

## RELATIONSHIP BETWEEN THEORETICALLY CALCULATED LUMO ENERGIES AND CATHODIC PEAK POTENTIALS OF SOME 2-BENZYLBENZOXAZOLE DERIVATIVES

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### ABSTRACT

Cathodic peak potentials of various bioactive 2-benzylbenzoxazole derivatives were measured by cyclic voltammetry and correlated with the lowest unoccupied molecular orbital calculated at the level of Extended Hückel molecular orbital theory.

### INTRODUCTION

Recent studies on the benzoxazole derivatives revealed that these compounds possess a significant antimicrobial activity especially against some enteric gram-negative rods<sup>1-3</sup>. Researches have clearly established that the abundant use of antimicrobial drugs, particularly in hospitalized patients, lead to the multiple resistance among gram-negative organisms to a variety of antibiotics occurs and can be transmitted to previously nonresistant strains of the same species<sup>4,5</sup>. Consequently, the development of the new and different antimicrobial agents is a very important step and much research effort is directed toward to the design of available drugs that are resistant to inactivation by bacterial enzymes.

A review of the literature revealed that many effective antimicrobial agents have heterocyclic systems in their molecules<sup>6</sup>. Benzoxazoles are the structural isomers of nucleotides owing bicyclic heterocyclic nuclei in their structures such as adenine and guanine that allows them to interact easily with the biopolymers. Furthermore, studies on this structure showed that the substituents at positions 2 and 5 and (or) 5 of the oxazole ring in the fused heterocyclic system were important for the microbiological activity<sup>7-10</sup>.

On the other hand, electrochemical behavior of these systems is an important part of the optimization process in the investigation of structure-activity relationships because redox potentials may give some idea about the bonding capability of the drug to biological systems via donor-acceptor type interactions.

Since long, it has been known that the highest occupied (HOMO) and the lowest unoccupied (LUMO) energies of chemical systems correlate with the respective redox potentials<sup>11-15</sup>. The theoretical relation between  $E_{1/2}(\text{red})$  and  $C_{m+1}$  (LUMO) have been proposed and extensively studied by Hoijtink<sup>13,14</sup> and it has also been reported that the modified

Hückel molecular orbital (HMO) calculations predict the observed differences on  $E_{1/2}$  of the related systems<sup>15</sup>.

In one of our quantitative structure-activity relationship (QSAR) studies<sup>7</sup>, it has been demonstrated that the antimicrobial activity of benzoxazole derivatives is a function of the theoretically obtained HOMO and LUMO energies.

Anodic and cathodic peak potentials of various molecules can be measured by cyclic voltammetry (CV) in nonaqueous solvents<sup>16-18</sup>. Cathodic peak potential ( $E_{p,c}$ ) is the potential at which an electron (or more) is transferred, preferentially into LUMO of the molecule from the cathode. Then, possibly a correlation is expected between the energy of the lowest unoccupied molecular orbital and  $E_{p,c}$  of structurally similar molecules.

In the present study, the cathodic peak potentials of various biologically active 2-benzyl-benzoxazole derivatives have been measured and tried to be correlated with theoretically calculated LUMO energies. For the measurements of  $E_{p,c}$  values, cyclic voltammetry was employed. The LUMO energies were calculated by the Extended Hückel molecular orbital (EHMO) consideration<sup>19</sup>.

### MATERIALS AND METHODS

The compounds were synthesized via coignate preparations described earlier<sup>2</sup> and purified by chromatographic methods.

Cyclic voltammograms were measured in acetonitrile (MeCN) using tetrabutylammonium tetrafluoroborate (TBAF) as the supporting electrolyte. The purification of solvent and electrolyte is described previously<sup>18</sup> and the pure solvent was stored over 4Å molecular sieves in the dark. A Pt bead is used as working electrode. Potentials are measured against a Ag/Ag<sup>+</sup> reference electrode under N<sub>2</sub> atmosphere at room temperature. The voltage scan rate was 200 mV/s. The

potential range was 0 to -3.4 V. A bank potentiostat Wenking model ST-88 and a function generator (Wenking model VSG 83) were used to program the potential.

The EHMO calculations were carried out by using a packaged computer program (Hyperchem release 4).

## RESULTS AND DISCUSSION

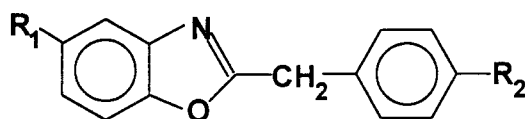
The cathodic peak potentials at several biologically active 2-benzylbenzoxazole derivatives were obtained in acetonitrile-

tetrabutylammonium tetrafluoroborate solvent/ electrolyte system was observed to be sufficiently high (ca. -3.4 V vs.  $\text{Ag}/\text{Ag}^+$ ) and reproducible, provided that both the solvent and the electrolyte are very pure and dry.

2-Benzylbenzoxazole derivatives were found to have similar cathodic behavior and to be reduced at higher cathodic potentials. The results of cyclic voltammetry measurements are summarized in Table 1.

TABLE 1.

The observed  $E_{p,c}$  values and calculated LUMO energies of some 2-benzylbenzoxazoles.



No	R <sub>1</sub>	R <sub>2</sub>	E <sub>p,c</sub> (V)	E <sub>LUMO</sub> (eV)
1	H	H	-2.80	-8.78773
2	H	OMe	-2.90	-8.78718
3	H	Br	-3.10	-8.78747
4	H	Cl	-2.95	-8.78740
5	H	NO <sub>2</sub>	-1.85	-10.86252
6	Cl	OMe	-3.50	-8.78589
7	Cl	NO <sub>2</sub>	-2.00	-11.49159
8	Cl	Cl	-3.40	-8.78562
9	NO <sub>2</sub>	H	-1.70	-11.38698
10	NO <sub>2</sub>	OMe	-1.85	-11.38692
11	NO <sub>2</sub>	Br	-1.70	-11.38691
12	NO <sub>2</sub>	Cl	-1.65	-11.38693
13	NO <sub>2</sub>	NO <sub>2</sub>	-1.85	-11.4923

All 2-benzylbenzoxazole derivatives have an irreversible reduction wave in between -2.7 and -3.3 V. In some cases, the reduction peak was obtained as a shoulder and partly overlapping with the discharge potential of the solvent/electrolyte. In the presence of a NO<sub>2</sub> substituent on benzo- or benzyl group, two reduction waves were observed. The first reduction peaks were in the range of -1.6 to -2.0 V and quasi-reversible and the second reduction peaks were in the range of -2.8 to -3.3 V. The quasi-reversible first reduction peak at scan rate of 200 mV/s become irreversible at lower scan rates (ca. 50 mV/s). Two examples of cyclic voltammograms, obtained for 4-chlorobenzylbenzoxazole (4) and 5-nitro-2-(4-methoxy-benzyl)benzoxazole (10) are given in Fig.1 and Fig.2, respectively.

In our earlier work<sup>10</sup>, the cathodic peak potentials of some 2-phenylbenzoxazoles were also found to be very high, and in the presence of a nitro substituent two reduction peaks were obtained. This indicates that the reduced group is the same

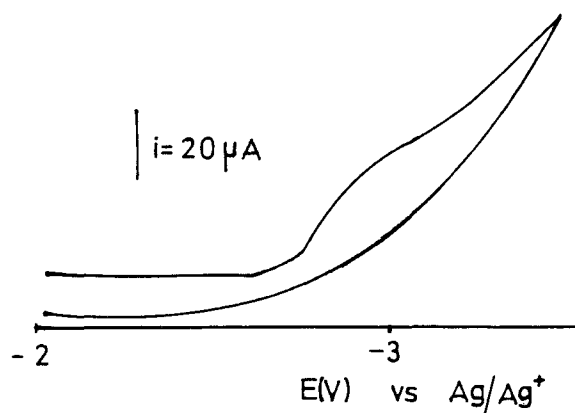


Fig.1 Cyclic voltammogram of 2-(4-chlorobenzyl)benzoxazole (4) in MeCN-TBAF system at a Pt cathode against a  $\text{Ag}/\text{Ag}^+$  reference electrode (no other peak was observed at potentials lower than -2.0 V at a scan rate of 200 mV/s).

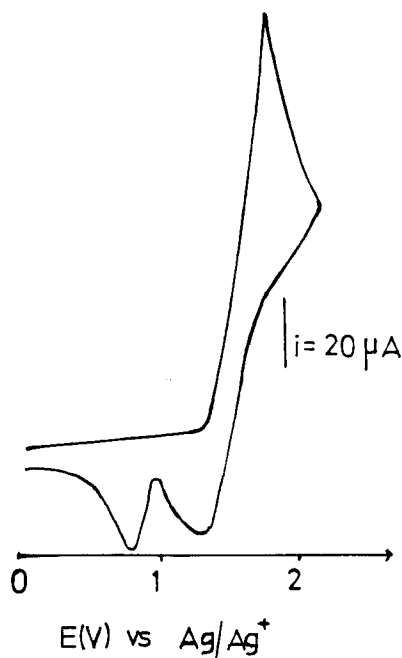


Fig. 2 Cyclic voltammogram of 5-nitro-2-(4-methoxybenzyl) benzoxazole (4) in MeCN-TBAF system at a Pt cathode against a  $\text{Ag}/\text{Ag}^+$  reference electrode (no other peak was observed at potentials lower than  $-2.0$  V at a scan rate of  $200$  mV/s).

at high cathodic potentials. It may be attributed to oxazole ring, though no further experiment was carried out in order to identify the products and the mechanism of cathodic reactions of benzoxazoles.

#### EHMO Calculations and Regression Analysis

The LUMO energy calculations are based on the EHMO considerations<sup>19,20</sup>, using a minimal basis set of valence Slater type orbitals and a Hückel constant of 1.75.

Since, it is known that  $E_{p,c}$  values linearly correlate with the LUMO energies of structurally related compounds<sup>14,21</sup>, a regression analysis applied to the experimental data in Table 1 gives equation 1.

$$E_{p,c} = -0.505318 E_{\text{LUMO}} - 7.53926 \quad (1)$$

The regression statistics<sup>22,23</sup> revealed that  $R^2$ , the coefficient of determination: 0.906335; correlation coefficient  $r_{YX}$ : 0.952016; unexplained standard deviation,  $S_Y$ : 0.226451; unbiased estimate of variance of the regression coefficient  $S_{bX}$ : 0.0489795,  $t_s$  and  $F$  tests give 10.3169 and 106.439, respectively. The theoretical  $F_{1,11}$  and  $t_s$  values are 9.65 and 2.718, respectively at 1% level of significance, thus the regression equation (Eq.1) is statistically significant. As the coefficients in equation 1 were obtained by a regression

analysis, they must maintained 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,  $E_{p,c}$  values of benzylbenzoxazole derivatives are less sensitive to electronic effects exerted by the substituents occupying p-position of the benzyl moiety. That is an expected result because of the methylene group intervening the benzoxazole and the phenyl ring systems.

Nitro group, an electron withdrawing substituent, at 5-position of the benzoxazole ring definitely lowers  $E_{p,c}$  value irrespective of the kind of the substituent on the benzyl group. On the other hand, inspection of  $E_{p,c}$  values of compounds 1-5 clearly shows the direction and magnitude of the effects of  $R_2$  groups.

Since the benzoxazole and phenyl rings in these systems are not in  $\pi$ -conjugation with each other, the observed  $E_{p,c}$  values, at least for some compounds, might originate from different  $\pi$ -systems (benzoxazole or phenyl). For instance, substitution of the second chlorine atom into compound 4 to produce compound 8 substantially raises up the  $E_{p,c}$  value (in absolute value). Whereas, When  $E_{p,c}$  values of compounds 5 and 13 are compared with the value of the unsubstituted 2-benzylbenzoxazole system, the second nitro group does not exhibit any detectable effect although EHMO calculations imply a strong effect. All these observations and contemplation suggest the possibility of the transfer of an electron from cathod into different  $\pi$ -groups of these systems. Indeed, some of them possess more than one reduction peak. In table 1, only the first peak potentials are tabulated. Obviously, such kind of effects disturb the regression statistics, hence goodness of fit and correlation coefficients of Eq.1 which comprises the nitrocompounds as well are about 0.90 and 0.95, respectively.

In conclusion, it is evident that microbiologically active 2-benzylbenzoxazole derivatives studied exhibit a linear relationship between their  $E_{p,c}$  values and LUMO energies. The  $E_{p,c}$  values are relatively low for the derivatives which contain  $\text{NO}_2$  substituents. On the other hand, electron releasing groups raise up the reduction potentials. Since, the reduction peaks above  $-3.00$  V are not well defined because of the partial solvent discharge for compounds for which the experimental determination of  $E_{p,c}$  is difficult or impossible above  $-3.00$  V. Eq.1 can also be used to estimate their  $E_{p,c}$  values. Moreover, Eq.1 can also be used to test how closely the reduction of any derivative of benzyl benzoxazole follows the general trend these type of compounds.

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