ANTIDEPRESSANT DRUG: SURfactant& POLYMER MEDIATED ACID CATALYSED HYDROLYSIS OF PHENYL UREA

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ABSTRACT: The Kinetics of acidic hydrolysis of Phenyl urea in drug surfactant, mixed micellar media have been studied at room temperature in the presence of 0.9M H$_2$SO$_4$. This study introduced surfactant behavior of the tricyclic antidepressant drug Imipramine hydrochloride [IMT$^+$] and IMT$^+$ - TX-100, IMT$^+$ - PEG (Polyethylene glycol MW-400), IMT$^+$ - CTAB (Cetyl trimethyl ammonium bromide), IMT$^+$ - SDS, (Sodium dodecyl sulphate) in acid media. Kinetic data studies show that, the reaction obeyed first order kinetics. The reaction kinetics can be well explained by micellar catalysis model Pseudo Phase Ion Exchange.

Keywords: Tricyclic – Antidepressant Drug, Imipramine - hydrochloride (IMI$^+$), Polymer, Surfactant, Phenyl urea hydrolysis

INTRODUCTION
Mixed-micelle has recently emerged as a new approach for simple and rapid quantization of organic reaction which has been widely studied in recent year 1-4. The hydrolysis of carboxylic acid ester and amides in acid mainly proceeds according to an addition-elimination mechanism 5-6, but limited work has been reported on polymer and surfactant catalyzed in presence of urea, especially Phenyl urea, despite the fact, that compound urea and its substituted have uses in so many fields like medicine, agriculture and industries 7. Polymer surfactant investigation are currently that subject of extensive investigation 8-15, due to new specific technological application 16-19. Imipramine hydrochloride IMI$^+$ [C$_{19}$H$_{24}$N$_2$]$^+$ HCl, are tricyclic antidepressant belonging first generation antidepressant 20-21. Those substances share a basic chemical structure comprising their ring core and alkyamine side chain (fig-1). Presence of the alkyamine side chain on IMI$^+$ molecules confers on them a “Surfactant like” behavior which may manifest in formation of aggregates in aqueous solution and show surfactant like property 22, 23. Their hydrophobic inner surface makes them the most important simple organic molecules capable to form non covalent bonded inclusion complex with variety of other molecules in aqueous solution 24.

The aim of this work is to examine catalytic-micellar effects of drug-substrate upon the acidic hydrolysis of Phenyl-urea at room temperature, so that reaction would occur either largely in the aqueous pseudo phase or with a more hydrophobic substrate, largely in micellar pseudo phase. The influence of micellar system on chemical reactivity is usually analyzed in term of pseudo-phase Ion Exchange (PPIE) model. The applications of such interaction are numerous, but many problems are still unsolved particularly the question how the drug-surfactant couples affect the reaction kinetics posses a challenge for chemist.

[Colored Figure: Molecular Structure of drug Imipramine hydrochloride]
**EXPERIMENTAL SECTION**

Phenyl urea, 97.5% was used as such from Lancaster, U.K. batch no.9001783. The acid used was analytical reagent grade (E Merck). Rate constant were measured by means of UV-Spectroscopy in watermethanal (9:1) mixture on Strysonic-Double Beam UV-VIS type-2201 spectrometer with 1cm quartz cell. The concentration of Phenyl urea was 4.9 x 10^{-4} mol L^{-1}. The acid strength 0.9M H_{2}SO_{4} was used throughout the experiment. Critical micelle concentration value determine by surface tension and conductivity method. Acid hydrolysis of Phenyl urea carried out at room temperature in presence of IMI^{+}, IMI^{+}-CTAB(Merck), IMI^{+}-PEG(SD-fine), IMI^{+}-TX-100(CD-fine), IMI^{+}- SDS(SD fine) in variable concentration of IMI^{+}, (1.5-4.8) x 10^{-4} mol L^{-1}, and fixed concentration of Surfactant 3 x 10^{-4} mol L^{-1}.

**RESULT AND DISCUSSION**

In this study important factor was surfactant - drug interaction in presence of the alkylmine side chain of IMI^{+} molecules from surfactant like behavior and form aggregates in aqueous solution. Due to hydrophobic inner surface, it catalyzed acid hydrolysis of phenyl urea and it increases rate by many fold. It shows certain change of rate constant in present of different concentration IMI^{+} shown Table -I. In this study important factor was surfactant effect of tricyclic- antidepressant drug IMI^{+} in presence of polymer and other surfactant. It has been well explained that surfactant polymer mixed micelles are form in aqueous solution. The same effect was also observed for nonionic and anionic surfactant-drug system. So the effect of this drug, drug-surfactant, drug-polymer couple on the acid hydrolysis of phenyl urea has been studied in micellar system. The pseudo-phase-first order rate constant for the acid hydrolysis of phenyl urea at different concentration of drug (1.5-4.8) x 10^{-4} mol L^{-1}, constant Surfactant concentration 3 x10-4 M of CTAB, SDS, TX-100, PEG (M.W. = 400) and acid concentration (0.9M) are given table-1. The drug and drug-surfactant produce catalytic effect on the reaction, i.e. the rate constant in present of different concentration IMI^{+} has been found following order IMI^{+}-CTAB>IMI^{+}-SDS>IMI^{+}-TX-100>IMI^{+}-PEG. The rate acceleration in micellar solution arises from different rate of reaction of the substrate in the micellar phase and in the bulk solution and the distribution of the substrate between those two phases. Basically these rate effects can be attributed to electrostatic and hydrophobic interaction between the substrate and the surfactant aggregate. Micellar effects upon reaction rate are generally analyzed in term of Pseudo-Phase-Ion exchange (PPIE) model. Micelles and bulk aqueous medium are treated as distinct reaction media with their own property, which is question that why the micelles are regarded as a submicroscopic solvent.

The variation of the rate constant with surfactant is generally treated on the assumption that substrate “S” is distributed between the aqueous and micellar pseudophases, designated by subcribes ‘W’ and ‘M’ respectively (Scheme1) and can react in each pseudo-phase with the first order rate constant being Kw and Km.

\[
\text{Sw} + \text{Dn} \rightarrow \text{SDn} \quad \text{Product}\]

The concentration of micellized surfactant is designed to be the total concentration (D) less that of monomers surfactant, which will be approximately equal to the critical micelle concentration (CMC) under Kinetic conditions.

\[
\text{Dn} = [\text{D}_T] - \text{CMC}
\]

Ks is the equilibrium for substrate binding. This model (Scheme 1) leads to the relationship

\[
\frac{1}{\text{Kw} - \text{K}\psi} = \frac{1}{\text{Kw} - \text{Km}} + \frac{1}{\text{Kw} - \text{Km}} . \frac{1}{\text{Ks}([\text{D}_T] - \text{CMC})}
\]
\( K_y \) is observed pseudo-first order rate constant, \( N \) is the micellar aggregation number & \( K_s \) represent substrate binding constant. By plotting \( 1/K_w - K_y \) against \( 1/D_{C M C} \) is possible to calculate \( K_m \) and \( K_s \) [table 2] The CMC value of IMI\(^+\), IMI\(^+\)-CTAB, IMI\(^+\)-TX-100, IMI\(^+\)-PEG, IMI\(^+\)-SDS determine at room temperature. The quantitative explanation offered above for the observed enhancement would mean that the reaction occurs mostly in the micellar phase and that the reaction occurs in bulk aqueous phase is negligible.

**CONCLUSION**

All the result indicate that both the nature of the surfactant head group and the number of carbon in the surfactant tail, have an effect on drug-surfactant interaction and reaction kinetic. Cationic, anionic and non-ionic surfactant has shown acceleration affect up to \( 10^{-4} \) M drug concentration. It is not yet possible to formulate general rules concerning the actual rate of drug-surfactant, drug-polymer interaction on the reaction mechanism. The uses of polymer-drug-surfactant for the surfaces modification present a rich opportunity for producing unique reaction mediums. Further studies are carried out in our laboratory regarding more conclusive findings.

**Table -1 : Effect of Drug-Surfactant, Polymer upon the rate constant of phenyl urea in 0.09 M H\(_2\)SO\(_4\) at Room Temp.**

<table>
<thead>
<tr>
<th>IMI(^+) Drug</th>
<th>IMI(^+)</th>
<th>IMI(^+)-TX-100</th>
<th>IMI(^+)-PEG</th>
<th>IMI(^+)-SDS</th>
<th>IMI(^+)-CTAB</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>0.134</td>
<td>0.134</td>
<td>0.134</td>
<td>0.134</td>
<td>0.134</td>
</tr>
<tr>
<td>1.5</td>
<td>0.486</td>
<td>0.437</td>
<td>0.425</td>
<td>0.466</td>
<td>0.510</td>
</tr>
<tr>
<td>1.8</td>
<td>0.498</td>
<td>0.462</td>
<td>0.430</td>
<td>0.487</td>
<td>0.612</td>
</tr>
<tr>
<td>2.1</td>
<td>0.512</td>
<td>0.470</td>
<td>0.450</td>
<td>0.504</td>
<td>0.728</td>
</tr>
<tr>
<td>2.4</td>
<td>0.534</td>
<td>0.498</td>
<td>0.462</td>
<td>0.524</td>
<td>0.892</td>
</tr>
<tr>
<td>2.7</td>
<td>0.560</td>
<td>0.510</td>
<td>0.476</td>
<td>0.542</td>
<td>0.978</td>
</tr>
<tr>
<td>3.0</td>
<td>0.78</td>
<td>0.542</td>
<td>0.497</td>
<td>0.560</td>
<td>1.12</td>
</tr>
<tr>
<td>3.3</td>
<td>0.620</td>
<td>0.570</td>
<td>0.532</td>
<td>0.610</td>
<td>1.34</td>
</tr>
<tr>
<td>3.6</td>
<td>0.642</td>
<td>0.601</td>
<td>0.562</td>
<td>0.636</td>
<td>1.78</td>
</tr>
<tr>
<td>3.9</td>
<td>0.692</td>
<td>0.650</td>
<td>0.625</td>
<td>0.680</td>
<td>1.89</td>
</tr>
<tr>
<td>4.2</td>
<td>0.860</td>
<td>0.810</td>
<td>0.796</td>
<td>0.840</td>
<td>2.04</td>
</tr>
<tr>
<td>4.5</td>
<td>0.998</td>
<td>0.950</td>
<td>0.916</td>
<td>0.986</td>
<td>2.76</td>
</tr>
<tr>
<td>4.8</td>
<td>1.34</td>
<td>1.09</td>
<td>0.979</td>
<td>1.20</td>
<td>3.25</td>
</tr>
</tbody>
</table>

C TAB, SDS, TX-100, PEG = Surfactant 3x10\(^-4\) mol L\(^-1\)
Variable IMI\(^+\) = [1.5- 4.8]10\(^-4\) mol L\(^-1\)

**Fig.2 Effect of drug and drug-Surfactant upon the rate constant of Phenyl urea**
Table -2: Correlation rate data by PPIE Model

<table>
<thead>
<tr>
<th>Drug- Surfactant</th>
<th>Dn rang x 10^{-4}</th>
<th>Ks / N</th>
<th>Correlation Coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMI</td>
<td>1.5-3.6</td>
<td>0.43</td>
<td>0.923</td>
</tr>
<tr>
<td>IMI - TX -100</td>
<td>1.5-3.6</td>
<td>0.47</td>
<td>0.931</td>
</tr>
<tr>
<td>IMI - PEG</td>
<td>2.3-6</td>
<td>0.76</td>
<td>0.966</td>
</tr>
<tr>
<td>IMI - SDS</td>
<td>1.4-3.5</td>
<td>0.39</td>
<td>0.928</td>
</tr>
<tr>
<td>IMI - CTAB</td>
<td>0.3-3</td>
<td>0.11</td>
<td>0.980</td>
</tr>
</tbody>
</table>

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