Journal of Molecular Structure 1262 (2022) 133071

Contents lists available at ScienceDirect

Journal of Molecular Structure

journal homepage: www.elsevier.com/locate/molstr

Understanding electrooxidation mechanism of anticancer drugs utilizing ultrafast pump probe spectroscopy

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ARTICLE INFO

Article history:
Received 3 November 2021
Revised 18 March 2022
Accepted 10 April 2022
Available online 12 April 2022

Keywords:
Electrooxidation mechanism
Anticancer drugs
Charge transfer
Ultrafast pump probe spectroscopy

ABSTRACT

In an attempt to gain deeper insight on the charge transfer mechanism of anticancer drugs and their electrochemically oxidized products, steady state absorption, fluorescence and ultrafast time resolved spectroscopy measurements were performed. All selected compounds exhibit the charge transfer fluorescence in methanol solution. Fluorescence intensity of the studied compounds is significantly quenched in 0.1M H_2SO_4 solution due to the increasing of intramolecular charge transfer. Ultrafast charge transfer (under 100 fs) mechanism is observed between the singlet exited states and charge transfer states. Femtosecond time resolved spectroscopy results indicate that, the charge transfer rates are faster in methanol:0.1M H_2SO_4 (20:80;v/v) mixture than that of methanol and the lifetime of the charge transfer states increases in methanol as compared to methanol: 0.1 M H_2SO_4 (20:80;v/v) mixture. It is also found that the lifetime and rates of the charge transfer state can be altered by electrochemically oxidation of the drugs. Our results reveal that, the structure of compounds transforms to form of semiquinone structure in the studied solution medium. Using the combination of electrochemical and ultrafast pump probe spectroscopy measurements, the determination of *in vitro* electrochemical oxidation mechanisms of the drugs, mimicking in the body, via intramolecular charge transfer can be easily suggested.

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1. Introduction

The term of cancer actually encompasses a group of closely related diseases that have in common unregulated cell division. Different types of cancers can be described and all types of cancer cells continue to grow by dividing instead of dying and form new abnormal cells. Cancer generally forms as a solid tumor. However, some cancers like leukemia which also known as blood cancer, do not form tumors. Instead, leukemia cells involve the blood and blood forming organs and circulate through other tissues where they grow [1–3].

Antineoplastic drugs are used in the treatment of malignant cancer cells, when surgery or radiotherapy is not possible or has proved ineffective, as an adjunct to surgery or radiotherapy, or, as in leukemia, as the initial treatment. Therapy with antineoplastic is notably successful in a few malignant conditions and may be used to palliate symptoms and prolong life in others [4–7]. Generally, antineoplastic drugs such as Idarubicin, Doxorubicin, Daunorubicin and Epirubicin are given by intravenous injection [8–11].

Electrochemical techniques are one of the powerful analytical tools about stability and giving information about metabolism of drugs and they permit the mimic behavior of electrooxidative reactions involved in drug metabolism and drug stability [12–15]. Electrochemical methods in drug analyses, especially cyclic voltammetric techniques, gives *in vitro* information about the journey of the drug through the human body. As the electroactive drugs taken to body they undergo redox reactions which can be follow *in vitro* by electrochemical studies. Cyclic voltammetric methods based on measuring the current obtained against the altered potential, generally used for the mechanism of the electroactive compounds and the kinetic of electron transfer. Moreover, electrochemical nature of the drug in terms of mechanism such as adsorption controlled, diffusion controlled or adsorption under diffusion can also be estimated by using scan rate studies by cyclic voltammetric techniques [16–20].

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https://doi.org/10.1016/j.molstruc.2022.133071
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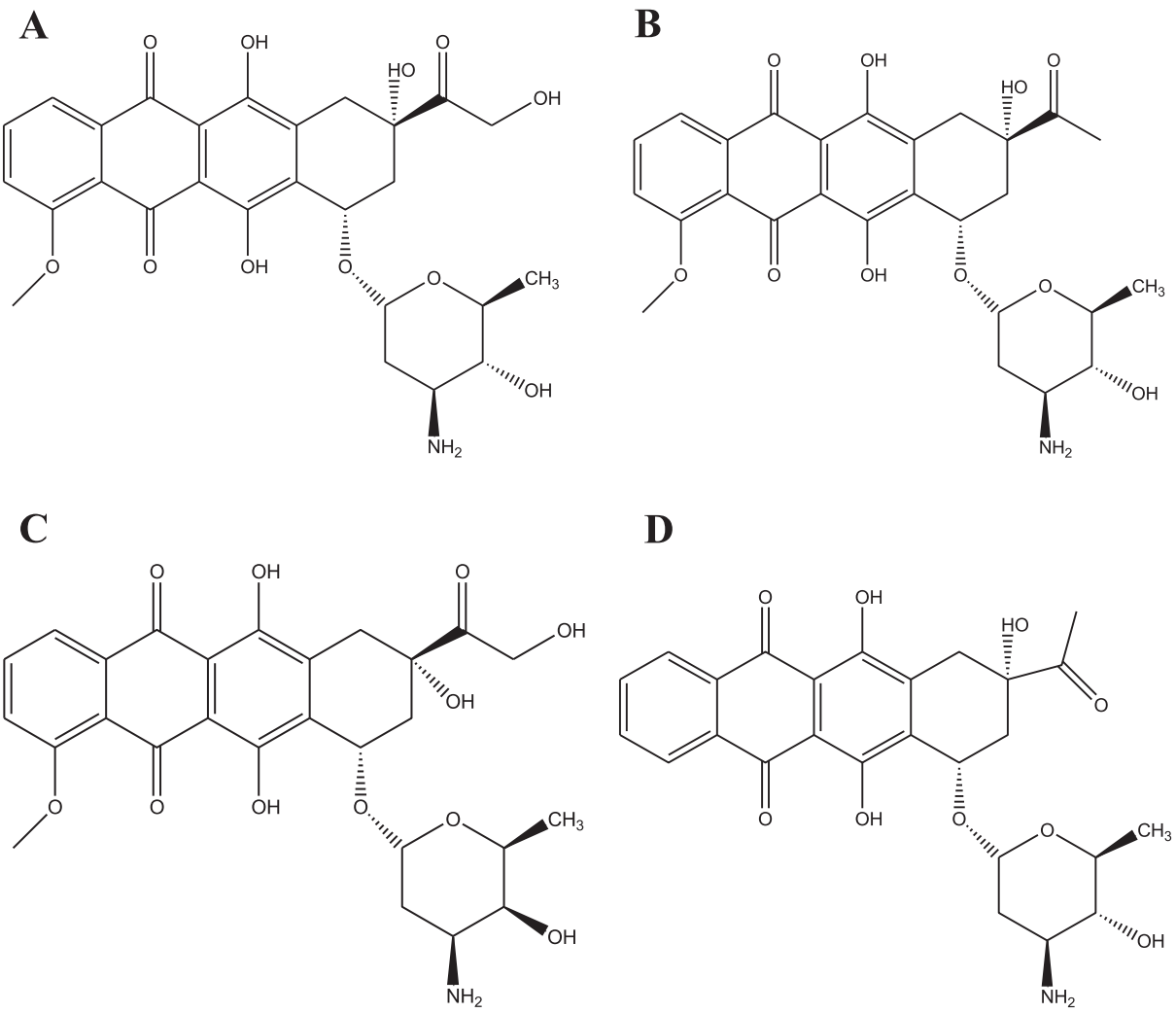


Scheme 1. Molecular structures of studied drugs (A) Epirubicin (B) Daunorubicin (C) Doxorubicin (D) Idarubicin.

In the literature there are many studies which investigated absorption and emission features, laser induced fluorescence properties [21], physicochemical interaction with nanocariers [22] for studied compounds. Moreover, electrochemical studies related with the anticancer drugs have been studied suggesting that idarubicin showed adsorption controlled electrochemical response [23] whereas Epirubicin showed diffusion controlled.[24,25] The electrochemical behavior of these drugs are crucial since the mechanism can mimic the behavior of the drug inside the body. The mechanism of these drugs can be enlightened by cyclic voltammetry or other electroanalytical techniques. However, there are not enough studies revealing the charge transfer mechanism of these compounds [26–28]. These mechanisms are not investigated and proved experimentally alone, the results are only incorporated by suggesting sort of a mechanism.

Therefore, in this work, it was aimed to discuss and prove the electrochemical oxidation mechanisms of these drugs more deeply using linear optical measurements, ultrafast pump probe spectroscopy results and mass spectra. We investigated ultrafast charge transfer dynamics of anticancer drugs in different solvents and the effect of electrochemically oxidation process on charge transfer mechanism. Since the chemical structures of the Idarubicin, Doxorubicin, Daunorubicin and Epirubicin are similar, studies were performed mainly on Idarubicin as details.

2. Experimental

2.1. Reagents

Idarubicin, Epirubicin, Doxorubicin, Daunorubicin was supplied from EBV Pharm. Inc. (Istanbul, Turkey) and the molecular structure of these compounds were given in Scheme 1. All solutions were protected from light and used within 24 h to avoid decomposition. All chemicals such as H_2SO_4, methanol were of analytical reagent grade and doubly distilled water was used throughout the experimental work.

2.2. Materials and method

The electrochemical measurements were recorded using a BAS 100 W (Bioanalytical System, USA) electrochemical analysis system. Bulk electrolysis system was used containing, a conventional three-electrode cell with an Ag/AgCl (BAS; 3 M KCl), a platinum auxiliary electrode in an auxiliary electrode chamber and reticulated vitreous carbon working electrode (BAS).

Mass spectral analysis was performed on an Agilent 6224 TOF LC/MS spectrometer. The recording was in the range of m/z 50–1000 in +ESI mode. The m/z value of molecular ion peak in TOF spectra was recorded up to five decimal precisions for accurate mass measurement.

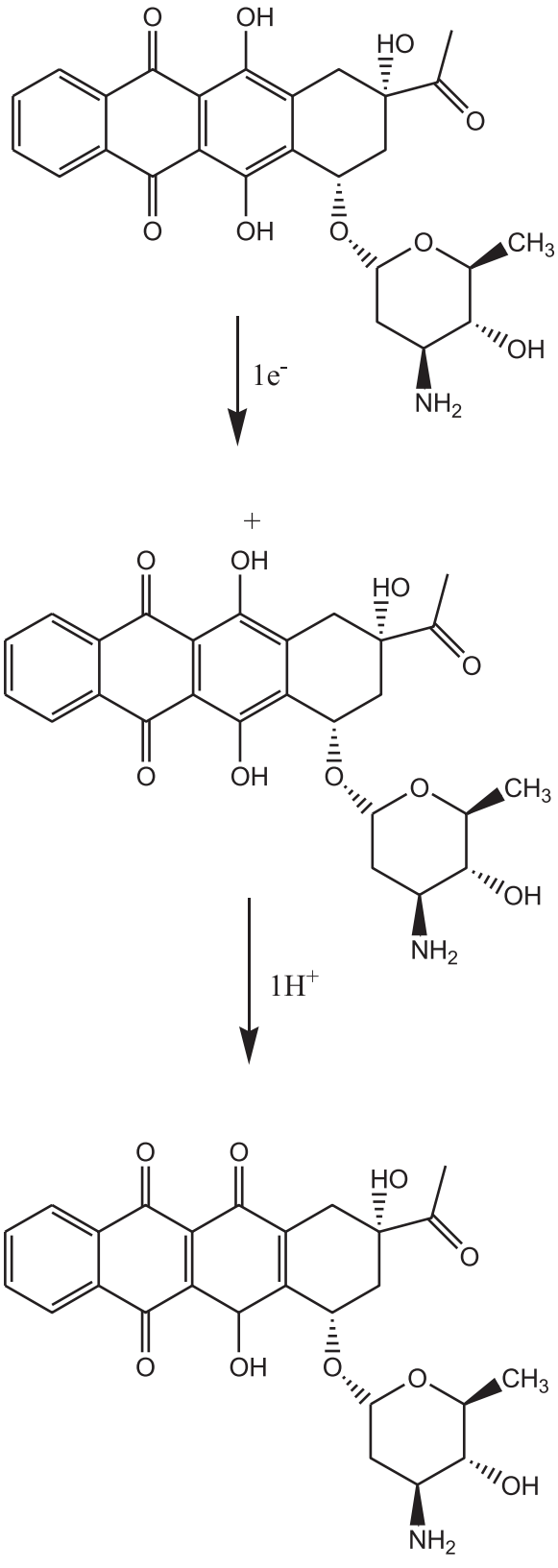
The linear absorption spectra of studied drugs were taken with UV-Vis absorption spectrometer (Shimadzu UV-1800) and fluorescence spectra were recorded on a Perkin Elmer LS55 spectrofluorometer. The absorption values of the studied compounds were adjusted to 1 absorbance to excite equal number of electrons in methanol and methanol: 0.1 M H_2SO_4 (20:80; v/v) mixture solvent for the femtosecond time resolved transient absorption spectroscopy measurements. The ultrafast pump probe spectroscopy measurements were carried out by using a Ti: Sapphire laser optical parametric amplifier system (Spectra Physics, Spitfire Pro XP, TOPAS) and commercial setup (Spectra Physics, Helios). Pulse duration was measured as 120 fs by cross-correlation inside the pump probe setup. The pump beam as sent into the OPA (optical parametric amplifier) system to obtain specific pump wavelength. Wavelength of the pump beam was chosen according to the steady state absorption spectra (500 nm) of studied compounds. The probe beam was delayed by using linear delay stage and then focused on the sapphire crystal to generate white light continuum. White light continuum was used for probe beam. The angle of the polarization between pump and probe beams was set the perpendicular, then the pump and probe beams were overlapped on the samples. After the samples, the probe beam was coupled into an optical fiber and into a spectrometer. Data acquision were supplied by using a LabVIEW software. Experimental data was analyzed by using Surface Xplorer software that is supported by Ultrafast Systems. The decay traces were fitted to multi exponential to extract transient dynamics of the studied compounds. We determine the time components according to the dynamics of the compound.

3. Results and discussion

3.1. CV measurements

Cyclic voltammetry can easily give insight how the electrooxidation takes places using repetitive cyclic voltammograms. Since the drugs, Idarubicin, Doxorubicin, Daunorubicin and Epirubicin have similar structures; our studies were mainly focused on Idarubicin and Epirubicin (Scheme 1). For 1×10^{-4} M Idarubicin, between 0 V and +1.6 V, three repetitive cycles were obtained as shown in Fig. 1. In the first cycle, the well oxidation peak obtained and in the reduction side reduction couple related with the 1st oxidation peak can be followed. It is suggested that, these redox peak are occurred due to OH groups in Idarubicin drug. Hence, if it is one electron one proton, or two electron two proton system, is not certain. Related with the quinonic structures in the structure, $1e^-$ and 1 H^+ electrochemical mechanism is suggested as shown in Scheme 2. To enlighten this suggestion, here in this paper, we conducted, firstly bulk electrolysis of these compounds and then mass analysis of the obtained oxidized compounds were realized. At the same time, linear optical and ultrafast pump probe spectroscopy experiments were also carried out to support our suggestion.

Bulk electrolysis, is an electrochemical technique, where a controlled constant potential is applied to the system to complete electrolysis of all species in the solution. In this work, all the drugs were dissolved in methanol, as they are soluble in methanol. Then electrolysis of these drugs were performed in methanol: 0.1 M H_2SO_4 (20:80; v/v) system, as the electrochemical reactions need some electrolyte solutions such as buffer systems or acids, according to our previous studies [23–25] methanol: 0.1 M H_2SO_4 (20:80; v/v) mixture was used for bulk electrolysis system other electrolyte systems such as phosphate buffer (0.2 M, pH 2.0-8.0), acetate buffer (0.2 M, pH 3.5–5.5) and Britton-Robinson (BR) buffer (0.04 M, pH 2.0–12.0). Using “bulk electrolysis” method, the neutral form of the drug active compounds were completely oxidized and the fully oxidized forms of these drugs were used for confirmation of the suggested electrochemical mechanism using mass



Scheme 2. Suggested electrooxidation of Idarubicin.

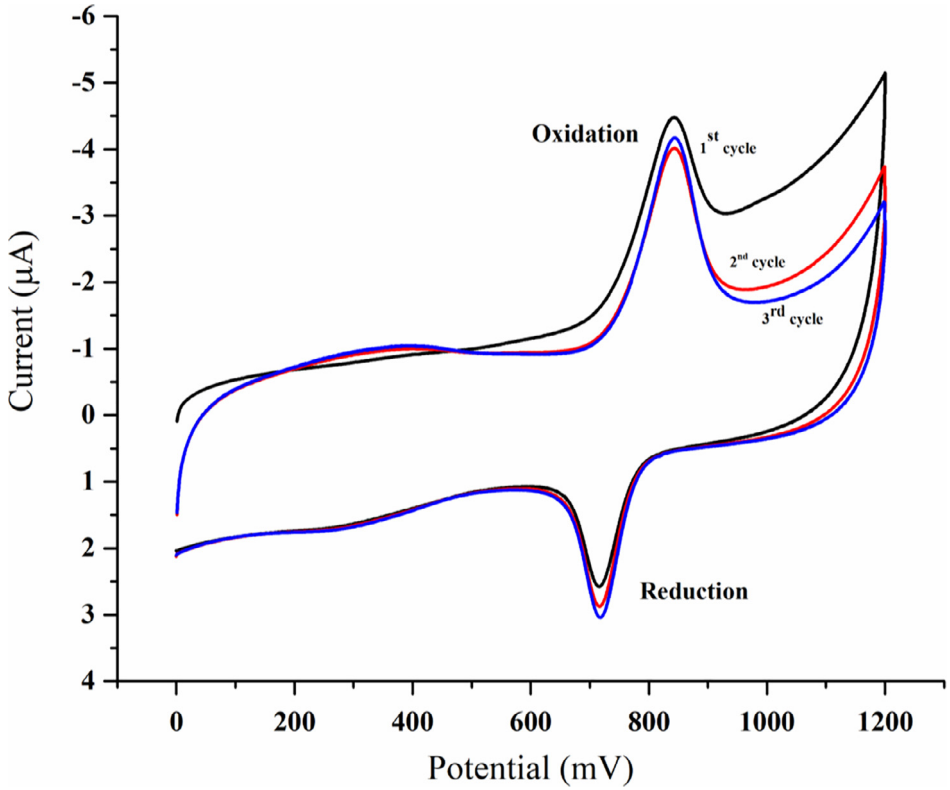


Fig. 1. Cyclic voltammetry of 1×10^{-4} M Idarubicin in 0.1 M H_2SO_4.

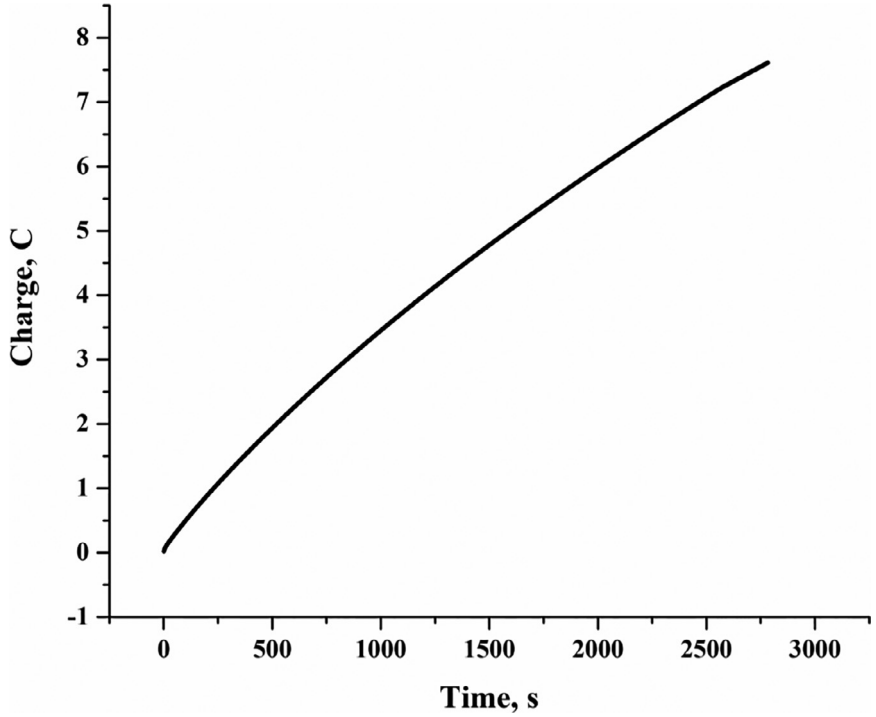


Fig. 2. Bulk electrolysis of 1×10^{-3} M Idarubicin in 0.1 M H_2SO_4.

analysis, linear optical and ultrafast pump probe spectroscopy experiments. The charge decrement in Fig. 2 shows the electrolysis of 1×10^{-3} M Idarubicin in 0.1 M H_2SO_4:H_2SO_4 (20:80; v/v) solution.

HRMS (TOF-ESI) (m/z) for electrochemically oxidized Idarubicin compound was calculated as 497.16863 ($C_{26}H_{27}NO_9$), found: 498.17753 $[M+H]^+$, Δ=3.36 ppm. HRMS (TOF-ESI) (m/z) for Idarubicin calculated as 497.16863 ($C_{26}H_{27}NO_9$), found: 498.17667 $[M+H]^+$, Δ=1.63 ppm. The mass spectra of electrochemically oxidized idarubicin and idarubicin were given in Fig. S1 and S2, respectively.

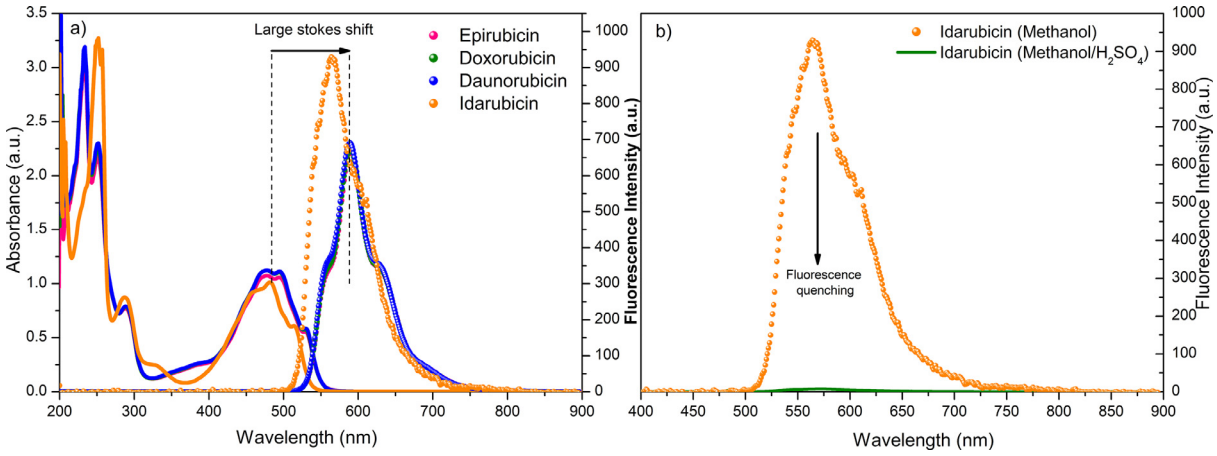


Fig. 3. (a) Linear absorption and fluorescence spectra of studied drugs in Methanol solution (b) Fluorescence spectra of Idarubicin in Methanol and Methanol:H_2SO_4 (20:80; v/v) mixture, λ_{exc} = 485 nm, c=1 × 10^{-4} M.

3.2. Linear optical properties

The UV/VIS absorption and emission spectra of Epirubicin, Doxorubicin, Daunorubicin and Idarubicin drugs are shown in Fig. 3a. All drugs have broad absorption band between 400 and 500 nm wavelength region and similar characteristics in absorption spectrum. The Idarubicin has bit difference absorption and emission spectra as compared to other studied drugs. Since there is no methoxy group in the Idarubicin molecule, the absorption is shifted to blue region, and also the fluorescence intensity of Idarubicin drug is higher than that of the other drugs. The large red shift of studied drugs in fluorescence spectra can be explain by charge transfer fluorescence in methanol solution as known from the literature [29,30]. In addition to that, we also studied these compounds in methanol and methanol:0.1 M H_2SO_4 (20:80; v/v) mixture to investigate protonation effect on linear absorption and emission properties. We found that there is no significant difference on the absorption spectra of all drugs in both media. In fluorescence spectra, while there is an intense fluorescence signal in methanol solution, the signal drastically decrease in methanol: 0.1 M H_2SO_4 (20:80; v/v) mixture due to the charge transfer for all drugs (Fig. 3b). On the other hand, in order to understand the oxidation effects on charge transfer process, Idarubicin is electrochemically oxidized using bulk electrolysis system. It was observed that the density of main absorption band decreased (Fig. S3). The decreasing in the absorption intensity may explain that, when it is oxidized electrochemically in 0.1 M H_2SO_4 solution, the decrease in the number of aromatic groups of aromatic leads to decrease in the intensity of the main absorption band (Fig. S3). The anthracycline molecule idarubicin has two phenyl groups on its aromatic scaffold that forms a quinonic structure. The quinone-hydroquinone conversion of the IDA molecule is well known [31]. When it is oxidized electrochemically, decrease in aromaticity has leaded to a decrease in the intensity of the main absorption band. The absorption band localized between 400 and 500 nm is therefore decreased in the absorption spectrum depending on oxidation. The high resolution mass spectra of the both samples (electrochemically oxidized compound taken from the test media and idarubicin in acetonitrile, respectively) showed the $[M+H]^+$ molecular ion peaks that may indicate the incompleted oxidation in methanol: 0.1 M H_2SO_4 (20:80; v/v) environment, resembling the formation of semi-quinoid structure. Indeed, although it is very difficult to observe the semiquinone derivatives, due to fast disproportionation in cyclic voltammograms, It is known that different solution environments could stabilize the semiquinone derivatives [32]. Regardless, the oxidation profile in repetitive cyclic voltammograms shows that oxidation caused dictinctive changes in the absorption properties of the compound. Therefore, In an attempt to reveal solvent and oxidation effects on intramolecular charge transfer and fluorescence properties of the studied drugs, ultrafast pump probe spectroscopy experiments were carried out in methanol: 0.1 M H_2SO_4 (20:80; v/v) media.

3.3. Ultrafast pump probe spectroscopy

In order to investigate the charge transfer mechanism and decay process of the excited states of Epirubicin, Daunorubicin, Doxorubicin and Idarubicin drugs, we performed ultrafast pump probe spectroscopy experiments with white light continuum. All drugs have broad absorption band in the range of 400–550 nm and an intense maximum at approximately 485 nm wavelength in methanol and methanol: 0.1 M H_2SO_4 (20:80; v/v) mixture (Fig. 3a). Excitation wavelengths for ultrafast pump probe experiments were chosen as 500 nm wavelength, which corresponds to steady states absorption maximum of the compounds.

Transient absorption spectra with different time delays were shown in Figs. 4 and 5 for Epirubicin and Idarubicin drugs, respectively, upon 500 nm excitation. Although there are minor differences, all of the drugs exhibit similar characteristics in pump probe spectra. In transient absorption spectra, all of the drugs have two broad negative signals in the range of 400–500 nm and 600-700 nm in methanol and methanol: 0.1 M H_2SO_4 (20:80; v/v) mixture (Figs. 4 and 5). The negative signals around 400–500 nm region can be attributed to ground state bleaching. The extra bleach signal in the range of 600–700 nm can be related to the combination of stimulated emission (SE) and charge transfer state since there is no any steady state absorption signals above the 575 nm wavelength in the linear absorption spectra. The intramolecular charge transfer rate occurring from exited singlet state to charge transfer state is ultrafast (under 100 fs) for all the drugs. The charge transfer bleach signals (600–700 nm) and the charge transfer rates are significantly affected by the acidic media [33]. While the bleach signal has long lifetime in methanol solution, this signal decrease fast and turn to excited state absorption (ESA) in methanol: 0.1 M H_2SO_4 (20:80; v/v) mixture (Fig. 4b) solution, due to increasing the number of the charge transfer states in methanol: 0.1 M H_2SO_4 (20:80; v/v) mixture solution. Therefore, the bleach signal decays faster in methanol: 0.1 M H_2SO_4 (20:80; v/v) solution as compared to in methanol solution (Fig. S4). After about 3 ps time delay the bleach signal increases again. This oscillation oc-

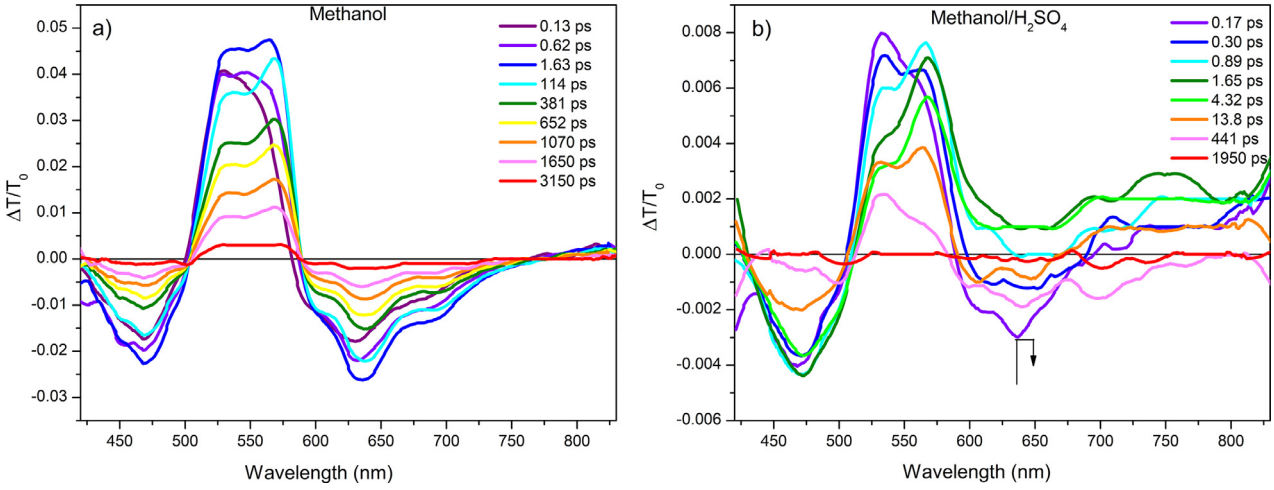


Fig. 4. Transient absorption spectra for Epirubicin drug with increasing time delays at 500 nm excitation wavelength in (a) Methanol and (b) Methanol:H_2SO_4 (20:80; v/v) mixture.

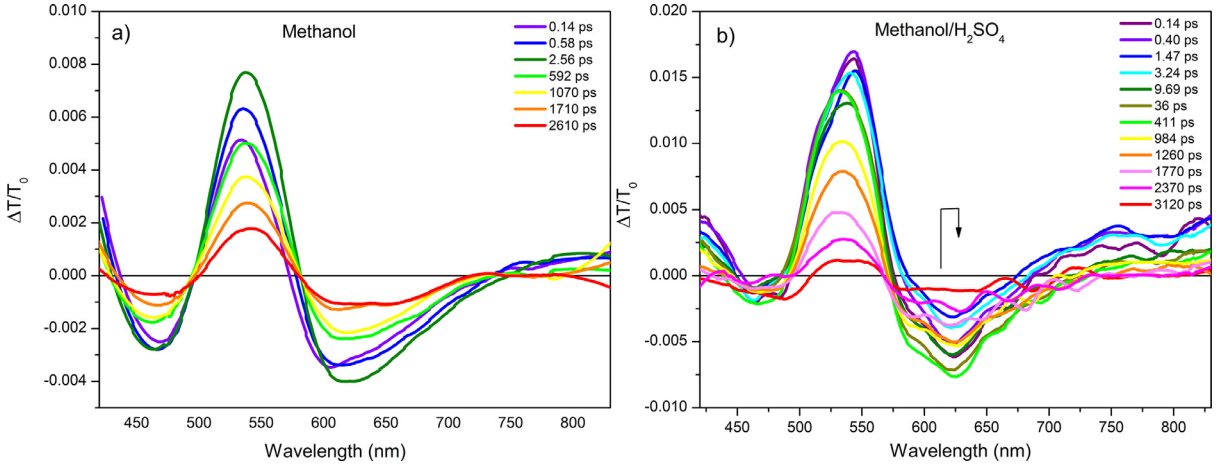


Fig. 5. Transient absorption spectra for Idarubicin drug with increasing time delays at 500 nm excitation wavelength in (a) Methanol and (b) Methanol:H_2SO_4 (20:80; v/v) solutions.

curs because of the electron transfer between the charge transfer states that are occurred in acidic environment.

There are also ESA signals localized at 530 nm and 570 nm in transient absorption spectra for the studied drugs (Figs. 4 and 5). The ESA signal at 530 nm is related to the S_1-S_n absorption of the compounds, while ESA signal at 570 nm corresponds to radical cation or anion absorption from charge transfer state [34–39].

The decay traces of the transient absorption spectra were fitted by using a multiexponential fitting function with the following equation;

$$S(t) = e^{-\left(\frac{t-t_0}{t_p}\right)^2} * \sum_i A_i e^{-\frac{t-t_0}{t_i}}, t_p = \frac{IRF}{2 \cdot ln2} \quad (1)$$

where *IRF* is the width of instrument response function (full width half maximum, the value is 120 fs for our system), t_0 is time zero, A_i and t_i are amplitudes and decay times respectively, * is convolution.

The decay kinetics of the charge transfer bleach signals with 620 nm probe wavelength for studied compounds were compared with each other in methanol solution as seen in Fig. 6. According to the decay kinetics of charge transfer state of the Idarubicin drug, it has long lifetime while compared to the other drugs. This result is evidence why the fluorescence intensity of Idarubicin drug is higher than that of the other studied drugs. In addition to, the decay kinetics of charge transfer state bleach signals show interesting properties in methanol: 0.1 M H_2SO_4 (20:80; v/v) mixture (Fig. 7). We observed the oscillation of the charge transfer bleach signals for all working compounds and the oscillation is given for Epirubicin and Idarubicin drugs in acidic environment is given in Fig. 7. The bleach signals turn to ESA signal for Epirubicin drug but it did not switch for Idarubicin, because of the fact that Idarubicin has longer excited state lifetime than Epirubicin. The charge transfer state of Idarubicin has longer lifetime as compared to the Epirubicin, the state does not decay fast. Therefore, the bleach signal of Idarubicin is getting increase without decaying completely.

On the other hand, we also investigate the oxidation effects on ultrafast dynamics of the studied drugs. When Epirubicin drug is oxidized electrochemically in methanol: 0.1 M H_2SO_4 (20:80; v/v) mixture, the lifetime of the bleach signal increases because of the decreasing the number of the charge transfer states (Fig. 8). While the bleach signals turn to ESA in methanol: 0.1 M H_2SO_4 (20:80; v/v) solution, after the electrochemically oxidation process, the bleach signal starts to increase without switching ESA. That is because, the lifetime of the charge transfer states increase upon oxidation process. The other oxidized drugs exhibited similar characteristic behaviors in ultrafast transient absorption spectra.

In the literature, the effect of electrochemical oxidation process on molecular structure is incorporated by suggesting sort of a mechanism. In this study, transformation of the structure to semiquinone after electrochemical oxidation process was observed

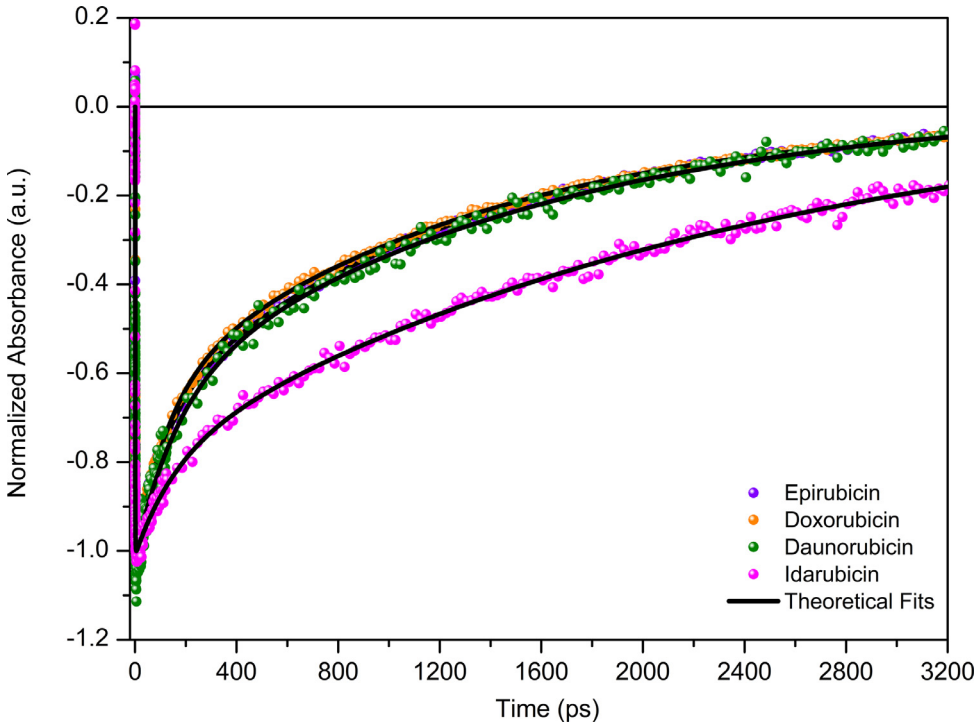


Fig. 6. Comparison of the decay curve of studied drugs at 620 nm probe wavelength with 500 nm excitation in methanol solution.

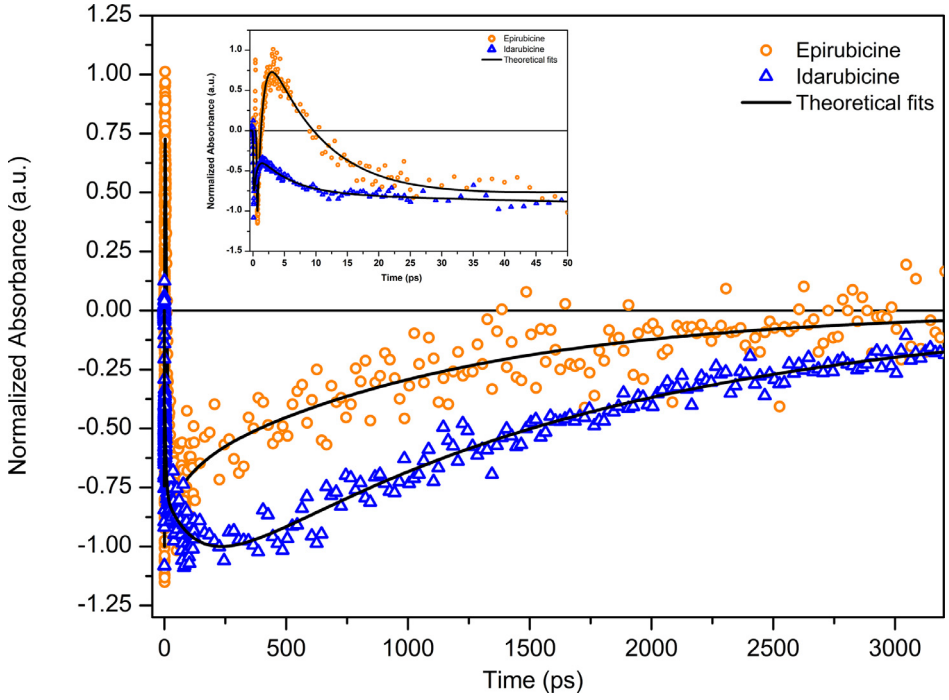


Fig. 7. Comparison of the decay curves of Epirubicin and Idarubicin drugs at 620 nm probe wavelength with 500 nm excitation in Methanol:H_2SO_4 (20:80; v/v) solution.

and the charge transfer mechanism was investigated by using CV, mass measurements and ultrafast pump-probe spectroscopy experiments.

4. Conclusion

Electrochemistry combined with other methods such as mass spectrometry (EC–MS) is an emerging analytical technique in the imitation of oxidative drug metabolism at the early stages of new drug development and *in vitro* drug metabolism. Here, we present the benefits of electrochemical oxidation by cyclic voltammetry for the oxidation of selected anticancer drugs on a glassy carbon electrode. In addition, in order to understand the effect of solvent polarity and electrochemical oxidation on charge transfer dynamics of anticancer drugs, steady state absorption, fluorescence and ultrafast pump probe spectroscopy experiments were performed. Idarubicin was oxidized at constant potential and the reaction products were analyzed by mass spectrometry. The ox-

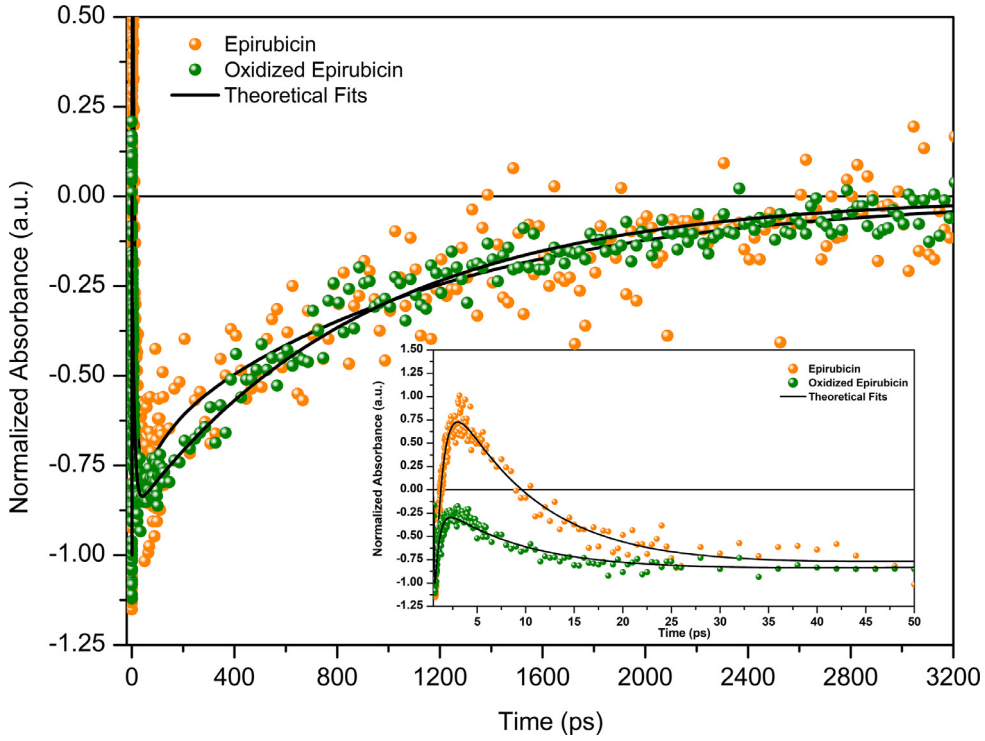


Fig. 8. Comparison of the decay curves of Epirubicin and oxidized Epirubicin drugs at 620 nm probe wavelength with 500 nm excitation Methanol:H_2SO_4 (20:80; v/v) mixture.

idation product was only obtained by electrochemical oxidation. This considerably widens the scope of direct electrochemistry-based oxidation reactions for the imitation of *in vivo* oxidative drug metabolism.

All of the studied drugs demonstrate charge transfer fluorescence in methanol solution. While the fluorescence signal is efficient in methanol solution, this signal significantly is quenched in methanol: 0.1 M H_2SO_4 (20:80; v/v) mixture. The lifetime of the charge transfer state increase in methanol solution than that of methanol:0.1 M H_2SO_4 (20:80; v/v). This is the evidence of the occurrence of the new charge transfer states in the acidic medium. Occurrence of the new charge transfer states proves that, the fluorescence is quenched in methanol: 0.1 M H_2SO_4 (20:80; v/v) mixture. The experimental results which are obtained from ultrafast pump probe spectroscopy indicated that, ultrafast charge transfer (under 100 fs) from singlet-excited state to charge transfer state and the transfer rates are faster in methanol: 0.1 M H_2SO_4 (20:80; v/v) mixture than that of only methanol. On the other hand, ultrafast pump probe spectroscopy results revealed that, electrochemically oxidation process also affects the charge transfer state lifetime and charge transfer rates of the compounds. Moreover, the mass spectra of the products, which were obtained by the bulk electrolysis, confirmed the formation of semi-quinoid structure via $1e^-$ and 1 H^+ oxidation mechanism.

The main idea of this manuscript is to enlighten the electrooxidation mechanism of the drugs with the confirmation of using ultrafast pump probe spectroscopy. As we always use electrochemical methods to estimate the possible behavior of drug active compounds in the human body, with this study, for the first time, we tried to understand the real electrochemical mechanism using real oxidized forms of these drugs by ultrafast pump probe spectroscopy. To the best of our knowledge, this is the first report studying of the ultrafast dynamics to support enlightening electrochemical mechanism of these anticancer drugs using by ultrafast pump probe spectroscopy and mass techniques accompanied with cyclic voltammetry.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Ahmet Karatay: Project administration, Conceptualization, Methodology, Writing – review & editing. **Sevinc Kurbanoglu:** Resources, Investigation, Writing – review & editing, Data curation. **Gokhan Sevinc:** Investigation, Data curation, Writing – review & editing. **Elif Akhuseyin Yildiz:** Investigation, Data curation, Writing – review & editing. **Mustafa Hayvali:** Conceptualization, Methodology, Writing – review & editing. **Sibel A. Ozkan:** Supervision, Conceptualization, Methodology, Writing – review & editing. **Ayhan Elmali:** Supervision, Conceptualization, Methodology, Writing – review & editing.

Data availability statement

All data that support the findings of this study are included within the article (and any supplementary files).

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.molstruc.2022.133071.

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