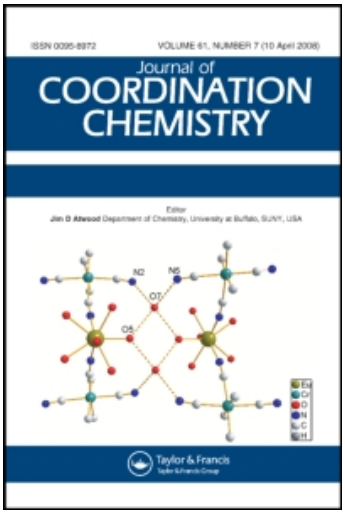

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ANAEROBIC REDUCTION OF ANTHRACYCLINE ANTIBIOTICS AND THEIR MODEL COMPOUNDS BY FE(II) COMPLEXES

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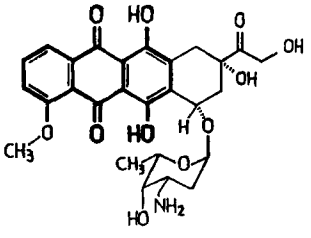
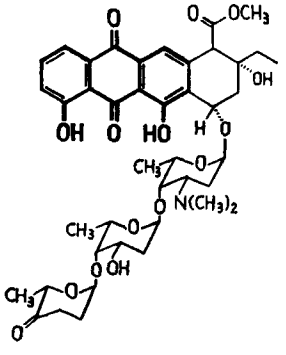
Abstract Hydroxyanthraquinones, model compounds for anthracycline antibiotics, are reduced by Fe(II)-ADP and Fe(II)-phosphate complexes to produce semiquinone radicals. In case the corresponding hydroquinone is stable, two electron reduction is caused by the Fe(II)-phosphate complex, rather strong reducing agent.

Keywords: Hydroxyanthraquinones, semiquinone radicals

INTRODUCTION

Anthracyclines, such as Adriamycin (ADM, 1), Aclacinomycin A (3), etc., widely used as anti-cancer drugs, have serious side effects on organs like heart or liver where oxygen pressure is high[1]. Many studies have shown that these side effects are triggered by anaerobic reduction of anthracyclines, followed by oxygen activation causing damage to the phospholipid membrane of the living cell. It has been confirmed that the process is accelerated by



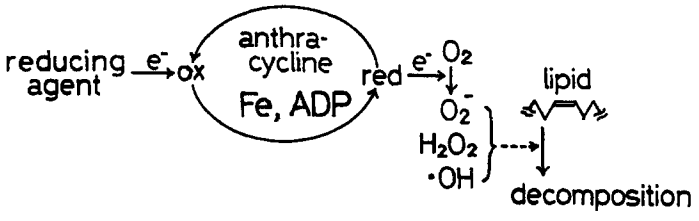


left: Adriamycin (1) and
1,4-DHAQ (2, bold-line)

right: Aclacinomycin A (3) and
1,8-DHAQ (4, bold-line)

both iron and ADP as shown in Scheme I[2]. The question is how iron is involved in the process: is it involved as a complex reagent to the drugs which are possible ligand when their dihydroxyanthraquinone (DHAQ) moiety is deprotonated, and/or as a reducing agent? The question is still unresolved and this may in part due to the complexity of the systems utilized in the biochemical studies. We employed therefore a series of ternary systems containing i) 1,4-DHAQ (2) or 1,8-DHAQ (4) as a model compound of anthracycline, ii) ferrous salt, and iii) ADP or phosphate salt, simplified systems so as to seek the role of iron in anaerobic reduction of anthracyclines.

SCHEME I. Mechanism of Anthracycline-Dependent Lipid Peroxidation.



EXPERIMENTAL

Adriamycin was kindly supplied by Kyowa Hakko Kogyo Co., Ltd.; other reagents were of the reagent grade available except leucoquinizarin, purified by sublimation in vacuo though it still contained a little amount of 1,4-DHAQ. Aqueous solution of ferrous sulphate mixed with six molar equivalent ADP or monobasic potassium phosphate was used as the respective source of the Fe(II) complexes. They are denoted as "Fe(II)-ADP" and "Fe(II)-phosphate", respectively, throughout the paper. All the sample preparations and the experiments were carried out under inert atmosphere. EPR and UV-visible measurements were made at room temperature.

RESULTS AND DISCUSSION

EPR Spectra

One to three molar equivalent Fe(II)-ADP or Fe(II)-phosphate were added to a DMSO solution of 1,4- or 1,8-DHAQ. EPR measurements on the resulting solutions were made and the spectra are collected in Fig. 1, from which one can see that DHAQ's are reduced by Fe(II) complexes to generate corresponding semiquinone radicals. The analyses of the spectra show that each of them consists of four sets of two equivalent protons, indicating that the hydroxyl groups of the semiquinone radical are completely protonated. With UV-visible spectroscopic technique we have observed[3] that in DMSO solution of ferrous sulphate and DHAQ's, Fe(II)-DHAQ complexes are formed with deprotonation at the hydroxy residue of the ligands. It is clear that DHAQ's and iron form no chelate complex in the present ternary systems.

Though all the spectra in Fig. 1 were taken under the same experimental conditions, spectral intensities in the Fe(II)-phosphate solutions are stronger than those of Fe(II)-ADP. So, we

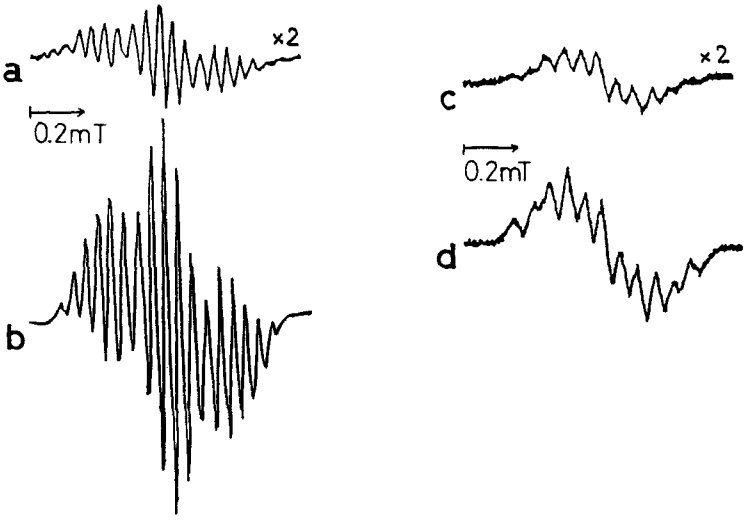


FIGURE 1. EPR Spectra of 1,4- and 1,8-DHAQ Semiquinone Radical Produced by Fe(II) Complexes at room temperature.
a: 1,4-DHAQ + Fe(II)-ADP, b: 1,4-DHAQ + Fe(II)-phosphate,
c: 1,8-DHAQ + Fe(II)-ADP, d: 1,8-DHAQ + Fe(II)-phosphate.

examined time-dependence of the EPR spectral intensities after addition of the Fe(II) complexes to the 1,4-DHAQ solution. The results are shown in Fig. 2. One can see that the radical concentration increases in a long time-scale for Fe(II)-phosphate, while it does not for Fe(II)-ADP. It should be noticed that slow rate of semiquinone formation in the former system is hard to explain in terms of single step reduction.

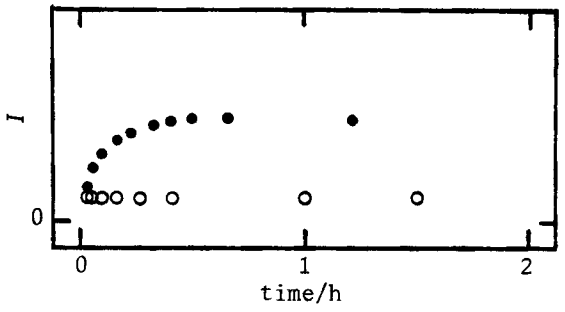


FIGURE 2. Time-Dependent Changes of EPR Spectral Intensities (I) of 1,4-DHAQ Semiquinone Radical after Addition of Fe(II)-ADP (O) and Fe(II)-phosphate (●) at room temperature. Initial concentration of Fe(II) and DHAQ are set 1×10^{-3} mol/dm^3.

When a little amount of O_2 was injected to the system, quenching of the semiquinone radical was observed for each case. However, in the case of Fe(II)-phosphate and 1,4-DHAQ, unexpected reappearence of the radical occurred with the same hyperfine splitting pattern as that observed before the radical quenching. Time-dependent changes of EPR spectral intensities are plotted in Fig. 3, which shows that it takes three hours and a half to reach the equilibrium. It is strongly suggested that there should be some routes to reproduce semiquinone radical in a slow reaction rate.

UV-visible Spectra

UV-visible measurements were made for the same systems. After addition of each of the Fe(II) complexes, there appears small but sharp absorption maximum at 497 nm[4] corresponding to the 1,4-DHAQ

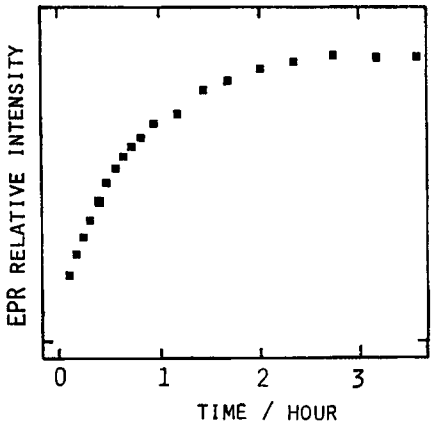


FIGURE 3. Time-Dependent Changes of EPR Signal Intensities of 1,4-DHAQ Semiquinone Radical Measured at Room Temperature after Quenching of the Radical by Injection of O_2 to the Fe(II)-phosphate System.

semiquinone radical overlapped with 1,4-DHAQ's broad absorption having maxima at 460 and 480 nm. The Fe(II)-ADP system reaches an equilibrium immediately after addition of the complex, while the Fe(II)-phosphate system does not: new absorption maxima slowly appear at 397 and 412 nm, accompanied by the decrease of 1,4-DHAQ. The final spectrum of the latter case is presented by curve a in Fig. 4. The new maxima at 397 and 412 nm coincide with those of leucoquininzarin (LQ), two-electron reduced compound of 1,4-DHAQ (See Fig. 5).

UV-visible spectral change after injection of O_2 was also examined. Fig. 4 gives more information than that from the observation of EPR. Before the injection of O_2 (curve a), the absorbance at 480 nm (A_{480}) is slightly larger than A_{460} because of the overlapping of the semiquinone absorption maximum at 497 nm. By the injection of O_2, A_{460} and A_{480} increase and become the same height (curve b). Curve c however shows that A_{480} becomes larger than A_{460} again 3 hr after the quenching: the radical is reproduced. Moreover, it is easily seen from the figure that these changes are accompanied by the decrease of LQ: LQ is the source of the

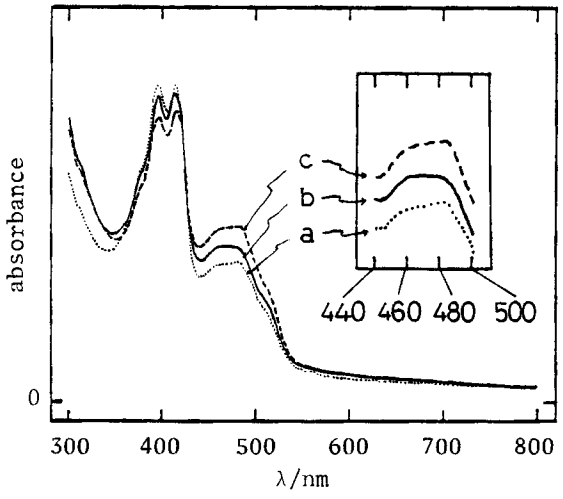


FIGURE 4. UV-visible Spectral Changes after Injection of O_2 into the System (1,4-DHAQ + Fe(II)-phosphate). a: before injection of O_2, b: after 5 minutes, c: after 3 hours.

radical reappeared after the quenching.

To know what is required for the semiquinone generation after the quenching of the radical by O_2, EPR and UV-visible spectra of DMSO solution of LQ were measured. LQ in pure DMSO under inert atmosphere gives neither EPR signal nor UV-visible spectral changes unless a little amount of O_2 is added, which induces the slow generation of the semiquinone radical detected by both the spectroscopic methods. UV-visible spectral change is shown in Fig. 5. After addition of water, absorption maxima from 1,4-DHAQ disappear and the sharp maximum at 497 nm due to the semiquinone radical appears, with consumption of a few LQ. The observation, which indicates that H_2O is required to drive the reaction, suggests that the mechanism for the semiquinone generation after O_2 injection is proton-catalysed comproportionation presented as

Hydroquinone + Quinone → 2 Semiquinone

This proton catalysed mechanism well explains the slow reaction rate observed in the Fe(II)-phosphate system.

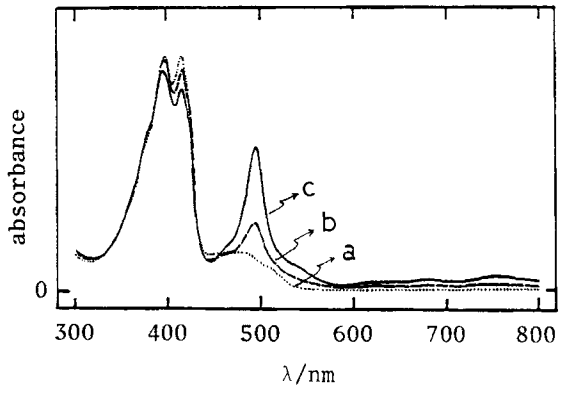


FIGURE 5. UV-visible Spectral Changes after Addition of H_2O to a DMSO Solution of LQ and a little 1,4-DHAQ.
a: before reaction, b: after 1.5 hours, c: after 5 hours.

Reduction of Adriamycin by Fe(II) Complexes

Experiments under the same conditions were carried out for ADM, the mother compound of 1,4-DHAQ. EPR spectra show that addition of the Fe(II) complexes gives rise to the ADM semiquinone radical (Fig. 6a), though the spectral intensities are weaker than those of the model compound. In fact, UV-visible changes by the addition of the Fe(II) complexes to the ADM system are so little that we hardly obtain information from the UV-visible spectra. However, time-dependent changes of EPR intensities (Fig. 6b) show the characteristics very similar to the behaviour observed for the model compound (See Fig. 2). The similarity in time-dependent changes between the drug and its model compound indicates that ADM is reduced in the same way as 1,4-DHAQ. Fe(II)-ADP works as a weak one-electron reducing agent for the quinones, while Fe(II)-phosphate has a redox potential negative enough to drive two-electron reduction of the anthracycline as in the case of the model compound[5].

CONCLUSION

We have two important results. One is that the semiquinone radi-

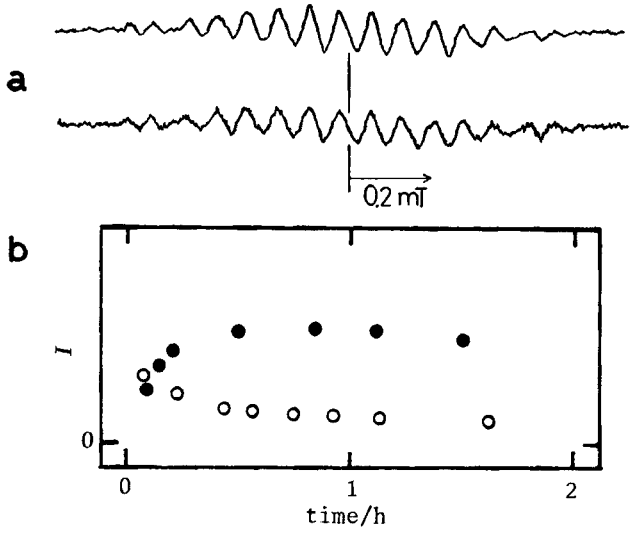


FIGURE 6. EPR Spectra of ADM Semiquinone Radical (a) and Time-Dependent Changes of the Spectral Intensities after Addition of Fe(II) Complexes (b).
a-top; b-○ : reduced by Fe(II)-ADP, a-bottom; b-● : reduced by Fe(II)-phosphate.

cals of anthracycline do not coordinate to Fe(II) ion, especially in the presence of ADP or phosphate. The other is that Fe(II) complexes, which have been considered as electron carrier in the anthracycline-dependent peroxidation of the lipid, can cause various redox behaviour depending on their ligands. Correlation between redox potentials of the Fe(II) complexes and their stoichiometry and structure is under study.

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