International Journal of ChemTech Research
CODEN(USA): IJCRGG ISSN : 0974-4290
Vol.1, No.4, pp 1335-1338, Oct-Dec 2009

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

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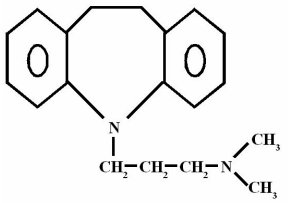
ABSTRACT: The Kinetics of acidic hydrolysis of Phenyl urea in drug surfactant, mixed micellar media have been studied at room temperature in the presence of 0.9M H_2SO_4. This study introduced surfactant behavior of the tricyclic antidepressant drug Imipramine hydrochloride [IMT^+] and IMI^+ -TX-100, IMT^+-PEG (Polyethylene glycol MW-400), IMI^+ - CTAB (Cetyl trimethyl ammonium bromide), IMI^+ - 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 alkylmine side chain (fig-1). Presence of the alkylmine 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.

Imipramine Hydrochloride



$[C_{19}H_{24}N_2]$ HCl
Fig.1: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 water-methanal (9:1) mixture on Systronic-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_2SO_4 was used through out 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 - durg 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 -1. 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 increase will drug concentration in order IMI^+ - PEG < IMI^+ - TX -100 < IMI^+ < IMI^+-CTAB. The increase is sharper in the lower concentration of drug and polymer. It is noted that in cationic surfactant-drug system the rate increasing effect is very significant.

But it is not possible to formulate general rule for drug-polymer & drug micelle interaction, cationic, anionic and non-ionic surfactant have

been shown to undergo interaction on the premise that the polymer has sufficient hydrolysis the Kψ values (table-1) increase with increasing alkyl chain length of the surfactant i.e. increasing aggregation number micelles.

The pseudo first order rate constant (Kψ) for investigated reaction in micellar solution of drug, drug-PEG, drug-TX-100, drug-SDS, drug-CTAB as shown in table1. The drug, drug-cationic, drug-anionic and drug-nonionic mixed drug-surfactant micelle enhanced the rate of hydrolysis. The micellar catalysis effect has been found following order IMI^+-CTAB>IMI^+>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 pseudo-phases, designated by subscribes 'W' and 'M' respectively (Scheme1) and can react in each pseudo-phase with the first order rate constant being Kw and Km.

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.

$$Dn = [D_T] - CMC$$

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

$$\frac{1}{Kw-K\psi} = \frac{1}{Kw-Km} + \frac{1}{Kw-Km} \cdot \frac{1}{Ks[(D_T)-CMC]}$$

Kψ is observed pseudo-first order rate constant, N is the micellar aggregation number & Ks represent substrate binding constant. By plotting 1/ Kw-Kψ against 1/ D_T-CMC is possible to calculate Km and Ks [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_2SO_4 at Room Temp.

IMI^+ Drug	Kψ 10^{-3}				
10:4 Conc.	IMI^+	IMI^+ - TX-100	IMI^+ - PEG	IMI^+ - SDS	IMI^+ - CTAB
0.0	0.134	0.134	0.134	0.134	0.134
1.5	0.486	0.437	0.425	0.466	0.510
1.8	0.498	0.462	0.430	0.487	0.612
2.1	0.512	0.470	0.450	0.504	0.728
2.4	0.534	0.498	0.462	0.524	0.892
2.7	0.560	0.510	0.476	0.542	0.978
3.0	0.78	0.542	0.497	0.560	1.12
3.3	0.620	0.570	0.532	0.610	1.34
3.6	0.642	0.601	0.562	0.636	1.78
3.9	0.692	0.650	0.625	0.680	1.89
4.2	0.860	0.810	0.796	0.840	2.04
4.5	0.998	0.950	0.916	0.986	2.76
4.8	1.34	1.09	0.979	1.20	3.25
C TAB, SDS, TX-100,PEG = Surfactant $3x10^{-4}$ mol L^{-1} Variable IMI^+ = [1.5- 4.8]10^{-4} mol L^{-1}					

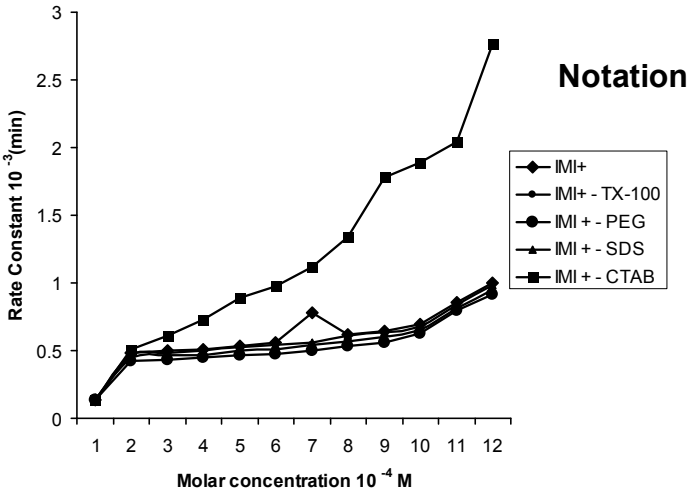


Fig.2 Effect of drug and drug-Surfactant upon the rate constant of Phenyl urea

Table -2: Correlation rate data by PPIE Model

Drug- Surfactant	Dn rang x 10^{-4}	Ks / N	Correlation Coefficient
IMI^+	1.5-3.6	0.43	0.923
IMI^+ - TX -100	1.5-3.6	0.47	0.931
IMI^+ -PEG	2-3.6	0.76	0.966
IMI^+ - SDS	1.4-3.5	0.39	0.928
IMI^+ -CTAB	0.3-3	0.11	0.980

ACKNOWLEDGMENT

Authors are thankful to Shri I.P.Mishra, President of Gangajali Education Society Bhilai, Dr. P.B.Deshmukh, Director S.S.C.E.T. Bhilai, Dr.K.B.Bummerker, Head, Department of Applied Chemistry S.S.C.E.T. Bhilai for providing laboratory facility in Shri Shankaracharya College of Engineering and Technology Bhilai.

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