Int. J. Electrochem. Sci., 7 **(2012)** 6127 - 6133

International Journal of
ELECTROCHEMICAL
SCIENCE
www.electrochemsci.org

Short Communication

Electrochemical Calculations of Some Non-Steroidal Anti-Inflammatory Drugs: Solvent Effect and Antioxidant Activity

A. Ghaempanah[1], *S. Jameh-Bozorghi*[2,*], *M. Darvishpour*[3], *M. H. Fekri*[3]

[2] Department of Chemistry, Arak Branch, Islamic Azad University, Arak, Iran.
[1] Department of Chemistry, Toyserkan Branch, Islamic Azad University, Toyserkan, Iran.
[3] Department of Chemistry, Khorramabad Branch, Islamic Azad University, Khorramabad, Iran.
[*]E-mail: SJamebozorgi@gmail.com

Received: 25 March 2012 / *Accepted:* 28 May 2012 / *Published:* 1 July 2012

The electrode potentials of some oxicam derivatives in three solvents (MeOH, EtOH and CH_3CN) have been calculated. The calculations are carried out at the level of Hartree- Fock theory with the 6-311G basis set. The polarizable continuum model (PCM) is used to calculate salvation energies. The calculated values were compared with the experimental values. The results show that this method is likely to be useful in the prediction of electrode potentials of molecules in different solvents. In this work, solvent effect is stronger in piroxicam and tenoxicam compared with meloxicam and lornoxicam, Also antioxidant activity, in acetonitrile solvent for all of the compounds is less another solvents.

Keywords: Oxicams, Solvent effect, Antioxidant activity, Electrode potentials, Polarizable continuum model (PCM)

1. INTRODUCTION

Molecular modeling is centered on applying the fundamental laws of physics and chemistry to the study of molecules. Its ultimate aim is to create models and simulations, which can help by predicting, rationalizing, and estimating the properties of molecules and their interactions [1-6].

The ability to calculate redox potentials accurately is advantageous in a number of different areas, particularly where the experimental measurement is difficult due to complex chemical equilibria and where the design of molecules with particular redox properties is of interest [7-9].

Non-steroidal anti-inflammatory drugs (NSAIDs) are of great interest in medicine as they are widely used for mild to moderate pain relief as well as in the treatment of osteoarthritis and rheumatoid

arthritis. Their action is attributed to the inhibition of the cyclooxygenase enzyme, which in turn prevents the biosynthesis of certain prostaglandines [10].

It should be mentioned that the solvent used may affect the underlying oxidation mechanism in the case of ionizable compounds like phenols, promoting radical reaction or electron transfer, while in polar organic solvents, even ionization may be possible [11, 12].

The antioxidant activity of a compound is related to electrochemical parameters, especially its oxidation potential, which provides an estimate of the energy required to donate an electron. Indeed, the lower the oxidization potential, the more easily will the compound donate an electron and the higher will its expected antioxidant activity be [13].

The determination of the oxidation potential and, generally, the investigation of the electrochemical behavior of a compound can easily be performed by applying cyclic voltammetry.

Cyclic voltammetric results can be correlated with those coming from antioxidant protocols [14] because redox behavior of an antioxidant at an electrode is related to its behavior in chemical redox reaction with a radical [15]. Nevertheless, oxidation potentials and, hence, oxidation convenience in an electrode is affected in most cases by the solvent used due to its interactions with reactants or their intermediates [16]. Antioxidants are involved in the prevention of cellular damage. The common pathway for cancer aging and a variety of diseases. They help to protect the body from free radical damage. Free radicals are atoms or group of atoms with an odd (unpaired) number of electrons and can be formed when oxygen interacts with certain molecules. They are very unstable and always trying to capture the needed electron to gain stability. Generally free radicals attack the nearest stable molecule by stealing is electron. When the attacked molecule loses its electron, it becomes a free radical itself, beginning a chain reaction [17].

In this work, electrode potentials of oxicam derivatives in three solvents with different polarity were studied (fig. 1).

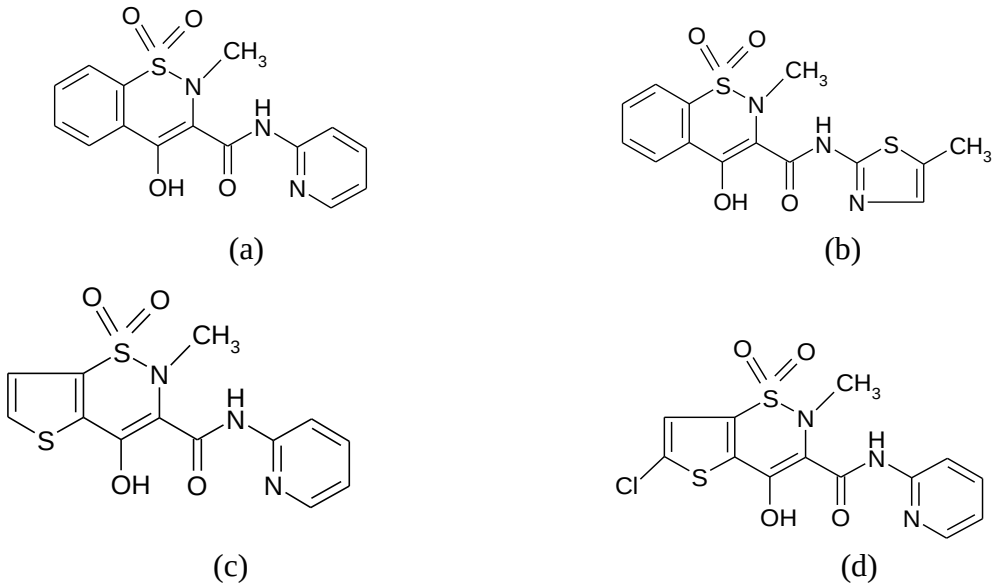


Figure 1. Structures of **a** piroxicam, **b** meloxicame, **c** tenoxicam, and **d** lornoxicam.

2. COMPUTATIONAL DETAIL

2.1. Computetional Program

In this paper, the vibrational frequencies for oxicams are calculated for validation of the structure because the molecular parameters are controlled by the structure. Furthermore, standard electrode potential of reaction for oxicams is also calculated using the optimized structure at Gaussian 03 program.

Many study results have indicated that hartee-fock theory is a powerful method for predicting the geometry and hormonic vibration of organic compounds [18-22] Therefore, the HF /6-311G with polarized continuum model (PCM) solvation containing CPCM were carried out to study the molecular structure, solvation energies, sum of electronic, thermal free energies, and the vibrational frequencies of both reduced oxicams (X) and their oxidized form (X^-) at electrode.

2.2.Method of calculations

Reaction 1 depicts the one electron oxidation reaction of the oxicams (X). The oxidized form (X^-) can also be converted to its reduced form (X) using one of the oxicams as reference (lornoxicam=L), according to the following isodesmic reaction.

$$\text{Reaction 1 :} \qquad X^- + L \rightarrow X + L^-$$

Geometry optimizations for all of the compounds were performed in gas phase and solution phase on HF/ 6-311G level of theory. The gas-phase Gibbs free energy change ($\Delta G°gas$) of reaction 1 was calculated using Eq.1.

$$\text{Eq.1} \qquad \Delta G°gas = \{G^o_{gas}(X) + G^o_{gas}(L^-)\} - \{G^o_{gas}(X^-) + G^o_{gas}(L)\}$$

The used dielectric constants were ε= 32.63 , 24,55 and 36.64 to model MeOH , EtOH and CH_3CN solution, respectively. A common practice to calculate Gibbs free-energy changes of an reaction ($\Delta G°_{total}$) is by summing $\Delta G°_{gas}$ and $\Delta\Delta G°_{solv}$ using the thermodynamic cycle of Scheme 1 and Eq. 2.

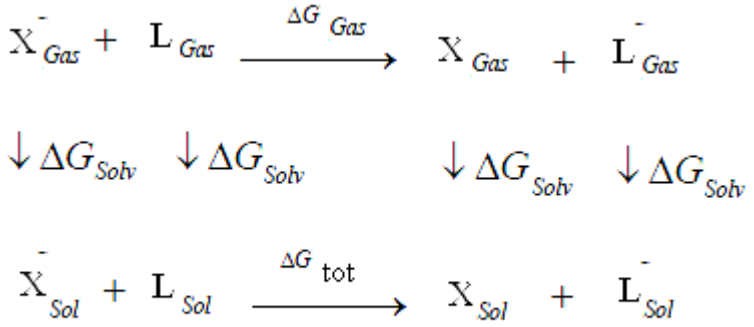
$$\text{Eq. 2.} \qquad \Delta G°_{tot} = \Delta G°_{gas} + \Delta\Delta G°_{solv}$$

$$\Delta G°_{tot} = G^o_{gas}(X) + G^o_{gas}(L^-) - G^o_{gas}(X^-) + G^o_{gas}(L) + \Delta G°_{solv}(X) + \Delta G°_{solv}(L^-) - \Delta G°_{solv}(X^-) - \Delta G°_{solv}(L)$$

Finaly, E^o is calculated according Eq. 3.

$$\text{Eq. 3.} \qquad \Delta G° = nf\,(E° - E°_{ref})$$

Where ΔG° is total free energy for reaction 1, $E°_{ref}$ is the experimental potential for a reference molecule (lornoxicam) E° is the calculated potential and F is the faraday constant (F=96500Cmol^{-1}). Experimenral values of $E°_{ref}$ were reported in reference [23].



Scheme 1. The thermodynamic cycle proposed to convert the standard Gibbs energy of an isodesmic reaction in the gas phase to the standard Gibbs energy of reaction in solution,

3. RESULTS AND DISCUSSION

The electrochemical behavior of the investigated NSAIDs was studied using computational calculations. Free energy and half-wave potentials ($E_{1/2}$) of all studied species in three solvent (MeOH, EtOH and CH_3CN) are included in Table 1-3.

In all cases, no cathodic peaks were observed in the reversed scan even at higher scan rates investigated up to 200 mvs^{-1}, showing that the oxidation of oxicams is an irreversible process[23].

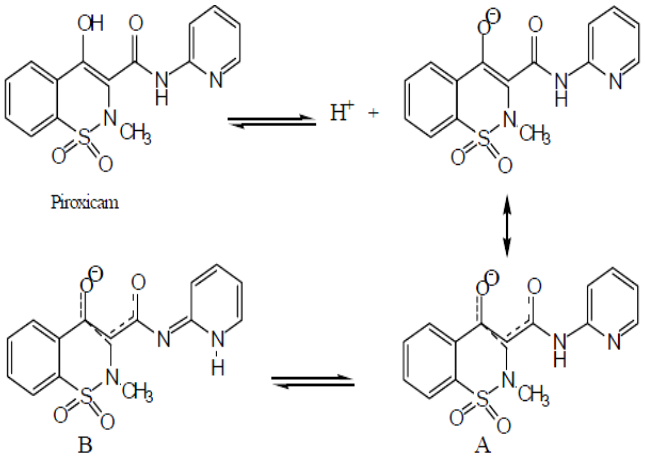
Acidic character of piroxicam stabilized tautomers was shown in scheme 2. Within oxicams, the sensitivity towards the solvent replacement is not similar. In all cases, no cathodic peaks were observed in the reversed scan even at higher scan rates investigated.

As it is shown, by decreasing the solvent polarity, the oxidation potential increases, and, therefore, the oxidation becomes more difficult.

Table 1. Gibbs of studied oxicam derivatives for both reduced (X) and (X^-) forms in the gas phase calculated using 6-311G basis set at HF level of theory.

Comp.[1]	ΔU^0_{gas} (a.u)[2]		ΔG^0_{gas} (a.u)		ΔG^0_{gas} (kj mol^{-1})
	X	X^-	X	X^-	
a	-1435.155782	-1434.626027	-1435.221511	-1434.692424	-37.8288
b	-1794.730109	-1794.240624	-1794.846656	-1794.310358	-56.7606
c	-1755.756835	-1755.234770	-1755.822630	-1755.301177	-17.9872
d	-2214.652672	-2214.137350	-2214.721944	-2214.207265	00.0000[3]

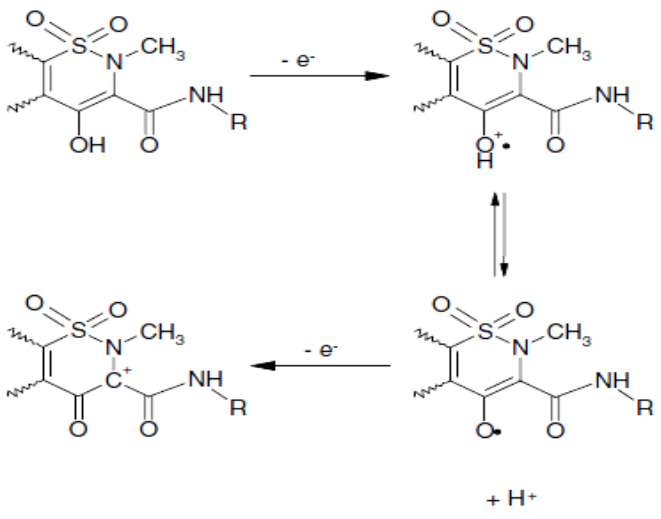
[1]See fig.1 for the list of molecules studied.
[2]The energies are in atomic units, Hartree (1Hartree=2625.49975 kj mol^{-1}).
[3]d compound is as reference.



Scheme 2. Acidic character of Piroxicam stabilized tautomers A & B.

the cases of lornoxicam and meloxicam, the peak is broadened and its position becomes disputable eventually due to the presence of a second peak. In this case rather, an E_{ap} range can be characterized. By contrast, tenoxicam and piroxicam give a defined single peak. The presence of two peaks may be justified on the basis of the oxidation mechanism. In general, oxicams' oxidation can be performed in two steps, according to the mechanism illustrated in Scheme 3.

The first step refers to the oxidation of the enolic –OH to form the corresponding free radical, which can be deprotonated(chemical step). The second step is the further oxidation of the deprotonated derivative, and the formation of a carbonyl and a positive charge localized on a carbon atom, which is stabilized by the lone pair of the neighboring nitrogen [23]. This cation is of course susceptible of nucleophilic attack by the solvent (MeOH, EtOH, and CH_3CN).



Scheme 3. Electrochemical oxidation mechanism of oxicams.

In this aspect, the peak range of meloxicam and lornoxicam observed in the presence of acetonitrile indicates that the two oxidation steps become distinct, since the first oxidation step requires relatively lower energy starting at lower potential, while the second oxidation, demanding higher energy, takes place at higher oxidation potential. On the contrary, the single peak of piroxicam and tenoxicam at higher potential implies that both oxidation steps require higher energy, taking place simultaneously at higher potentials.

Table 3 shows piroxicam and tenoxicam are stronger affected by solvent replacement, while the corresponding phenomenon is observed for meloxicam and lornoxicam at less polar solvents.

The results (Table 3) shows calculation potential values for the four compounds, in the presence of methanol and ethanol solvents are close together. The values for piroxicam and meloxicam are higher than lornoxicam and tenoxicam. On the other hand, any amount, oxidation potentials a molecule is lower, more easily oxidized. Consequently, its antioxidant power, is higher. The values of E, in all four studied compounds in acetonitrile solvent, in general, is higher than the other two solvents. Also, we conclude from Table 3, which $E_{1/2}$ for tenoxicam and lornoxicam in three solvents is less. Thus, antioxidant activity, for these two compounds will be more. In addition, antioxidant activity, in acetonitrile solvent is less than all.

Table 2. Solvation energies of the studied oxicams in reduced (X) and oxidized (X^-) forms ($\Delta G_{solv.}$) in MeOH, EtOH and CH_3CN.

Comp.	Solvent	$\Delta G^0_{solv.}$ (a.u)		$\Delta\Delta G^0_{solv.}$ (kj mol^{-1})	$\Delta G_{tot.}$ (kj mol^{-1})
		X	X^-		
a	MeOH	-0.269889	-0.324503	11.254	-26.471
b		-0.251612	-0.315382	35.299	-21.460
c		-0.231328	-0.286163	11.841	-06.146
d		-0.215959	-0.266284	00.000	00.000
a	EtOH	-0.266548	-0.322956	17.365	-20.462
b		-0.250534	-0.312819	32.792	-23.968
c		-0.229944	-0.284189	11.683	-05.501
d		-0.214472	-0.264267	00.000	00.000
a	CH_3CN	-0.252885	-0.310512	17.989	-19.838
b		-0.236018	-0.299701	33.889	-22.870
c		-0.216420	-0.271773	12.019	-05.967
d		-0.200091	-0.250866	00.000	00.000

Table 3. Gibbs energies of reaction 1 in MeOH EtOH and CH_3CN.and the calculated standard electrode potentials of studied molecules in (V).

Comp.	MeOH		EtOH		CH_3CN	
	$E^0_{cal.}$ (V)	$E^0_{exp.}$ (V)	$E^0_{cal.}$ (V)	$E_{0exp.}$ (V)	$E^0_{cal.}$ (V)	$E^0_{exp.}$ (V)
a	0.935	0.710	0.882	0.780	1.030	0.850
b	0.882	0.710	0.918	0.720	1.067	-1
c	0.723	0.640	0.727	0.690	1.450	0.840
d	0.660	0.660	0.670	0.670	0.830	0.830

4. CONCLUSIONS

The underlying solvent has a considerable influence to the oxidation potentials of the investigated NSAIDs and, hence, to their antioxidant activity, mainly by affecting the solvation of their more polar intermediates. The peak broadening of oxicams, observed for a certain fraction of acetonitrile in water, imply complex electrochemical behavior and the presence of an oxidation mechanism with two successive oxidation steps. Solvent effect is stronger in the case of piroxicam and tenoxicam compared with meloxicam and lornoxicam,

In conclusion, computational studies for calculation of $E^0_{1/2}$an be considered as a suitable to evaluate the antioxidant activity with application to both pure substances and to pharmaceutical formulations.

References

1. S. A. Beyramabadi, M. R. Bozorgmehr and A. Morsali, *Int. J. of the Phys. Sci*., 6 (2011) 5726-5730.
2. Y. Yositake, H. Nakagawa and K. Harano *Chem. Pharm. Bull.* 49(11) (2001) 1433-1439.
3. P. Hazarica, R. L. sarma, M. Karim, B. Bezbaruah, R. Kalita and C. Medhi *Indian J. Chem.* 48 (2009) 520-525.
4. T. Wang, G. Brudvig and V. S. Batista *J. Chem. Theory Comput.* 6 (2010) 755–760.
5. S. Angelova, V. Enchev, N. Markova, P Denkova and K. Kostova *Journal of Molecular Structure (Theochem)* 711 (2004) 201–207.
6. T. Güray, E. Açıkkalp, C. Öğretir and S. Yarlıgan *Journal of Molecular Graphics and Modelling* 26 (2007) 154–165.
7. M. Namazianm and P. Norouzi J. Electroanal. Chem. 573 (2004) 49-53.
8. C. A. Reynolds *J. Am. Chem. Soc.* 112 (1990) 7545.
9. C. A. Reynolds, P. M. King and W. G. Richards *Nature* 334 (1988) 80.
10. K. Parfitt and W. Martindale (1999) The complete drug reference. Pharmaceutical, London
11. L. Valgimigli, J.T. Banks, K.U. Ingold and J. Lusztyk *J. Am. Chem. Soc.* 117 (1995) 9966–9971.
12. M.C. Foti, C. Daquino and C. Geraci *J Org Chem* 69(2004) 2309–2314.
13. S. Mannino, O. Brenna, S. Buratti, M.S. Cosio *Electroanalysis* 10 (1998) 908–912.
14. K.E. Yakovleva, S.A. Kurzeev, E.V. Stepanova, T.V. Fedorava, B.A. Kuznetsov and O.V. Koroleva *Appl Biochem Microbiol* 43 (2007) 661–668.
15. S. Martinez, L. Valek, J. Resetic, D. Ferenec Ruzic *J. Electroanal. Chem.* 588(2006) 68–73.
16. D.S. Bhuvaneshwari, K.P. Elango *Int J Chem Kinet* 39 (2007) 289–297.
17. G. Bounous and J. H. Molson *anticancer research* 23 (2003) 1411-1416.
18. P. Scott, L. Radom *J. Phys. Chem.* 100 (1996) 16505.
19. P. Denis, O. N. Ventura, *J. Mol. Struct.* 537 (2001) 173.
20. A. J. Abbowicz-Bienko, D. C. Bienko, Z. Latajka *J. Mol. Struct.* 552 (2000) 165.
21. R. Jacob, G. Fiscker *J. Mol. Struct.* 613 (2002) 175.
22. K. Banclersen, M. Langgard, J. Sparget-Larsen, *J. Mol. Struct*. 509 (1999) 153.
23. F. Tsopelas, M. Ochsenkühn-Petropoulou, N. Zikos, E. Spyropoulou, I. Andreadou and A. Tsantili-Kakoulidou *J Solid State Electrochem* (2010).