EXTENDED HUCKEL PARTIAL ATOMIC CHARGES OF NITROIMIDAZOLE AND PREDICTION OF DNA DAMAGE


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ABSTRACT
Nine nitroimidazoles drugs representing different class were found in the literature to have their respective half wave potential and one electron reduction potential measure under near-identical conditions. The structures of these nine nitroimidazoles were optimized, and resulting physicochemical parameters were regressed against one electron reduction potential (OERPs). A very significant linear correlation (QSAR) was found between OERPs and Extended Huckel Partial Atomic Charges. These findings suggest that it may be possible to estimate OERPs of nitroimidazole in advance to its synthesis. Insofar as the OERPs correlating to DNA damage, radiosensitization efficiency, aerobic cytotoxicity, mutagenicity and hypoxic cytotoxicity; the Extended Huckel Partial Atomic Charges can predict well all these biological activity prior to synthesis of novel nitroimidazoles.

Keywords: One electron reduction potential, nitroimidazole, partial charge, half wave potential.

INTRODUCTION
Nitroimidazole comprises a large group with useful clinical activity as antibacterial, antiprotozoal and anticancer agents. With all nitro compounds their activity is solely depend upon reduction of nitro group, the metabolic products of which are responsible for the DNA damage. The key to understanding the basis of selective toxicity and biological activity of these drugs lies in the knowledge of the range of polarographic determined one electron reduction potentials exhibited by such compounds. Fig: 1 shows the one electron reduction potential of electron affinity exhibited by nitroaromatic compounds [1].
The redox spectrum showing the electron affinity ($E_{71}$) of nitroaromatic drugs. Oxygen is the most electron affinic and drugs of lower potential are less easily reduced.

Figure: 1

The boundary falls at -0.350 V to the right of this division, redox reactions are easily performed under the aerobic conditions; in fact the most negative of redox reactions carried out by the aerobic cell is that involving NAD(NADP)-NADH(NADPH) couples at -0.35V. Thus redox reactions more negative (lower) the -0.350 V is not possible under aerobic conditions, but are possible under anaerobic conditions. The redox potential of bioreducible drugs is therefore crucial beginning in understanding how these compounds may be applied to combat diseases which flourish under redox environment.

The basis of structure-activity relationships in the development of electron-affinic nitroheterocyclic hypoxic cell, radiosensitizers, DNA damage and anaerobic activity is a linear correlation of the type:

$$-\log C = b_0 + b_1 E + b_2 \log P + b_3 (\log P)^2$$

(1)

$C$ = the drug concentration required to cause specific relevant biological effect.

$E$ = the electron affinity usually expressed as the one-electron redox potential ($E_{71}$)

$P$ = the octanol/water partition coefficient of the drugs.
Adams et al. has shown that there is negligible effect of lipophilicity (P) on radiosensitizing and cytotoxicity. Thus the coefficient b2 and b3 may be omitted.

\[-\log C = b_0 + b_1 E \]  \hspace{1cm} (2)

Thus it is well-established that the $E_{1/2}^1$ value correlates positively with radiosensitization efficiency\cite{3}, aerobic cytotoxicity \cite{4}, mutagenicity\cite{5} and hypoxic cytotoxicity\cite{6}. The more electron-affinic the drug (the more positive the $E_{1/2}^1$ value) the greater the radiosensitization and cytotoxicity, which varies in general by an order of magnitude for each 100mV change in $E_{1/2}^1$.

The objective of the research work is to find out some physicochemical parameter which can correlates with experimental determined one electron reduction potential.

**MATERIAL AND METHODS**

A) Electrochemical method

Knox et al\cite{7} reported the $E_{1/2}$ as the Polarographic half-wave potential (HWPs) in volts measured against Ag/AgCl reference electrode at pH 7.0 and $E_{7}^1$ as one-electron reduction potential (OERPs) in volts measured against the normal hydrogen electrode. Table I, shows the $E_{1/2}$ and $E_{7}^1$ of nine standard nitroimidazole compounds considered in the study along with their structure and DNA damage.

B) Computational method

The molecular geometries of each of the nine compounds in Table I were built by using standard bond lengths and angles with Chem. Office Ultra 11.00 (Chem Draw ultra 2008)\cite{8}. These structures were initially optimized using MM2 force field method until the root mean square gradient value becomes smaller than 0.001 Kcal/mol. The resulting optimized structure was processed through the Extended Huckel Partial Atomic Charges on oxygen of nitro group in nitroimidazole \cite{9}, LUMO and HOMO as electronic parameters. The CLogp and Molar volume was considered as lipophilic and steric parameter in the study. The various physicochemical parameters were regressed against one electron reduction potential and Log DNA damage using multiple linear regression analysis.

**RESULTS AND DISCUSSION**

The calculated Extended Huckel Partial Atomic Charges on oxygen of nitro group in nitroimidazole as depicted in the figure:2, shows a good correlation with one electron...
reduction potential while other parameters like Clog P, LUMO, HOMO and molar volume does not contributes significantly.

![Figure: 2](image.png)

Extended Huckel Partial Atomic Charges on oxygen of Nitroimidazole.

Thus Extended Huckel Partial Atomic Charges on oxygen of nitro group is considered as important parameter in generation of model while omitting the lipophilic and steric physicochemical parameters.

**Table 1: Electronic Parameters of Nitroimidazole**

<table>
<thead>
<tr>
<th>No</th>
<th>Drug</th>
<th>$E_{1/2}(V)$ (HWPs) (Obsd)</th>
<th>$E_1^+(V)$ (OERPs) (Obsd)</th>
<th>Log DNA damage (Obsd)</th>
<th>Extended Huckel Partial Atomic Charges on oxygen of nitro group</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pimonidazole</td>
<td>-0.180</td>
<td>-0.346</td>
<td>-0.660</td>
<td>-0.668</td>
</tr>
<tr>
<td>2</td>
<td>Benznidazole</td>
<td>-0.200</td>
<td>-0.380</td>
<td>-0.569</td>
<td>-0.690</td>
</tr>
<tr>
<td>3</td>
<td>Azomycin</td>
<td>-0.374</td>
<td>-0.418</td>
<td>-0.222</td>
<td>-0.778</td>
</tr>
<tr>
<td>4</td>
<td>Nimorazole</td>
<td>-0.345</td>
<td>-0.457</td>
<td>-0.393</td>
<td>-0.804</td>
</tr>
<tr>
<td>5</td>
<td>Tinidazole</td>
<td>-0.340</td>
<td>-0.464</td>
<td>0.104</td>
<td>-0.805</td>
</tr>
<tr>
<td>6</td>
<td>Ornidazole</td>
<td>-0.345</td>
<td>-0.467</td>
<td>-0.131</td>
<td>-0.809</td>
</tr>
<tr>
<td>7</td>
<td>Dimetridazole</td>
<td>-0.388</td>
<td>-0.475</td>
<td>0.017</td>
<td>-0.811</td>
</tr>
<tr>
<td>8</td>
<td>Secnidazole</td>
<td>-0.390</td>
<td>-0.480</td>
<td>0.013</td>
<td>-0.815</td>
</tr>
<tr>
<td>9</td>
<td>Metronidazole</td>
<td>-0.382</td>
<td>-0.486</td>
<td>-0.022</td>
<td>-0.823</td>
</tr>
</tbody>
</table>

The correlation between one electron reduction potential and Extended Huckel partial atomic charges on oxygen of nitro group of nitroimidazole is established as shown in graph 1.
TABLE 2: VALIDATION OF ONE ELECTRON REDUCTION POTENTIAL OF STANDARD NITROIMIDAZOLE AND EXTENDED HUCKEL PARTIAL ATOMIC CHARGE ON OXYGEN.

<table>
<thead>
<tr>
<th>Description</th>
<th>( r )</th>
<th>( r^2 ) (adj)</th>
<th>F value</th>
<th>Least squared error</th>
</tr>
</thead>
<tbody>
<tr>
<td>OERPS=0.8336*(Partialcharge) +0.2072</td>
<td>0.9768</td>
<td>0.9542</td>
<td>146.0945</td>
<td>0.0112</td>
</tr>
</tbody>
</table>

The DNA damage activity of standard nitroimidazole, showing a good correlation with Extended Huckel Partial atomic charge as shown in the graph 2.
The reported $E_{\text{l}}^1$ (One electron reduction potential) of compound was found in the range of -0.257 V to -0.500 V which indicate the range of active nitroimidazole. A good correlation between one electron reduction potential and calculated Extended Huckel partial atomic charge on oxygen of nitro group was obtained having, $r = 0.9768$, $r^2=0.9542$, $r^2_{\text{(adjusted)}} = 0.9477$, F value = 146.0945, standard error = 0.0112 as shown in graph 1. Further the direct correlation between Calculated Huckel Extended partial negative charge on oxygen and Log DNA damage activity is also established. $r = 0.9633$, $r^2=0.9281$, $r^2_{\text{(adjusted)}} = 0.9160$, F value = 77.41, standard error = 0.08248 as per graph 2. The active range of various nitroimidazole class drugs as per Extended Huckel partial atomic charge on oxygen of can be established as -0.778 to -0.820.

**CONCLUSION**

Computed Extended Huckel partial atomic charge on oxygen can be used to predict radiosensitization efficiency, aerobic cytotoxicity, mutagenicity and hypoxic cytotoxicity, DNA damage and anaerobic activity of various novel nitroimidazole class drugs prior to synthesis. The advantage of this model is that it does not require any experimentally calculated one electron reduction potential.

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**REFERENCES**


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