Convention Special Issue – 2020

J. Indian Chem. Soc.,
Vol. 97, No. 12a, December 2020, pp. 2633-2642

Electrochemical reduction of purpurin, its Mn(II) complex in DMF and aqueous-DMF mixed solvent: A cyclic voltammetric study†

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Manuscript received online 18 November 2020, revised and accepted 26 December 2020

Purpurin studied in pure and aqueous-dimethyl formamide (DMF) medium undergoes successive two one-electron reductions accompanied by comproportionation generating semiquinone radical anion realized by considering either complete reduction of it by two-electrons or reversing the scan immediately after reduction by one electron in cyclic voltammetry experiments. Difference in the oxidation peak corresponding to the conversion of a semiquinone radical anion to quinone ($Q^{\bullet-} \rightarrow Q$) was identified. For a complete reduction of purpurin by two electrons, the oxidation peak corresponding to $Q^{\bullet-} \rightarrow Q$ was greater than when the scan was reversed immediately after reduction by one electron. This difference in current during oxidation of a semiquinone radical anion ($Q^{\bullet-}$) to quinone (Q) is an indication of the presence of extra $Q^{\bullet-}$ if purpurin is reduced by two electrons; a consequence of comproportionation. Such electrochemical behavior of purpurin to eventually form $Q^{\bullet-}$, suggests it to be the main species in solution following reduction. This is particularly important considering that anthraquinones are an important component of the anthracycline family of anticancer drugs and semiquinones have a major role to play in drug efficacy. Apparent comproportionation constants in pure DMF and in aqueous-DMF mixtures were calculated showing influence of water on comproportionation rates. Cyclic voltammetry in aqueous media at different pH revealed unlike other members of the hydroxy-9,10-anthraquinone family, where a one-step two-electron reduction is observed in aqueous solution, in case of purpurin, the first one-electron reduction peak forming $Q^{\bullet-}$ did not disappear completely, although the second peak became progressively strong as water content was increased in DMF. Similar experiments were performed on the Mn(II)-purpurin complex revealing slightly different behavior and indicating a decrease in formation of $Q^{\bullet-}$. Cyclic voltammetry of the complex clearly demonstrate either removal of dianion species (Q^{2-}) or radical species ($Q^{\bullet-}$) by an EC mechanism or by an internal complex rearrangement to compensate extra electron density.

Keywords: Anthracycline, purpurin, Mn^{II}-purpurin, semiquinone, quinone-dianion comproportionation, aqueous-DMF.

Introduction

Chemotherapy by anthracycline anticancer agents is attributed to their ability to generate reactive intermediates (like semiquinone radical anion) that in presence of molecular oxygen generate reactive oxygen species via the formation of superoxide[1–5]. For these drugs, generation of the semiquinone radical anion is crucial, since on the one hand it is essential for cytotoxic action (causing damage to different cell organelles) and on the other it makes the drugs cardiotoxic[1–3, 6–8]. Hence, for a safe use of anthracyclines there is a need to control the formation of semiquinone so that the amount generated *in situ* is sufficient for cytotoxic action, not leaving much in excess to cause cardio-toxic side effects[2,3,6–8]. Chemotherapy-induced cardio-toxicity is a serious problem limiting the use of anthracycline-based anticancer agents[6–8]. Different research groups, medical practitioners had long expressed concern at such chemotherapy-induced cardio-toxicity[8]. Many amongst them question their use on cancer patients mentioning time and again "today's cancer patients are tomorrow's cardiac patients"[9,10].

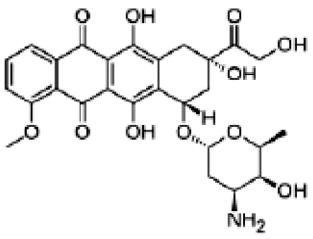
Even when anthracycline-induced cardio-toxicity is irreversible, their use could not be avoided owing to the drugs' efficacy[6–10]. For this reason the use of anthracyclines demand extra caution particularly in case of pediatric patients[9,10]. Therefore, inspite of all controversies, anthracyclines have remained in use since for a number of cancers

†Invited Lecture.

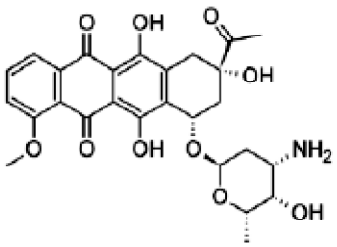
we are yet to find alternatives that match their efficacy. At the same time, problems of cardio-toxicity have been a matter of concern. A logical approach to use of anthracyclines is to suitably modify them; that maintains drug efficacy and lowers cardiotoxic side effects[8–16]. One such way being through the formation of metal complexes.

Simpler analogues like hydroxy-9,10-anthraquinones or naphthaquinones are effective anticancer agents as well[13–23]. Two reasons why researchers have tried hydroxy-9,10-anthraquinones are that (i) it is an integral part of anthracyclines and (ii) having a simpler structure, if found effective it should be biologically as well as economically viable[13–23]. Since generation of semiquinone radical anion or protonated semiquinone on anthracyclines occur at the hydroxy-9,10-anthraquinone, such formation should be same whether formed on an anthracycline or on a hydroxy-9,10-anthraquinone itself[24–31]. Hence, formation of reactive intermediates on anthracyclines may be realized by performing experiments on hydroxy-9,10-anthraquinones as similar species are generated[16,18,29–31]. Since structural differences in anthracyclines either at the aglycon or at sugar residues affect efficacy and toxic side effects, a choice of a proper representative hydroxy-9,10-anthraquinone helps one to understand both chemical and biological aspects of such drugs[9]. Several studies involving either a variation in position or in the number of hydroxy groups present on an anthraquinone of anthracyclines were reported to influence drug efficacy and cardio-toxicity[32–34]. Hence, to realize how one anthracycline is different from another there is a need to experiment with different hydroxy-9,10-anthraquinones analyzing them from different perspectives[16,18–23,28–31,35,36]. Here we report an electrochemical study on 1,2,4-trihydroxy-9,10-anthraquinone (purpurin), that closely resembles the hydroxy-9,10-anthraquinone units of doxorubicin, daunorubicin, epirubicin etc. and its Mn(II) complex. The amount of semiquinone generated by the compounds under different solvent compositions and in aqueous media at different pH was realized. We discussed how and why complex formation modulates formation of semiquinone radical anions and why various complexes of anthracyclines were prepared (hoping they might be better anticancer agents). This study correlates facts related to ROS generation, efficacy and cardio-toxicity, drawing examples from previous work on generation of reactive intermediates where complexes were either comparable or better than anthracyclines[10,12,18,20–23,37–41]. Findings of electrochemical experiments on the chosen compound (purpurin) and its Mn(II) complex are useful in explaining results on cancer and normal cells[21,23,35,36].

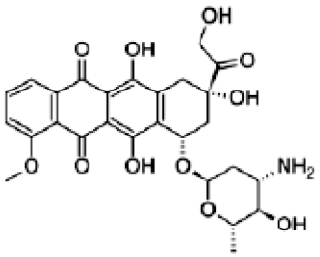
In aprotic media, reduction of a quinone takes place via two successive one-electron steps generating $Q^{\bullet-}$ and Q^{2-}



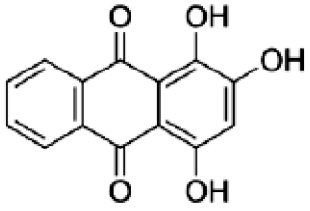
Doxorubicin



Daunorubicin



Epirubicin



Purpurin

respectively with formal potentials depending on the polarity of the solvent[14,28,29,42]. In aprotic media, cations of supporting electrolytes play a vital role in deciding whether reduction would be in two steps or in a single step[27,29,42,43]. Electrochemical behavior of quinone systems alter significantly in presence of acidic additives; hydrogen bonding playing an important role in determining the redox behavior of hydroxy-9,10-anthraquinones[31,44–49]. The present study looks at some of these aspects through electrochemical investigations on purpurin to reflect on this unit's performance in anthracyclines in biological systems. Electrochemical studies on Mn(II)-purpurin[35] identified changes due to complex formation, an important issue since as mentioned earlier, subtle variations in the position of hydroxy groups in the hydroxy-9,10-anthraquinone unit in anthracyclines show significant differences not only in chemotherapy but in chemotherapy-induced cardio-toxicity.

Experimental

Materials used:

Purpurin was purchased from Sigma Aldrich and purified by re-crystallization from ethanol. The Mn(II) complex was prepared and characterized earlier[35]. Dimethyl formamide (DMF), purchased from E. Merck, India was used as solvent during electrochemical experiments. NaCl, $NaNO_3$, KCl, tetrabutyl ammonium bromide (TBAB) and TRIS-buffer (all AR grade) were purchased from E. Merck, India. Triple distilled water was used to prepare aqueous solutions.

Electrochemical behavior of purpurin and its Mn(II) complex:

Cyclic voltammetry was performed to study electrochemical behavior of purpurin and its Mn(II) complex in protic (aqueous) and aprotic (DMF) media. 0.12 *M* KCl was used as supporting electrolyte for aqueous solutions while 0.12 *M* TBAB was used for aprotic media. pH (~7.4) was maintained with the help of Tris buffer. Before each experiment, solutions were de-aerated using high purity Argon for a minimum of 30 min. Electrochemical measurements were performed in a 50 ml electrochemical cell using a conventional three-electrode system; Glassy carbon (Metrohm, 6.1241.060) was used as working electrode, a Pt wire as auxillary electrode and Ag/AgCl, KCl_{3M} (Metrohm, 6.0733.100) as reference electrode. Cyclic voltammetry data was recorded using a computer-aided potentiostat/galvanostat (AUTOLAB, PGSTAT101). Cathodic peak current (I_{pc}) in amperes corresponding to the first of the two single electron reductions of the compounds either in pure DMF or in DMF-aqueous solution were plotted against square root of potential sweep rate ($\nu^{1/2}$). Diffusion coefficient of the analyte D_0 (in $cm^2\ s^{-1}$) was calculated from the slope of the plot of peak current (I_{pc}) against square root of potential sweep rate using Randles-Sevcik equation (eq. (1))[50,51].

$$I_{pc} = (2.69\times10^5).n^{3/2}.D_0^{1/2}.A.C.\ \nu^{1/2} \quad (1)$$

n is the total number of electrons involved in the electrochemical process, A is the surface area of the electrode in cm^2, C the concentration in mol cm^{-3}, ν scan rate in V/s. Ratio of peak current at different potential sweep rates was calculated using the Nicholson equation (eq. (2))[51,52].

$$I_{pa}/I_{pc} = (I_{pa})_0/I_{pc} + 0.485\times(I_{sp})_0/I_{pc} + 0.086 \quad (2)$$

I_{pc0} denotes current at E_λ, the switching potential, and I_{pa0} refers to uncorrected anodic peak current with respect to zero current (baseline). The characteristic half wave potential ($E_{1/2}$) for each compound was determined from average of peak potentials (E_{pc} and E_{pa}) depending on the nature of the system. Difference in peak potential, $\Delta E_p = E_{pc} - E_{pa}$ was considered equal to "0.059/n" in volt unit[51].

Results and discussion

For purpurin, cyclic voltammograms were recorded under changing solvent conditions starting with pure DMF and gradually increasing the water content (Fig. 1). The electrolyte was suitably adjusted between KCl and TBAB with increase in concentration of water. Two single step one-electron reduction peaks at –634 mV ($Q^{\bullet-}$) and –1132 mV (Q^{2-}) in pure DMF were separated by ~500 mV. The two peaks moved closer to each other as the percentage of water increased. Cyclic voltammograms of purpurin in pure DMF and in different DMF-water compositions are shown in Fig. 1.

Unlike that reported earlier for sodium 1,4-dihydroxy-9,10-anthraquinone-2-sulphonate, for purpurin, two peaks did not merge to give a single step two-electron reduction at any water-DMF composition[16]. In fact, even for pure aqueous purpurin, two single step one-electron reductions were observed which is unusual compared to what is known and reported for such systems. In this case, the first peak due to semiquinone was smaller than that for quinone dianion. For

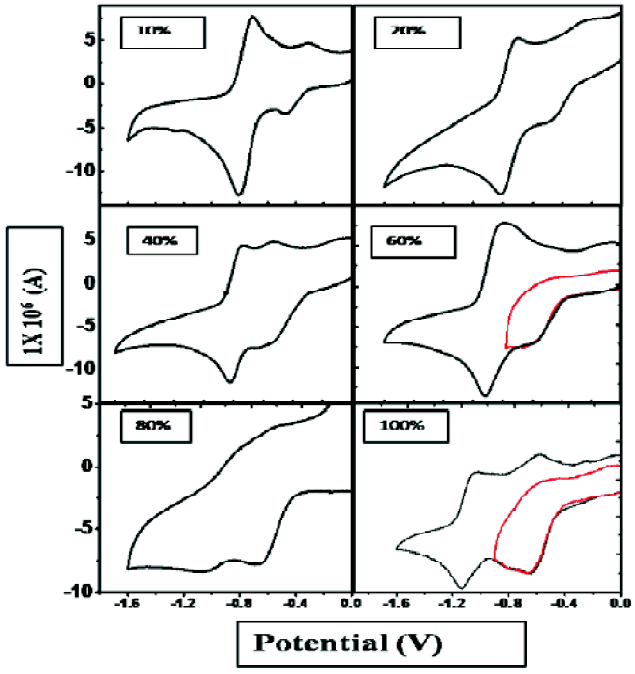
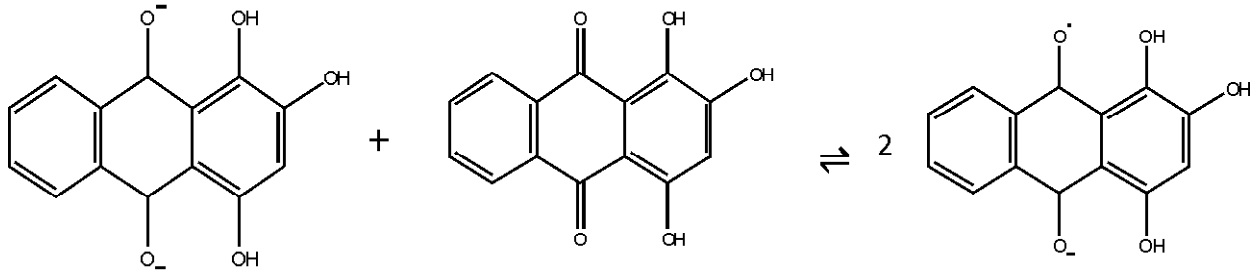


Fig. 1. Cyclic voltammograms for 0.5 mM purpurin showing two successive one-electron reductions in pure (100%) DMF and gradual shifting of peaks as percentage of water increased to produce compositions of 80%, 60%, 40%, 20% and 10% DMF. Glassy carbon was the working electrode; a scan rate of 300 mV/s was applied. Red lines indicate voltammograms for which the scan was reversed immediately after the first reduction.

100% and 60% DMF (Fig. 1), voltammograms in red obtained by reversing the scan immediately after the first reduction were different from those when the scan was reversed after the second reduction. For these two solvent compositions, oxidation peak current for voltammograms in black i.e. when purpurin was reduced to quinone-dianion and then reversed was more than the ones in red (when the scan was reversed immediately after the first reduction). This difference in anodic wave in terms of current is an indication of a difference in semiquinone generation in the two cases. When reduction of purpurin is allowed to proceed to quinone-dianion, a chemical reaction responsible for an increased anodic peak current occurs, indicative of the formation of some extra semiquinone. In fact, semiquinone formation is greater when the scan is reversed after the second reduction suggestive of comproportionation between Q^{2-} and Q forming $Q^{\bullet-}$ that shows up during the conversion of $Q^{\bullet-}$ to Q as an increase of the anodic wave[16,18,50,53].

The first reduction is almost completely reversible, while the second, quasi-reversible. At each DMF-water composition when the scan was reversed immediately after the first reduction, the peak current due to the anodic wave ($Q^{\bullet-}$ to Q) was less than if it were reversed after the second reduction (after Q^{2-} formation) serving as an evidence for extra semiquinone formed if the scan was allowed to proceed to the second one-electron reduction[50,53]. What is important here is that anthracyclines or hydroxy-9,10-anthraquinones apart from forming semiquinone directly (i.e. if the first step of the two-step one-electron reduction occurs) can also form semiquinone through comproportionation while they function as drugs in biological systems. Therefore, even if a reducing agent present in a biological environment is unable to reduce a hydroxy-9,10-anthraquinone or an anthracycline by one electron forming semiquinone but reduces it to quinone di-anion, even then semiquinone radical anion may form making it an extremely crucial intermediate for interaction with biological targets[54]. Semiquinones also disproportionate to quinone di-anion and quinone depending on the medium and prevailing conditions. It may react with molecular oxygen to form superoxide radical anion[1,4,7,8,24,26,28,37, 51]. The semiquinone radical anion is hence an important intermediate with a lot of significance in anthracycline related biology[23,24,26,28,37,54].



Scheme for comproportionation of quinone dianion (Q^{2-}) and free quinone (Q)

Table 1. Reduction potentials (E_1 and E_2), comproportionation constants (K_{comp}) and diffusion coefficient (D_0) of purpurin at different compositions of aqueous-DMF

% DMF	% H_2O	E_1 (mV)	E_2 (mV)	K_{comp}	D_0 ($cm^2 s^{-1}$)
100	0	–634	–1132	2.6×10^8	4.0×10^{-6}
80	20	–639	–1015	2.3×10^6	2.8×10^{-6}
60	40	–600	–913	2.0×10^5	2.3×10^{-6}
40	60	–513	–817	1.4×10^5	2.1×10^{-6}
20	80	–488	–812	3.0×10^5	1.9×10^{-6}
10	90	–476	–805	3.7×10^5	0.5×10^{-6}

Results in Table 1 indicate as percentage of water increases, potentials for the two reductions change and there is also observed a change in the nature of the voltammograms suggesting electrochemical reduction of purpurin is influenced by solvent polarity (protic and aprotic solvents). At 80% DMF, the two successive reduction waves are much closer to each other (–639 mV and –1015 mV respectively) than in pure DMF. The gap between two peaks kept decreasing upto 10% DMF when voltammograms showed a very small peak for the first reduction but an intense peak for the second (Fig. 1). Change in formal electrode potentials for successive one-electron reduction peaks for purpurin in different aqueous-DMF compositions are shown in Table 1.

Considering comproportionation, ($Q^{2-} + Q = 2Q^{\bullet-}$), the comproportionation constant (K_{comp}) was determined for all solvent compositions using eq. (3) (Table 1).

$$K_{comp.} = \exp[-F(E_2 - E_1)/RT] \quad (3)$$

F is Faraday, R, molar gas constant, T, temperature, E_1 is the formal potential for the first reduction and E_2 is for the second. Table 1 shows as concentration of water increased, K_{comp} decreased indicating increase in water provides stability to the quinone di-anion (Q^{2-}) for which its tendency to interact with a free quinone (Q) diminishes, affecting comproportionation rates.

In an earlier study on purpurin in pure DMF, we established comproportionation by incorporating a homogeneous chemical reaction using simulation[16]. Results showed the simulated data to be in good agreement with experiments[16]. In this study, varying compositions of aqueous-DMF solutions of purpurin were analyzed. A similar behavior suggests

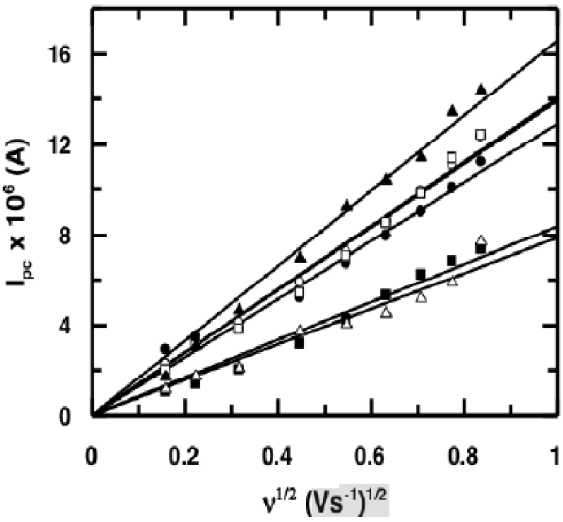


Fig. 2. Dependence of cathodic peak current on one-electron reduction of purpurin in different aqueous-DMF mixtures at pH 7.5. (= 100% DMF, Δ = 80% DMF, = 60% DMF, □ = 40% DMF, ● = 20% DMF, ○ = 10% DMF).

semiquinone was generated by comproportionation when the scan was reversed after the second reduction[16].

A plot of current associated with first reduction (I_{pc}) against square root of scan rate is linear. Since all plots passed through the origin it indicates reduction was diffusion controlled with no adsorption on the electrode surface. The diffusion coefficient (D_0) for purpurin was determined using eq. (1). Formal electrode potentials determined for the first and second reduction steps were plotted against concentration of DMF. Extrapolation of straight lines to 0% DMF (i.e. pure aqueous medium) enabled the determination of successive reductions in pure water from the graph. Thus reduction potentials (E_1 and E_2) for purpurin in pure aqueous medium were –473 mV and –803 mV respectively. Therefore, difference in peak potentials for purpurin when the solvent is pure water is 330 mV. This being reasonably large indicates why in a completely aqueous media, purpurin shows two single step one-electron reductions. This observation is different from what we reported earlier for 1,4-dihydroxy-9,10-anthraquinone-2-sulphonate where the difference between two peaks in aqueous solution could only be obtained from the graph and was much less (~ 58 mV)[50].

For purpurin, even experimentally the two peaks did not merge to a single wave one step two-electron reduction in

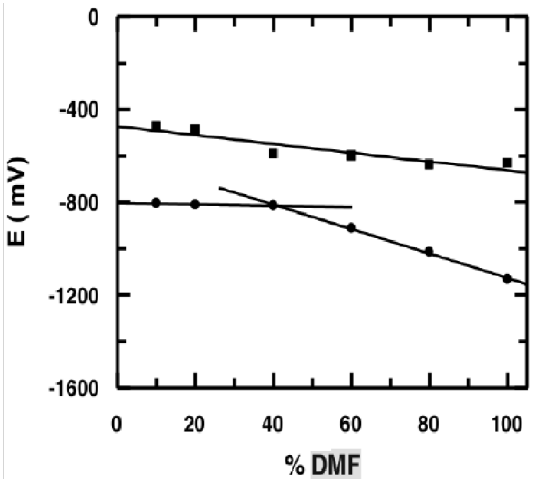


Fig. 3. Change of formal electrode potential on solvent composition: first one- electron reduction potential, E_1 ( ) and second one-electron reduction potential, E_2 (●).

pure aqueous media unlike that observed earlier[16]. This slightly an out of the way observation for purpurin in aqueous phase could be due to a tautomery that leads to the presence of two distinct species in equilibrium in water. This is quite a rare situation but has already been proposed in the past by several authors[55–57]. Although we obtained two peaks for purpurin in aqueous solution a graphical evaluation (Fig. 3) was necessary owing to poor solubility of purpurin in water at pH ≤ 7.4, where the experimentally observed peaks determined at low concentrations might have some error associated with them. Hence, theoretical evaluation of E_1 and E_2 for two successive reductions in pure water using the graphical extrapolation technique was very useful. In fact, the potentials obtained experimentally for the reduction of purpurin in pure water were close to those obtained from Fig. 3.

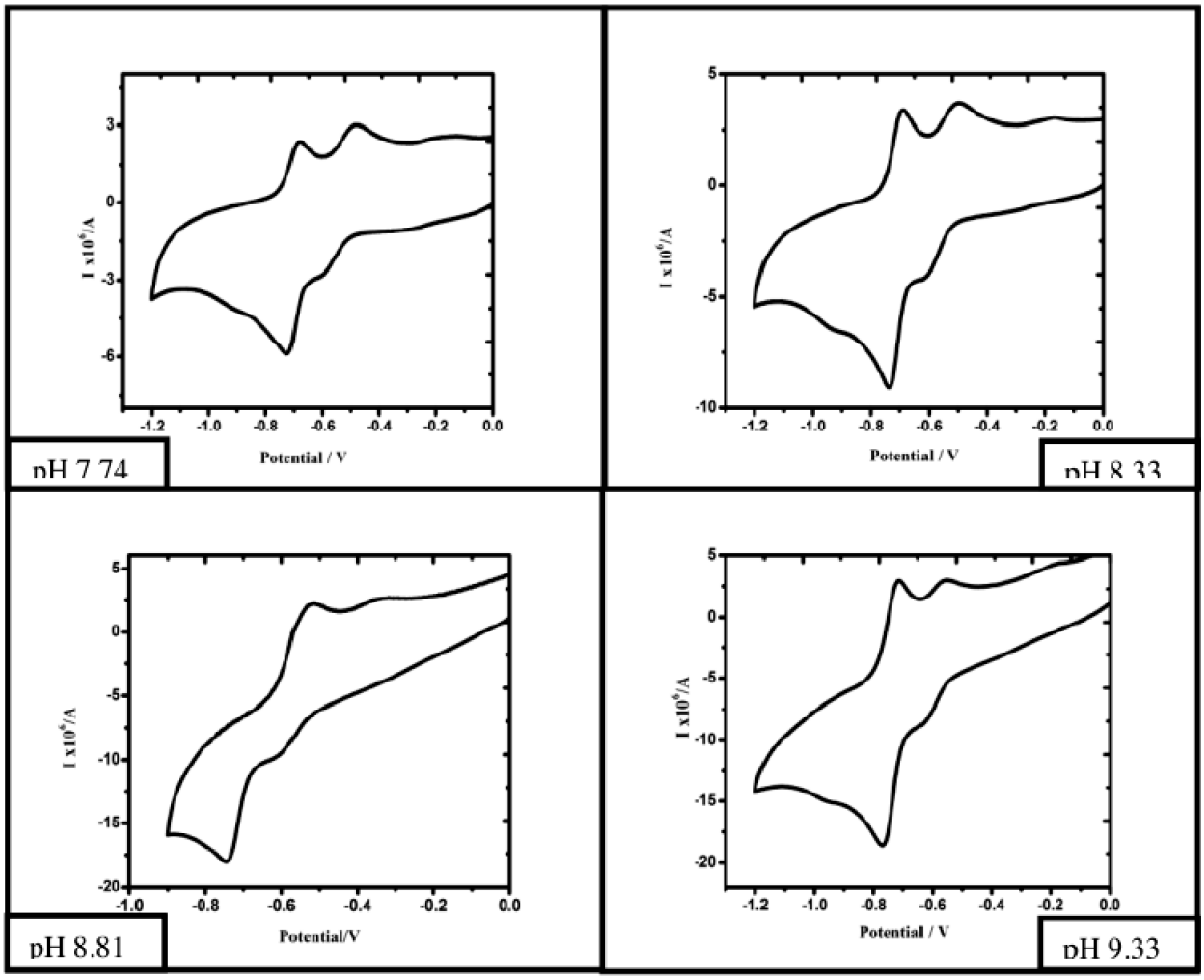


Fig. 4. Cyclic voltammogram of 0.5 mM purpurin showing two successive one-electron reductions in 0.1 *M* KCl in aqueous solution at different pH on a glassy carbon electrode at a scan rate of 300 mV/s.

To understand the influence of pH on peak potentials, cyclic voltammetry was performed on purpurin at different pH. Voltammograms indicate, at all pH, in the range from 7.45 to 9.33, the first reduction peak (E_{pc1}) was obtained as a shoulder having weak intensity while the second (E_{pc2}) was prominent (Fig. 4). E_{pc1} and E_{pc2} were plotted against pH. In aqueous solution, peak potentials, E_{pc1} and E_{pc2} were linear with pH; slopes were 14.36 mV/pH for E_{pc1} and 33.60 mV/pH for E_{pc2} (Fig. 5).

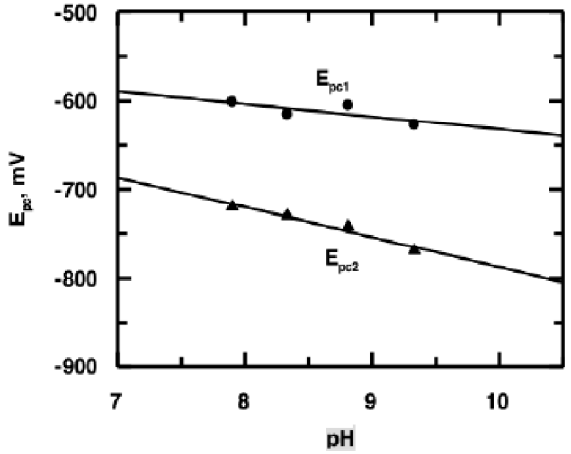


Fig. 5. Change of cathodic peak potentials (E_{pc1} and E_{pc2}) for the first single step one-electron reduction and the second single step one-electron reduction of purpurin with pH.

To see if there were changes in the electrochemical behavior of a complex of purpurin with change in solvent composition, similar experiments were performed with a Mn(II) complex of purpurin[35]. For the complex, although two peaks were obtained, they appeared at more negative potential than purpurin (Fig. 6). At 100% DMF, the first peak was found at –700 mV while the second appeared at –1400 mV indicating complex formation makes it difficult for the quinone present in the complex to be reduced. Like that mentioned for purpurin, with increase in water, peaks moved closer to each other. At 80% DMF, the two successive reduction waves for the complex were found at –656 mV and –1075 mV respectively while at 10% DMF they were at –790 mV and –1170 mV respectively. With increase in water content, the first reduction gradually became less intense while the second was much more prominent.

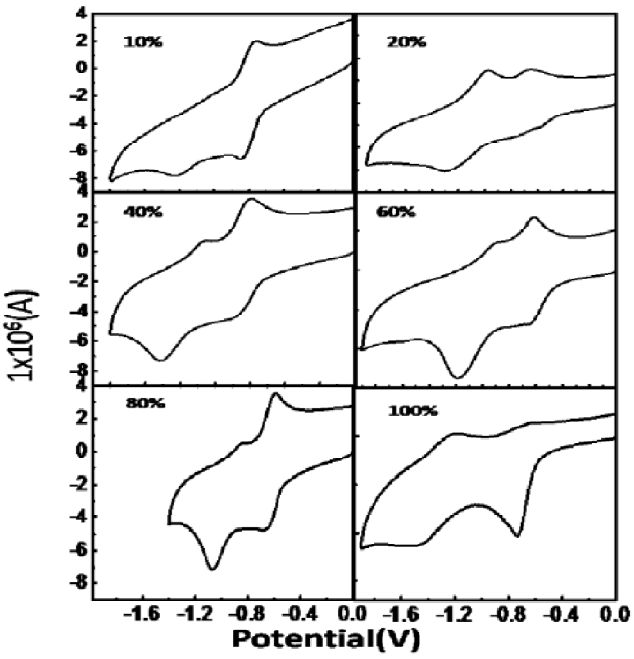


Fig. 6. Cyclic voltammogram of 0.5 mM Mn^{I}(II)-purpurin showing reduction in 0.1 *M* TBAB in pure (100%) DMF and under different aqueous-DMF compositions at pH 7.5 on a glassy carbon electrode; scan rate 300 mV/s.

What is however important for the complex is that, unlike purpurin, the second reduction peak did not increase progressively with decrease in the percentage of DMF indicating some $MQQ^{\bullet-}$ disappeared; MQQ i.e. MQ_2 represents the complex, M = Mn(II) and Q = purpurin. A decrease in concentration of the species ($MQQ^{\bullet-}$) upon formation was reported earlier for different metal complexes of anthracyclines or hydroxy-9,10-anthraquinones using NADH-cytochrome c reduction assay[12,18,20,21,23,35,36].

Reluctance on the part of free quinones (one on each ligand) in the complex to get reduced could be due to increase in electron density on the complex owing to the presence of the two hydroxy-9,10-anthraquinones as against that in purpurin. Like purpurin, for the complex also, two voltammograms were created at each aqueous-DMF solvent composition. One that was obtained after the scan was reversed immediately after the first reduction and another when the scan was reversed after the second reduction. For both situations, unlike purpurin, oxidation peak currents for the conversion of $MQQ^{\bullet-}$ to MQQ did not show much difference

in current for the two voltammograms. Almost similar anodic waves were obtained that do not indicate formation of extra semiquinone by a chemical reaction (comproportionation) following an electrochemical reduction of the free quinones in the complex. Values obtained for D_0 for the complex failed to show a regular pattern (Table 2). Experiments on cyclic voltammetry of the complex indicated three things (i) that it is difficult to generate a semiquinone on the complex, (ii) even if generated, majority gets removed in some pathway owing to the presence of a metal ion[58], (iii) generation of semiquinone by comproportionation was not observed.

Table 2. Reduction potential (E_1) and diffusion coefficient (D_0) of the Mn(II) complex of purpurin at different percentage of aqueous DMF

% DMF	% H_2O	E_1 (mV)	D_0 ($cm^2\ s^{-1}$)
100	0	–734	1.6×10^{-6}
80	20	–656	0.4×10^{-6}
60	40	–649	0.6×10^{-6}
40	60	–690	1.2×10^{-6}
20	80	–729	5.2×10^{-6}
10	90	–802	1.2×10^{-6}

Voltammagrams in Fig. 6, clearly demonstrate there is either removal of the dianion species or radical species by a mechanism that is either an EC process, or an intermolecular complex rearrangement to compensate for the extra electron density[58]. Electrochemical experiments performed on Mn(II) complex of purpurin clearly suggests substantial decrease in semiquinone formation as reported earlier through ROS generation by two independent enzyme assays; considered extremely important from a biological point of view[35]. Decreased semiquinone formation by the complex, on the one hand is beneficial, for it helps to check cardiotoxicity but on the other would affect efficacy on the target cancer cells[35]. It was however seen that in spite of decreased semiquinone formation, efficacy of this complex and other similar complexes either remained unaltered compared to their parent hydroxy-9,10-anthraquinone or were better[23,35,36]. Hence, the entire effort of using a complex of purpurin for anticancer activity instead of purpurin itself is not only justified but advantageous[35]. A previous study indicates the Mn(II) complex of purpurin inspite of showing decreased ROS generation was effective on target carcinoma cells[35].

Conclusion

Purpurin was studied in pure and aqueous-DMF solvents. It undergoes two successive one-electron reductions accompanied by comproportionation between unreacted quinone and dianions formed following a reduction by two electrons. Comproportionation resulted in the formation of semiquinone that was identified through cyclic voltammetry experiments and correlated to the importance of the semiquinone radical anion with regard to biological activity of anthracyclines or hydroxy-9,10-anthraquinones. Our approach by way of cyclic voltammetry resulted in a difference in the anodic wave corresponding to the conversion of a semiquinone radical anion to quinone ($Q^{\bullet-} \rightarrow Q$). A difference in oxidation peak current was attributed to greater presence of semiquinone due to comproportionation, a consequence of allowing the reduction of the original quinone (purpurin) to quinone dianion (Q^{2-}). Apparent comproportionation constants in pure and aqueous-DMF mixtures were calculated that indicate water influences comproportionation rates. In case of cyclic voltammetry of purpurin carried out in pure aqueous media at different pH, unlike that observed for other hydroxy-9,10-anthraquinones, where a one-step two-electron reduction wave in pure water was reported, here the first peak due to one-electron reduction, as obtained in case of aqueous-DMF mixtures was not completely gone but weak; the second one-electron reduction peak was very strong and appeared almost like a one-step two-electron reduction peak reported for most quinones in aqueous media.

Acknowledgements

BM expresses her gratitude to UGC, New Delhi for a Senior Research Fellowship. SD wish to thank the "RUSA 2.0" program of the Government of India operating at Jadavpur University under which "Research Support to Faculty Members" in the thrust area "Research in Sustainable Development" (Sanction Ref. no. R-11/438/19 dated 30.05.2019) was received. He gratefully acknowledges support received from UGC, New Delhi through funding for research on "Advanced Materials", as part of UPE II to Jadavpur University, from which funds were utilized for this work. He is grateful to the DST-PURSE program of the Government of India for financial support to the Department of Chemistry, Jadavpur University from where funds were used for this

study. He wishes to thank the UGC-CAS-II program that had just finished its tenure of five years at the Department of Chemistry, Jadavpur University for financial support.

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