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RELATIONSHIP BETWEEN CATHODIC PEAK POTENTIALS AND THEORETICALLY CALCULATED LUMO ENERGIES OF SOME 2-PHENYL BENZOXAZOLE DERIVATIVES

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ABSTRACT

Cathodic peak potentials ($E_{p,c}$) of twentyseven microbiologically active 2-phenyl-benzoxazole derivatives containing both electron withdrawing and electron donating groups on benzoxazole kernel and on phenyl moiety were measured by cyclic voltammetry in acetonitrile. The $E_{p,c}$ values were in the range of -2.8 V to -3.10 V except for those compounds which contained -NO_2 substituent at position-5. Those benzoxazole derivatives possessing a NO_2 group all had substantially lower reduction peak potentials, ranging from -1.60 to -1.80 V versus $Ag°/Ag^+$. The lowest unoccupied molecular orbital (LUMO) energies of these molecules were calculated by adopting the Hückel molecular orbital (HMO) approach. A linear relationship was found to be existing between the measured $E_{p,c}$ values and the calculated LUMO energies.

INTRODUCTION

Benzoxazole derivatives substituted at position-2 have been studied extensively, trusting that this position is decisive for the biological activity. Among these activities, antimicrobial[1-3], antihelmentic[4,5], antiinflammatory[6,7] and antidepressive[8] activities have been reported. Evans et al.[6,9] showed that 2-para substituted phenyl-5-benzoxazolealkanoic derivatives have the highest antiinflammatory activity as compared to their analogous compounds. Hence, in the present work, benzoxazoles which contain substituents on position-5 of the benzoxazole moiety and on the para position of the phenyl group attached to position-2 were studied. These derivatives which structurally resemble the heterocyclic bases present in the living organisms, such as adenine and guanine, have antimicrobial activity. Their activity could be due to the inhibition of nucleic acid synthesis by deactivating DNA dependent RNA polymerase, thus blocking the formation of mRNA.

Hückel showed rather early that how the reduction of aromatic compounds agrees with the simple molecular orbital picture in which additional electrons have been added to antibonding molecular orbitals of the π-systems[10]. Maccoll showed that the polarographic half-wave reduction potentials of several unsaturated hydrocarbons are linearly correlated with the HMO energy of the lowest unoccupied molecular orbitals of the hydrocarbons[11]. This correlation was rapidly confirmed and interpreted[11,13].

The theoretical relations between $E_{1/2}$(red) and C_{m+1} (LUMO) have been proposed and extensively studied by Hoijtink[14,15] and it has also been reported that the modified Hückel molecular orbital (HMO) calculations predict the observed differences on $E_{1/2}$(red) of the related systems[16].

In one of our quantitative structure activity relationship (QSAR) studies[17], it has been demonstrated that the antimicrobial activity of benzoxazole derivatives is a function of the theoretically obtained highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) energies[15].

Anodic and cathodic peak potentials of various molecules especially unsaturated ones can be measured by cyclic voltammetry (CV) in nonaqueous solvents[18-21]. Cathodic peak potential ($E_{p,c}$) is the potential at which an electron (or more) is transferred, possibly into LUMO of the molecule from the cathode. Then a correlation is expected between the energy of the lowest unoccupied molecular orbital, C_{m+1} and $E_{p,c}$ of structurally similar molecules.

In the present study, the relationship between the measured cathodic peak potentials ($E_{p,c}$) and the theoretically obtained LUMO energies for certain benzoxazole derivatives was investigated. For the measurement of $E_{p,c}$ values, cyclic voltammetry was employed. The LUMO energies were calculated by the Hückel molecular orbital consideration[15].

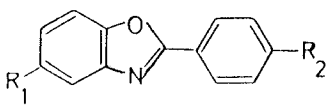
EXPERIMENTAL

The benzoxazole derivatives (Table 1) were synthesized by heating the appropriate benzoic acid derivatives with 4-substituted-2-aminophenols in polyphosphoric acid. The details of the syntheses are given elsewhere[22-26]. The compounds were further purified by successive recrystallizations until a single spot was observed on t.l.c.

The methods for purification of solvent and synthesis of electrolyte have been described previously[21]. Cyclic voltammograms were obtained in acetonitrile on Pt bead versus $Ag°/Ag^+$, under nitrogen atmosphere at room temperature using tetrabutylammonium tetrafluoroborate (TBAF) as the supporting electrolyte. The voltage scan rate was 200 mV/s. The potential range was 0 to -3.20 V. A Bank potentiostat Wenking model ST-88 and a function generator wenking model VSG 83 were used to program the potential.

TABLE 1.

$E_{p,c}$ values and the calculated LUMO energies of various benzoxazoles



No.	R_1	R_2	$E_{p,c}/V^a$	C_{LUMO}/β
1	H	H	-2.90	-.5387
2	H	OMe	-2.85	-.5698
3	H	t-Butyl	-2.80	-.5982
4	H	Cl	-2.80	-.5468
5	H	Br	-2.85	-.5444
6	H	NH_2	-3.05	-.5792
7	H	NHMe	-3.10	-.5786
8	Cl	Me	-2.85	-.5983
9	Cl	Et	-2.85	-.5875
10	Cl	NHCOMe	-3.00	-.5770
11	Cl	NHMe	-3.00	-.5787
12	NO_2	H	-1.75	-.0197
13	NO_2	Me	-1.90	-.0203
14	NO_2	t-Butyl	-1.75	-.0203
15	NO_2	NH_2	-1.60	-.0202
16	NO_2	Cl	-1.60	-.0198
17	NO_2	Br	-1.75	-.0197
18	NH_2	H	-2.90	-.5393
19	NH_2	Et	-2.90	-.5874
20	NH_2	Br	-2.85	-.5450
21	NH_2	F	-2.80	-.5668
22	NH_2	$N(Me)_2$	-3.10	-.5811
23	Me	Me	-3.10	-.5991
24	Me	Et	-2.85	-.4852
25	Me	F	-3.00	-.5571
26	Me	NHCOMe	-3.00	-.5491
27	Me	$N(Me)_2$	-2.95	-.5814

a) Obtained by cyclic voltammetry on a Pt bead versus $Ag°/Ag^+$, in acetonitrile at 25°C. The first reduction waves are tabulated only.

RESULTS AND DISCUSSION

Reduction peak potentials ($E_{p,c}$) of benzoxazole derivatives generally were found to be rather high except for those which have a nitro group as a substituent. For those compounds having no NO_2 group $E_{p,c}$ values were in the range of -2.85 to -3.10 V. When there was a NO_2 group substituted at position-5, two reduction peaks were observed. The first reduction peaks were found to be substantially low ranging from -1.6 V to -1.9 V versus $Ag°/Ag^+$. The second reduction peaks between -2.8 V to -3.3 V were in accordance with other results. Two typical cyclic voltammograms, of phenyl benzoxazole and 5-nitro-2-phenyl benzoxazole are given in Figures 1 and 2, respectively.

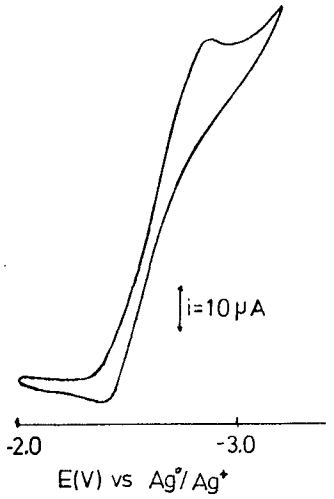


FIG. 1.

Cyclic voltammogram of phenyl benzoxazole obtained in acetonitrile-TBAF system at room temperature using platinium bead and $Ag°/Ag^+$ as working and reference electrodes (no other reduction peak was observed at potentials lower than -2.0 V.).

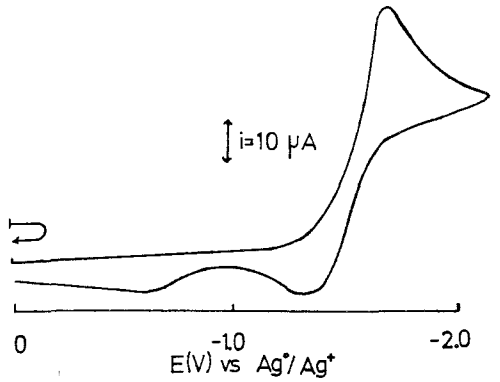


FIG. 2.

Cyclic voltammogram of 5-nitro-2-phenyl benzoxazole obtained in acetonitrile-TBAF system on a platinium wire versus $Ag°/Ag^+$ at room temperature.

Cyclic voltammograms (CV) obtained for most benzoxazoles showed an irreversible reduction wave. A quasi-reversible first reduction peak and an irreversible second reduction peak were observed for 5-nitro substituted benzoxazoles. It was found that at lower scan rates (ca. 50 mV/s) the quasi-reversible peaks become irreversible. This clearly indicates that the intermediate product of electron transfer is fairly stable in CV time scale and may give its electron(s) back to the cathode at higher scan rates (over 200 mV/s) in the reverse scan. The nature of the intermediate and final product(s) of benzoxazoles formed by electroreduction is hitherto unknown.

As mentioned above, most of the derivatives had more than one $E_{p,c}$ value, of those the lowest ones were used in the correlations with the theoretically calculated LUMO energies.

HMO CALCULATIONS

The LUMO energy calculations are based on the Hückel molecular orbital (HMO) considerations[15,27]. Within the zero differential overlap (ZDO) approximation[27]. The coplanar conformations of the molecules were considered. The inductive model of hyperconjugation was adopted for alkyl substituents[15]. The heteroatom parameters (h_ρ and k_μ) used in the calculations were excerpted from the literature[15]. The nitro group was treated as the nitroso group following the suggestion by Dewar[28].

Since, it is known that $E_{p,c}$ values linearly correlate with the LUMO energies of the set of structurally related compounds[15,27], a regression analysis applied to the experimental data in Table 1 gives equation 1.

$$E_{p,c} = 2.19239\, C_{LUMO} - 1.68601 \qquad (1)$$

The regression statistics[29,30] revealed that R^2, the coefficient of determination : 0.960872; correlation coefficient r_{yx} : 0.980241; unexplained standard deviation, S_y : 0.104944; unbiased estimate of the variance of the regression coefficient, S_{bx} : 0.0884827. t_s and F tests give 24.7776 and 613.931, respectively. The theoretical F and t_s values are 7.77 and 2.485, respectively at 1% level of significance, thus the regressed equation (eq. 1) is statistically significant. As the coefficients in equation 1 were obtained by regression analysis, they must maintain five decimal points for the best fit, however the resultant $E_{p,c}$ values should be round off down to two decimal points.

As it is seen in Table 1, the presence of nitro groups attached to benzoxazole moiety substantially decreases $E_{p,c}$ values by lowering the LUMO energies. Although, amino group is a mesomerically electron donating substituent and it is expected to raise up LUMO energy[31], however, its presence at the para position of the phenyl group cannot cancel out the influence of $-NO_2$ group, on the energy level of LUMO (Table 1).

On the other hand, chlorine atom at R_2 position lowers the LUMO energy more than bromine at the same position which implies that inductive effects are substantially important (compounds 4,5 and 16,17) in the case of halogens.

It is worth mentioning that amino group attached to para position of the phenyl ring is more effective than position-5 of the benzoxazole moiety in rising up the LUMO energy (compounds 6 and 18). In Table 1 it can be seen that the theoretically calculated C_{m+1} values for compounds 6 and 18 are -0.5792 β and -0.5393 β, respectively. This theoretically determined trend was proved to be valid by the experimental measurements of $E_{p,c}$ values for compounds, 6 and 18 as -3.05 V and -2.90 V, respectively.

In conclusion it can be said that the microbiologically active benzoxazole derivatives studied have a linear relationship between their $E_{p,c}$ values and LUMO energies. The $E_{p,c}$ values are significantly high for the derivatives which do not contain any NO_2 substituent. It is difficult to measure very high $E_{p,c}$ values. Especially the reduction peaks above -3.00 V are not well defined due to partial solvent discharge. For compounds where experimental measurement of $E_{p,c}$ is difficult or impossible above -3.00 V, Eq. 1 can be used to estimate their $E_{p,c}$ values, although it is obtained for coplanar forms of the benzoxazole derivatives.

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