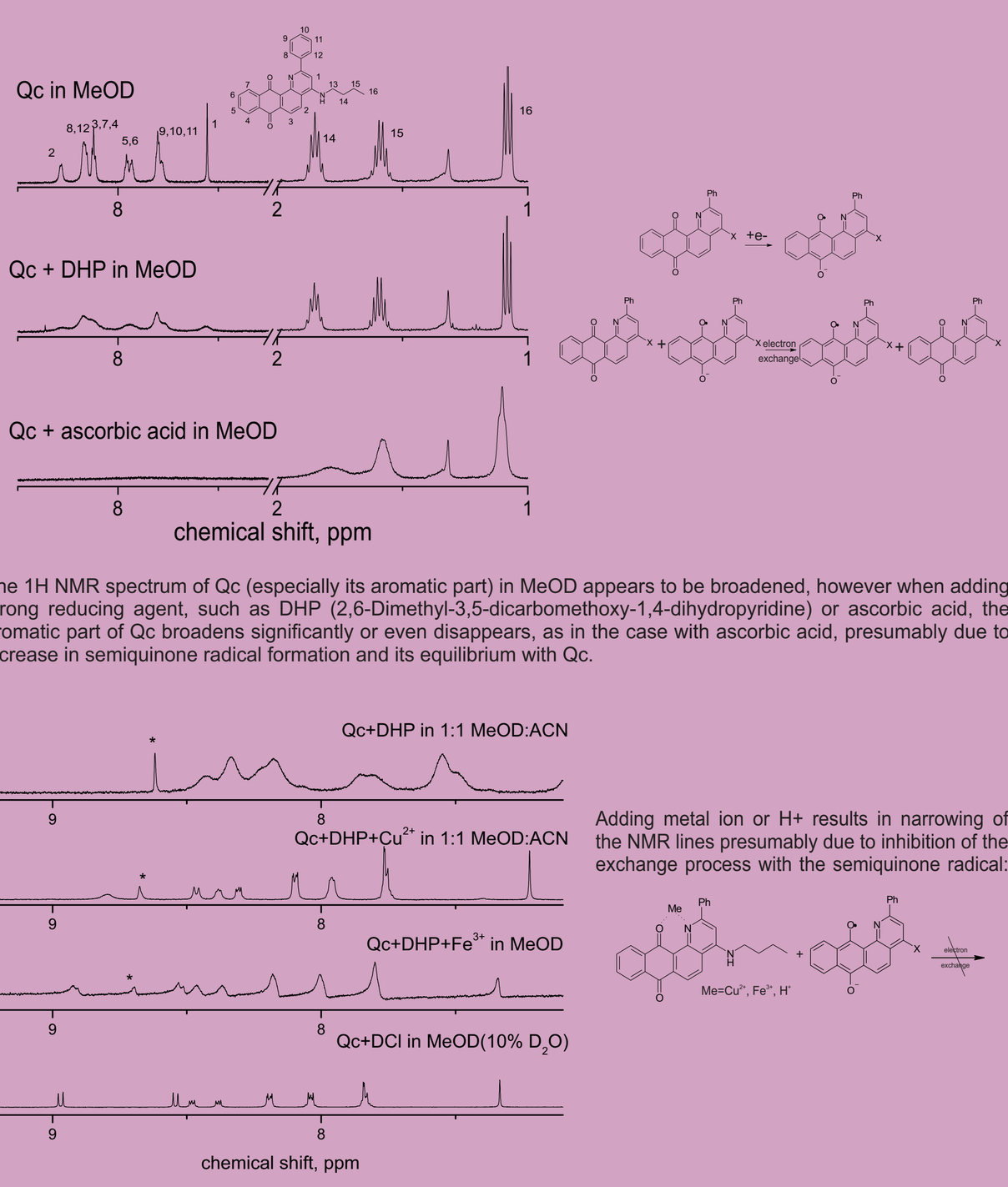


Chelate	Complex stoichiometry	Stability constants (M-1)
Qc+Fe(II)*	2:1	K1=4*10^5 K2=6*10^5
Qc+Ca(II)*	2:1	K1=2*10^5 K2=3*10^4
Qc+Zn(II)*	1:1	K1=3*10^6
Qc+Fe(III)*	1:1	K1>3*10^7
Qc+Cu(II)**	2:1	K1=1*10^6 K2=5*10^6

* Markova, I.D et al. Light-Stimulated Generation of Free Radicals by Quinones-Chelators, Z. Phys. Chem. – 2016. – Vol. 231. – P. 269-389

** O.Yu. Selyutina et al. The Interplay of Ascorbic Acid with Quinones-Chelators-Influence on Lipid Peroxidation: Insight into Anticancer Activity, Antioxidants – 2022. – Vol. 11(2). – P. 376

1H NMR spectra of Qc and its chelate complexes in solution



The 1H NMR spectrum of Qc (especially its aromatic part) in MeOD appears to be broadened, however when adding strong reducing agent, such as DHP (2,6-Dimethyl-3,5-dicarbomethoxy-1,4-dihydropyridine) or ascorbic acid, the aromatic part of Qc broadens significantly or even disappears, as in the case with ascorbic acid, presumably due to increase in semiquinone radical formation and its equilibrium with Qc.

Adding metal ion or H+ results in narrowing of the NMR lines presumably due to inhibition of the exchange process with the semiquinone radical:

1H CIDNP spectra of Qc chelate complexes with Cu^{2+} and Fe^{3+}

Photoinduced electron transfer between Qc and DHP

Reaction scheme:

$Qc \xrightarrow{h\nu,\ ISC} {}^3Qc$

$Qc{:}Me \xrightarrow{h\nu,\ ISC} {}^3Qc{:}Me$

${}^3Qc + DHP \xrightarrow{k_{q1}} Qc^{\bullet}(QcH^{\bullet}) + DHP^{+\bullet}$

${}^3Qc{:}Me + DHP \xrightarrow{k'_{q1}} Qc^{\bullet}(QcH^{\bullet}){:}Me + DHP^{+\bullet}$

$Qc^{\bullet}(QcH^{\bullet}) + DHP^{+\bullet} \xrightarrow{k_{r1}} Qc + DHP\downarrow$

$Qc^{\bullet}(QcH^{\bullet}) + DHP^{+\bullet} \xrightarrow{k_{r2}} Qc^{2-}(QcH_2) + Pyr\uparrow$

$Qc^{\bullet}(QcH^{\bullet}){:}Me + DHP^{+\bullet} \xrightarrow{k'_{r1}} Qc^{2-}(QcH_2){:}Me + DHP\downarrow$

$Qc^{\bullet}(QcH^{\bullet}){:}Me + DHP^{+\bullet} \xrightarrow{k'_{r2}} Qc^{2-}(QcH_2){:}Me + Pyr\uparrow$

CIDNP intensity is proportional to the enhancement factor per one radical pair times the concentration of the radical pairs (RP). Complex formation leads to decrease in $E^{1/2}$(red)(Qc) and results in increase of ${}^3Qc$ quenching rate constant (k_{q1}), which in turn results in increase of the concentration of the radical pairs and CIDNP intensity, which is seen on the left figure (Cu2+), however no such increase is observed on the right figure (Fe^{3+}).

Photoinduced electron transfer between Qc and amino acids

The amino acids (AA), N-acetyl L-tryptophan and N-acetyl L-tyrosine, similar to Qc, form chelate complexes with Cu^{2+}. Significant reduction of CIDNP intensity implies inhibition of the electron transfer reaction:

without Me:

$Qc \xrightarrow{h\nu,\ ISC} {}^3Qc$

${}^3Qc + AA \xrightarrow{k_1} Qc^{\bullet}(QcH^{\bullet}) + AA^{+\bullet}$

$Qc^{\bullet}(QcH^{\bullet}) + AA^{+\bullet} \xrightarrow{k_2} Qc + AA$

with Me:

$Qc{:}Me \xrightarrow{h\nu,\ ISC} {}^3Qc{:}Me$

${}^3Qc{:}Me + AA \xrightarrow{k'_1} Qc^{\bullet}(QcH^{\bullet}){:}Me + AA^{+\bullet}$

${}^3Qc{:}Me + AA{:}Me \xrightarrow{k'_2} Qc^{\bullet}(QcH^{\bullet}){:}Me + AA^{+\bullet}{:}Me$

$Qc^{\bullet}(QcH^{\bullet}){:}Me + AA^{+\bullet} \xrightarrow{k''_1} Qc{:}Me + AA$

$Qc^{\bullet}(QcH^{\bullet}){:}Me + AA^{+\bullet}{:}Me \xrightarrow{k''_2} Qc{:}Me + AA{:}Me$

$k_{q1} >> k^{\wedge}_{q1}, k^{\wedge\wedge}_{q1}$

Conclusions:

1. Qc possibly exists in equilibrium with its derivative - semiquinone radical and this equilibrium depends on the solvent and the presence of reduction agents.
2. The increase of radical production is observed for some chelate complexes (Qc with Cu^{2+}), whereas for other no such increase is observed (Qc with Fe^{3+}).

Acknowledgments:

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