Research Article

Electrochemical and spectroscopic characterization of biologically important Schiff bases

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Graphic abstract

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1 Introduction

Schiff bases are condensation products of the reaction between primary amines and carbonyl compounds. They are characterized by the presence of azomethine or imine ($-C=N$) in their structure [1]. Schiff bases attached to alkyl systems are relatively unstable and readily polymerize but those attached with aromatic systems are quite stable owing to conjugation [2]. Compounds having three nitrogen atoms in five membered ring formulates an important class of heterocycles referred as triazoles [3–7]. Heterocyclic organic compounds have vast history and bright prospects. They find use not only in medicines, pesticides, and detergents but also in polymers and material science as well as sensors [8–14]. Interest in this class emerged in early decade of twentieth century when it was found that certain derivatives of triazole class can act as convulsant and herbicides [14–16]. 1,2,4-triazoles are the subject of extensive investigations because of their various clinical, industrial, and agricultural applications. Triazoles are bestowed with extensive biological activities including antibacterial [17–19], anti-fungal [20], anti-viral [21–22], anti-cancer [23–25], anti-microbial, anti-tumour and cytotoxic activities [26–27]. Their biological applications are generally found to be related with their oxidation potential [28] that entails the transfer of a hydrogen atom through a proton coupled electron transfer reaction. This results in the formation of a resonance stabilized phenoxyl radical [29]. This resulting phenoxy radical also owe its stability to conjugation and do not lead to polymerization or chain reaction. A lone pair of electrons present on nitrogen atoms of triazole ring in addition to π electrons on the benzene ring as well as on the azomethine group is readily available for sharing to form a bond. Our selected Schiff bases contain phenol moieties along with triazoles and it further enhance its biological applications [28–30]. These types of compounds exhibit a very interesting phenomenon referred as keto-enol tautomerism due to which,

just like phenolic azo dyes, they show remarkable spectral alterations upon deprotonation [30–32]. This can be owed to different resonance structures based on acidity and alkalinity of media [32]. Colour discrepancy in different pH media also made triazol derivatives as promising pH indicator in laboratory. Another peculiar characteristic of triazoles is their solubility in variety of media despite of their acidic, neutral and alkaline conditions, thus the possibility of their investigations in media of different pH spurred us on to explore the mechanism of proton coupled electron transfer reactions of triazoles and to explore the activity of compounds in diverse pH range i.e. 2.0–12.0 [33–34]. A great variation in properties of these compounds is expected simply by altering the structure a bit and applying simple chemistry i.e. to observe the behavior by adding electron donating and electron withdrawing groups. It is continuous struggle in field of medicine to produce more and more drug derivatives with improved properties by incorporating different groups with it which can be useful in enhancing its properties. So, compounds with such structural importance are quite important in the field of medicine and detailed characterization of such compounds offer direction to comprehend the mechanism by which they exert their action.

2 Materials and methods

Compounds TMN and TMC were obtained by Sigma Aldrich and used without further purification. 2 mM stock solution of both compounds was prepared in analytical grade ethanol and fresh working solutions were prepared in 50% ethanol and 50% buffer by dilution method per desired. Britton-Robinson buffers (0.2 M ionic strength) of pH 2–12 used as supporting electrolyte and they were prepared by using a 1:1:1 mixture of 0.4 M each H_3BO_3 , H_3PO_4 and CH_3COOH adjusted to desired pH by using 0.2 M NaOH [32] (Scheme 1).

Scheme 1 Protonated and deprotonated forms of triazole and phenolic groups and their free forms

Fig. 1 CV of 1 mM TMN (a) in pH=7.0 in a potential window of ± 1.5 (b) in acidic, neutral and alkaline conditions at scan rate of 100 mVs^{-1}

Fig. 2 CV of 1 mM TMC (a) in pH=7.0 in a potential window of ± 1.5 (b) in acidic, neutral, and alkaline conditions at scan rate of 100 mVs^{-1}

2.1 Electrochemical characterization

Voltammetric studies were carried out using Autolab running with GPES 4.9 software (Eco-Chemie, The Netherlands). Measurements were carried out using a 3-electrode system in a one-compartmental electrochemical cell. Glassy carbon electrode (GCE) having surface area of 0.071 cm^2 was used as working electrode, Ag/AgCl (saturated with 3 M solution of KCl) as reference electrode and a platinum wire as counter electrode. GCE was polished with a diamond spray (particle size $1 \mu\text{m}$) and then rinsed with a jet of doubly distilled water before commencement of each experiment. Fresh surfaced electrode was then retained in desired buffer electrolyte and several DPV measurements were carried out until a steady state baseline voltammogram is attained. This method thus ensures reproducible results. Differential pulse voltammetry was carried out at a pulse amplitude of 50 mV, pulse width of

70 ms and a 5 mV s^{-1} scan rate. While in case of square wave voltammetry (SWV), the experiments were carried out at potential increments of 2 mV and a frequency of 50 Hz with 100 mV s^{-1} sweep rate. Purged solutions were used to avoid contamination due to dissolved oxygen. The temperature-controlled experiments were carried out by regulating temperature with water circulating bath (I-2400, IRMECO GmbH, Germany).

2.2 UV-Vis spectroscopy

Absorption spectra were recorded by using Shimadzu 1601 spectrophotometer and pH measurements were carried out by using INOLAB PH meter (model no. pH 720).

Fig. 3 Differential pulse voltammograms (overlaid form) of 1 mM solution of (a) TMN and (b) TMC recorded in the media of different pH at 5 mV s^{-1} scan rate

Table 1 Parameters obtained from electrochemical measurements

Compound	Peaks	an	α	n	p
TMN	Oxidation peak at pH > 7	0.49	0.49	1	1
TMC	Oxidation peak at pH > 7	0.56	0.56	1	1

2.3 Details of computational investigations

Hartree–Fock (HF) and density functional theory (DFT) were applied as computational methods to optimize the geometries of both compounds. At First, HF calculations were carried out with 6311-G basis set to optimize the geometries of these compounds. The HF-derived geometries were further relaxed by making use of DFT modeling 6311-G basis set. The Gaussian 3.0 package set of programs was applied to run these HF and DFT calculations. DFT helped to analyze the quantum chemical properties including graphics and eigenvalues of highest occupied molecular orbital (HOMO, E_{HOMO}) and lowest unoccupied molecular orbital (LUMO, E_{LUMO}) and thus the gap between HOMO and LUMO eigenvalues ($E_{\text{LUMO}} - E_{\text{HOMO}} = \Delta E$).

3 Results and discussion

3.1 Electrochemical investigation by cyclic voltammetry

Cyclic voltammograms of TMN and TMC were taken in a full potential window of $\pm 1.5 \text{ V}$ on the surface of clean GCE in a medium buffered at pH = 7.0 as shown in Fig. 1a and 2a respectively. Anodic signal appears at 0.652 V for TMN and for TMC it appears at 0.925 V. There is no corresponding cathodic signal in voltammogram of either compound indicating irreversible nature of the redox processes. The oxidation potential of TMC (0.925 V) is higher than that of TMN (0.652 V) indicating that oxidation of TMC is more difficult of the two compounds. To monitor whether these signal shows pH dependency or not, CV scans were taken in acidic (pH = 4.0), neutral (pH = 7.0) and basic (pH = 10.0) medium as shown in Fig. 1b for TMN and Fig. 2b. for TMC. The shift in peak potential with pH clearly indicates pH dependency. This is a clear indication of proton coupled electron transfer reaction [36].

Fig. 4 Plots of peak potential versus pH (a) TMN (b) TMC

Fig. 5 SWV of 1 mM (a) TMN (b) TMC in pH = 7.0 at different temperatures (inset is a plot of $\ln k_s$ versus $1/T$)

3.2 Differential pulse voltammetry (DPV) for calculating the number of protons and electrons involved in the oxidation process

The electrochemical behavior of these compounds was further investigated by differential pulse voltammetry (DPV) in a wide pH range 2.0–12.0. Differential pulse voltammograms (overlaid form) of both compounds are shown in Fig. 3. For TMN pH dependent anodic peak is observed. Oxidation potential of TMN is less than that of TMC at corresponding pH. It can be attributed to fact that TMN has more electron donating group (naphthalene) attached to it so this increases the electron density on the ring and thus make the removal of electron hence oxidation more facile. Oxidation of TMC is difficult comparatively because Chloro (–Cl) group induces withdrawing character decreasing the electron density and thus oxidation is somewhat difficult [37].

Peak width at half height ($W_{1/2}$) is a useful parameter which can be used to find the number of electrons involved in the subsequent oxidation steps using following expression.

$$W_{1/2} = \frac{3.52RT}{\alpha nF} \quad (1)$$

From Nernstian slope of E_p vs. pH, it can be deduced that there is involvement of equal number of electrons and protons in oxidation processes of both compounds.

$$\frac{dE_p}{dpH} = \frac{0.059p}{\alpha n} \quad (2)$$

pK_a can be found from inflection point of E_p vs. pH plot. The number of electrons and protons involved in redox

reaction along with transfer co-efficient α were found from DPV using given formulae and E_p vs. $\log \nu$ plot.

$$W_{1/2} = \frac{3.52RT}{\alpha nF} \quad (3)$$

$$E_p - E_{p/2} = \frac{1.857RT}{\alpha nF} \quad (4)$$

Number of electrons and protons involved in each oxidation peak along with values of α are listed in Table 1.

Apparent acid dissociation constant is calculated from inflection point of E_p vs. pH as shown in Fig. 4 that comes out around 6.5 for TMN and 7.9 for TMC.

3.3 Evaluation of kinetic and thermodynamic parameters by square wave voltammetry (SWV) at different temperatures

Influence of temperature on the oxidation signal was monitored and it was found that peak potential shift

cathodically as temperature rises as indicating facile oxidation at high temperatures.

Square wave voltammograms of 1 mM of solutions of selected compounds in 50% Ethanol and 50% BRB of pH = 7.0 were recorded at different temperatures given in Fig. 5. This was employed to evaluate various thermodynamic parameters like $\Delta G^\ddagger$, $\Delta H^\ddagger$, $\Delta S^\ddagger$ along with E_a and diffusion co-efficient D . As peak current show dependency on temperature, so Reinmuth expression was employed to evaluate heterogeneous electron transfer rate constant at different temperatures of 1 mM analyte solution in buffer of pH = 7.0

$$I_p = nFAk_s C \quad (5)$$

where I_p is the peak potential, n number of electrons involved in redox reaction, A is the area of electrode used, C is concentration of analyte and F is Faraday's constant.

$\Delta G^\ddagger$, $\Delta H^\ddagger$ and $\Delta S^\ddagger$ at different temperatures were evaluated by using following simple relations [39].

$$\Delta G^\ddagger = 5778.8(5.096 - \log k_s) \quad (6)$$

Table 2 Kinetic and thermodynamic parameters calculated from oxidation peak of TMN and TMC

Compound	Temperature/K	$k_s/10^{-3} \text{ cm s}^{-1}$	$E_a/\text{kJ mol}^{-1}$	$\Delta G^\ddagger/\text{kJ mol}^{-1}$	$\Delta H^\ddagger/\text{kJ mol}^{-1}$	$\Delta S^\ddagger/\text{J K mol}^{-1}$	$D/10^{-6} \text{ cm}^2 \text{ s}^{-1}$
TMN	288	1.04	15.85	46.68	13.46	-115.35	2.26
	298	1.34		46.06	13.37	-109.68	3.72
	308	1.56		45.66	13.29	-105.08	5.12
	318	1.97		45.08	13.21	-100.23	8.07
	328	2.33		44.66	13.13	-96.14	11.3
	288	0.71		47.63	16.14	-109.36	1.06
TMC	298	0.94	18.53	46.92	16.05	-103.58	1.86
	308	1.42		45.90	15.97	-97.19	4.19
	318	1.65		45.53	15.88	-93.25	5.65
	328	1.76		45.37	15.80	-90.13	6.8

Fig. 6 Mulliken charge distribution on (a) TMC (b) TMN

On using Arrhenius type equation and by plotting $\ln k_s$ vs. $1/T$, value of activation energy can be found which is useful in determining the values of $\Delta H^\ddagger$ at corresponding temperatures by utilizing following relation [40]

$$\Delta H^\ddagger = E_a - RT \quad (7)$$

While knowing the values of $\Delta G^\ddagger$ and $\Delta H^\ddagger$ at different temperatures, value of $\Delta S^\ddagger$ at corresponding temperatures can be evaluated by using following well known relation

$$\Delta G^\ddagger = \Delta H^\ddagger - T\Delta S^\ddagger \quad (8)$$

Temperature elevation intensified the peak current which was attributed to the fact that as temperature rise, solvation sphere between the electroactive moiety of the analyte and electrode surface shrinks, subsequently increasing the sensitivity of electrode and making the approach of analyte more viable towards electrode. Moreover, increase in temperature resulted in cathodic shift of peak potential. Facile oxidation with increased temperature can be attributed to more diffusion due to less viscosity of the system with increased temperature which is also obvious from the results of diffusion co-efficient obtained at higher temperatures i.e. value of diffusion co-efficient proliferates with increased temperature.

Kinetic and thermodynamic parameters of both TMN and TMC are listed in Table 2. Positive values of $\Delta G^\ddagger$ and $\Delta H^\ddagger$ indicates non-spontaneous and endoergic nature of redox process, decrease in values of these parameters with increased temperature is an indication that process become more and more spontaneous and degree of irreversibility decreased with increased temperature.

Negative value of entropy shows that analyte is more systematically arranged on the electrode surface then in the solution. Value of entropy became less negative with increasing temperature and it indicates that electrode reaction becomes less ordered with increased temperature. Dependence of $\Delta G^\ddagger$ and $\Delta S^\ddagger$ on temperature implies that processes are both enthalpy and entropy driven [38–40]. This also shows that these redox processes are nonspontaneous, and entropy opposed but become facile to some degree as temperature increases.

4 Computational studies

For optimized geometry of molecules, the energy related parameters like total electronic energy, energies of frontier orbitals (HOMO and LUMO), electronic distributions (charge densities), dipole moments, vertical electronegativity etc. were calculated by carrying out DFT calculations, 6311-G basis set. [45, 46] Energies of frontier orbitals and charge distribution of atomic structure make it possible to predict possible oxidizable and reducible moiety in the structure of molecule. [47] Charge distribution on these compounds is shown in Fig. 6.

In the discussion of relative reactivity another useful parameter is vertical electronegativity χ_v [41]

$$\chi_v = \frac{I.P + E.A}{2} \quad (9)$$

Or by considering Koopmans's theorem [42].

Table 3 Quantum mechanical parameters obtained by DFT calculations

Compound	E_{HOMO} (eV)	E_{LUMO} (eV)	ΔE (eV)	I.E (kJ/mol)	E.A (kJ/mol)	Dipole moment/ (D)	Electronegativity
TMC	−0.348	−0.052	0.296	33.53	5.01	5.20	0.043
TMN	−0.244	−0.075	0.169	23.50	7.23	3.56	0.159

Fig. 7 Pictorial representation of untreated cells and Hela cell cultures containing 150 μM of compounds

Fig. 8 Electronic absorption spectra of TMC and TMN at 20 mM concentration

$$\chi_v = -\frac{1}{2}(E_{\text{HOMO}} + E_{\text{LUMO}}) \quad (10)$$

Computationally obtained parameters of these compounds are reported in Table 2.

HOMO and LUMO are termed as frontier orbitals in conventional physics [43]. These orbitals play a key role not only in electrical and optical properties of a compound but also in its chemical reactivity. According to classical description HOMO is often associated with electron donating ability. The higher value of E_{HOMO} is direct indication of tendency of electron donating. $E_{\text{LUMO}} - E_{\text{HOMO}} = \Delta E$ gap is another stability index.

The low value of $E_{\text{LUMO}} - E_{\text{HOMO}} = \Delta E$ implies high chemical reactivity and low kinetic stability [44]. ΔE is less in case of TMN, so it can be rationalized that it is more reactive than TMC. The findings regarding HOMO/LUMO energies and their energetic difference in addition to other intrinsic quantum chemical properties are collected in Table 3.

Literature survey reveals that compounds having high value of E_{HOMO} are easily oxidizable while those having low value of E_{LUMO} are easily reducible [45–47]. TMN has higher value of E_{HOMO} , as indicated in Table 2, so its oxidation is comparatively easy. This result is also complemented by low oxidation potential value of this compound obtained by electrochemical results.

4.1 Biological evaluation

In view of various possible biological applications of selected compounds, a few tests were run to evaluate their activity.

4.1.1 Cytotoxicity

Cytotoxic effect of selected compounds was checked by SRB assay on Hela cancer cell line. Cells were exposed to 150 μM solution of compounds investigated for 24 h and then SRB assay was exploited to measure their cytotoxic effects. Untreated cells were taken as control. Figure 7. shows the results obtained after exposing cells to compounds under investigation. Both compounds retain cellular content of the control and there is no visible change indicating that these compounds are non-toxic at this concentration.

Fig. 9 Electronic absorption spectra of 20 μM solution of **a** TMN and **b** TMC. The embedded plots display absorbance values as a function of pH

Fig. 10 UV-Vis spectra of TMN and its oxidation product

4.2 Spectroscopic studies

Absorption spectra and molar extinction co-efficient depends upon the nature of solvent, electron donating and electron withdrawing substituents, inter or intra

molecular hydrogen bonding, steric effects, pH dependent formation of resonance structures having different conjugation as compared to parent compounds. Figure 8 shows the spectrum of all the selected compounds in stacked form. It has been found from literature review that a small peak appears for only triazole at around 205 nm.

So, signal appearing in case of all the compounds around 210–230 nm.

(TMN = 226 nm, TMC = 223 nm is attributed to π - π^* transition due to triazole moiety. A red shift observed in compounds may be due to attached aromatic system.

As is obvious from colour change (Analyte solution is colourless in acidic medium and become yellow to brownish as alkalinity is increased), there is different response of these compounds in different pH media. This can be attributed to different resonance structures based on donor-acceptor chromogens these compounds possessed by these compounds capable of changing colour with variation in pH [51]. Sensitive acid-base reaction property of compound can be explained by formation of π -system within the compound's structure.

UV-Vis spectroscopy was employed to monitor the pH dependent equilibrium that developed in compound in

Scheme 2 Proposed oxidation mechanism of TMN

Scheme 3. Proposed oxidation mechanism of TMC

acidic media and its deprotonated form in basic media. Alkylation of triazol ring is expected to increase its withdrawing character and leads to red shift of intermolecular charge transfer band as can be seen in Fig. 9.

4.3 Proposed electrode reaction mechanism of compounds

It has been proposed on the basis of experimental investigation and theoretical assessment that oxidation of TMN takes place by the loss of electron and proton from the attached hydroxyl group leading to the production of a radical with electron resonating from oxygen to nitrogen and mainly residing over these two sites due to more electronegative character. Thus, radical is expected to gain stability either by adsorbing over the surface of electrode through N or O or dimerization into the solution. To confirm that oxidation of TMN has taken place and some new oxidation product has been formed, oxidation product from the GCE has been scratched and its solution was formed in Ethanol. It can be seen in Fig. 4, 5 that there is hyperchromic shift in the peak attributed to triazol moiety and it also shows a bathochromic shift. A hypochromic and bathochromic shift in the peak attributed to π - π^* transition owing to benzoid system is also observed. This can be due to less availability of chromophore per molecule as oxidation leads to the production of dimers etc (Fig. 10).

Experimental investigation and theoretical assessment led us to propose that oxidation of TMC takes place by the loss of electron and proton from the attached hydroxyl group leading to the production of a radical with electron resonating from oxygen to nitrogen and mainly residing over these two sites due to more electronegative character. Thus, radical is expected to gain stability either by adsorbing over the surface of electrode through N or O or dimerization into the solution. E_p versus pH plot and half peak width value of oxidation peak suggests the loss of electron and proton from the oxidized species to yield dimer as the final product (Scheme 2).

5 Conclusion

Detailed pH and temperature responsive electron transfer mechanism of biologically active Schiff compounds were investigated with the aid of electrochemistry and spectroscopy. Results reveal that selected compounds follow irreversible, pH dependent and diffusion-controlled oxidation processes. The oxidation reactions were found entropy and enthalpy opposed. Increase in value of electron transfer rate constant with increasing temperature demonstrates the switching of reaction towards reversibility. Computational studies helped in identifying the most easily oxidizable electrophore. This not only

aids in explanation of electrochemical results but also helps in proposing the redox mechanism. Apparent acid dissociation constant was evaluated both by electrochemical and spectroscopic techniques and results were in good agreement with each other. Both compounds were found to be non-toxic up to 150 μM concentration. The current study offers useful insights about the biological action mechanism of phenolic pharmacophores containing compounds (Scheme 3).

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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