Behaviour of a Cationic Micelle on the Hydrolysis of Procaine Formulation

NIGHAT RAZVI* AND ANWAR EJAZ BEG

Department of Pharmaceutics, Faculty of Pharmacy, University of Karachi, Karachi-32, Pakistan.

(Received 24th March 1981)

Summary: The kinetic investigation into the effect of cetyltrimethylammonium bromide (CTAB) on the base-catalysed hydrolysis of procaine has been studied. These studied were carried out at pH 9.1 in the temperature range of 50° – 80°. Using accelerated stability analysis the shelf-life of procaine at 25° in absence and presence of cationic surfactant CTAB at various concentration has been evaluated.

Introduction

The mechanism of ester hydrolysis and reaction kinetics are well documented in standard texts[1-6]. The modifying influence of many agents on the rates of hydrolysis, including the effect of addition of surfactants has also been examined[7,8]

During the last few years there have been an increasing number of investigations into the modifying effect of surfactants effects which are still not fully understood[7,9-12].

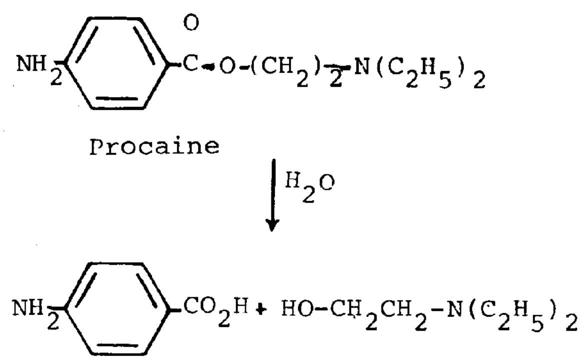
Examination of the literature shows that the effect of surfactants may be dependent upon the following factors[13]:

i) the type of surfactant, its concentration and chemical nature
ii) the chemical nature and ionic character of the substrate
iii) the substrate – surfactant ratio
iv) the basic (non-surfactant) mechanism of the reaction
v) the prescence of additives like inorganic and organic electrolytes
vi) the nature of the medium, dielectric constant, pH, temperature etc.

The effect of cetyltrimethylammonium bromide (CTAB) upon the hydrolysis of a series of neutral p-substituted aromatci carboxylic esters has been reported[14-16].

The degradation reaction of pharmaceutical interest in procaine (a disubstituted aminoethyl ester of p-aminobenzoic acid) is the hydrolysis of the ester linkage to yield diethylaminoethanol and p-aminobenzoic acid via the following reaction.

The rate of this degradation reaction increases with



increase in temperature. Since the stabilization of procaine solutions is carried out at higher temperature than at lower temperature[17], there is a need of study various means of stabilizing procaine formulation, one of which could be the shielding of the procaine molecules from water cantact via micellization. With this aim n view the present investigation was initiated in order to examine the effect of CTAB on the rate of hydrolysis of procaine at pH 9.1 and between 50° – 80° which has not been reported previously. pH 9.1 was selected for the study because the UV spectrum of procaine largely arises from the p-aminobenzoic acid (PABA) nucleus and hence the spectra of both are very similar. If, however, PABA is converted into its ions, by making the pH of the system sufficiently alkaline, the peaks in two UV curves are seperated so that a satisfactory analysis can be made.

Materials and Methods

Ester: This was procaine hydrochloride (USP Grade)

*To whom all correspondence be made.

obtained from Merck and was used as such 0.15% concentraion was kept throughout the work.

Surfactant: A cationic surfactant cetyltrimethylammonium bromide (CTAB) was used. The reagent grade of CTAB was purified according to the process prescribed by Jungermann, Duynstee and Grunwald, and Mukerjee and Mysels[18-20].

Buffer salts and Analytical reagents: Were all of Analar quality.

Water: Was freshly distilled from an all glass still using potassium permanganate which had a specific conductivity of $< 10^{-7}$ Ohm^{-1} Cm^{-1} and of surface tension of 72.05mNm^{-1} at 25°.

Buffer solution: This was borax of pH 9.1 prepared according to Bates[21].

pH measurements: These were made at the required temperature using a Radiometer digital pH meter supplied by Electronic Measuring Instruments, Copenhangen Denmark with an accuracy of ± 0.002 pH.

Spectrophotometric measurements: Were made in a Unican SP500 spectrophotometer using 1Cm cuvettes.

Constant temperature bath: This was viscometry bath supplied by Laboratory Thermal Equipment Ltd. having accuracy of ± 0.005° at 30°.

Method

Previously aged volumetric flasks of 50 ml capacity containing 40 ml of buffer were placed into water bath at appropriate temperature. The flasks were kept for (15-20 mins). 10 ml of stock solution of procaine was taken into the reaction vessel in absence of surfactant. The flask was shaken vigorously and returned to bath. Immediately 2 ml of the sample was withdrawn to a flask of 50 ml capacity containing around 30 ml of distilled water. After shaking the solution thoroughly and making up the volume with distilled water, absorbance of solution was measured at wavelength of 290nm. In case of CTAB studies, the volume of buffer was adjusted in such a way that after the addition of the appropriate amount of CTAB solution and 10 ml procaine solution, the final volume of the solution becoming 50 ml. The effect of CTAB concentration between 5×10^{-4}M – 5×10^{-2}M was investigated.

Results and Discussion

Percentage residual concentration of ester was plotted on a log scale against time on a linear scale according to first order kinetics. These line passed through 100% origins for all the system with a slope to standard deviation ratio > 50 showing that the plot is a good straight line. The low value of χ^2 and t-test calculated compared to those tabulated values indicated that the results obtained from these replicate experiments were reproducible.

Values from the apparent first order rate constant (k) were obtained from the slope of log% concentration-time data. The results are shown in table 1 In most of the case the kinetic plot was down to 20% residual concentrations with at least in duplicate for all conditions studied. Correlation coefficients were generally > 0.999. All first order plots gave intercepts within the range (99% – 101%).

In the present study CTAB was found to decrease the rate of hydrolysis of procaine above its CMC (critical micelle concentration), this increasing the degree of the stability of product. In order to compare the extent of its effect on hydrolysis, the data is conveniently presented in terms of "surfactant effect ratio"[22]. The SER shown in figure 1 decreases with increase in the concentration above its CMC (1×10^{-3}M). Meakin et al[14] and Cordes et al[23] in their surfactant-ester studies observed that SER increases with increase in CTAB concentration upto the region of 10^{-2}M. However, no such maxima in this concentration region of 10^{-2}M of CTAB is apparent from figure 1. Absence of maxima of the change in SER values in concentration of the region of 10^{-2}M CTAB in the present study may be attributed to different magnitude of the effect, related to the Hammett substituent constants of p-subsituent of the ester.

The values of activation energy (E_a) for the hydrolysis of procaine hydrochloride in the absence and presence of CTAB have been shown in table 1. The value in the absence of CTAB which is 13.07 Kcal/mol is in agreement with previous report[17]. (Marcus and Baron[25] have reported a value of 16.8 Kcal/mol for acid catalysed hydrolysis of procaine hydrochloride). In the presence of CTAB, these values sufficiently increase and lie in the range of 16.07 – 17.97 Kcal/mol.

Using accelerated stability analysis the shelf-life of procaine hydrochloride at 25° in absence and presence of various concentrrations of surfactant has been evaluated and is given in table 1. The data in the table shows that the shelf-life of the preparation is highly increased

Table 1. The effect of CTAB on the rate of hydrolysis of 0.15% procaine hydrochloride in absence and presence of various concentration of CTAB at different temperatures.

Molar Concentration of CTAB	Mean value of Rate Constant $min^{-1} \times 10^2$ at 50°	Mean value of rate Constant $min^{-1} \times 10^2$ at 60°	Mean value of Rate Constant $min^{-1} \times 10^2$ at 70°	Mean value of Rate Constant $min^{-1} \times 10^2$ at 80°	E_a Kcal/mol	Shelf-life hr^{-1} at 25°
Nil	0.68743	1.12999	2.02440	4.05500	13.07	1.56
8×10^{-4}M	0.53745	1.18734	2.65771	4.69948	16.02	2.47
4×10^{-3}M	0.51966	1.11929	2.39000	5.04900	16.34	3.43
2×10^{-2}M	0.17835	0.40024	1.05559	1.67180	16.64	6.97
5×10^{-2}M	0.08905	0.19800	0.47000	0.96300	17.97	24.71

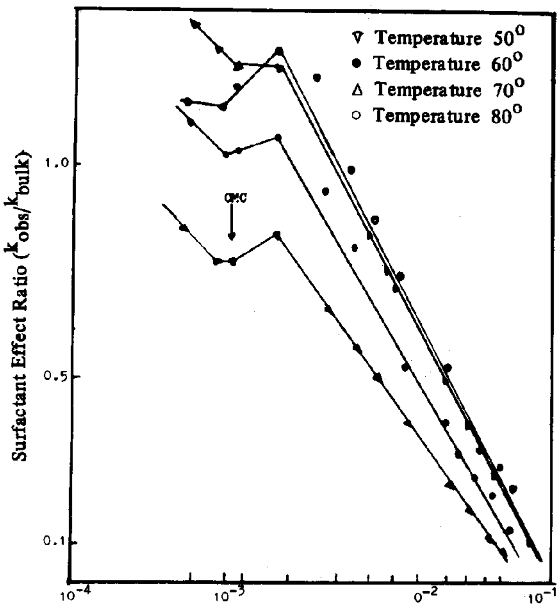


Fig. 1: The Effect of CTAB on the Hydrolysis of 0.15% Procaine Hydrochloride at pH 9.1 and at Various Temperatures Expressed as a Ratio (k_{obs}/k_{bulk}) of the First Order Rate Constants Obtained in the Presence (k_{obs}) and Absence (k_{bulk}) of Surfactant.

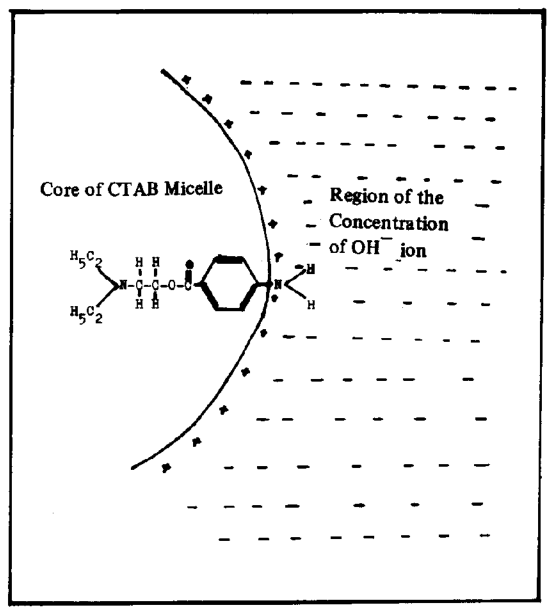


Fig. 2: Diagramatic Representation of Procaine Molecule Oriented with Respect of CTAB Micelle.

by CTAB giving a value of 24.71 hr^{-1} in presence of 5×10^{-2}M CTAB, the highest concentration studied.

The degree of stabilization could be due to the shielding of the ester linkage of procaine molecule from water of OH^- ion contact via micellization. Due to the presence of positive charge on $-NH_2$ of procaine (owing of resonance in the benzene ring of the moleucle) it is possible that procaine molecule oriented itself with respect to CTAB micelle in such a way that its $-NH_2$ group is directed towards the bulk region of the micelle concentrated with hydrolyl ion while its ester linkage (the seat of attack of OH^- ions) is penetrated deep within the micelle into which hydroxyl ions find difficulty in diffusing.

This condition has been represented diagramatically in figure 2. This situation would thus protect the molecule from hydrolysis and in turn increases the shelf-life of the preparation.

References

1. C.K. Ingold, "Structure and Mechanism in Organic Chemistry", 2nd Edition, Cornell University Press, N.Y. (1969).
2. T.H. Lowry, and K.S. Richardson, "Mechanism and Theory in Organic Chemistry", 443, (1976).
3. K.J. Laidler, "Chemical Kinetics", MCGraw-Hill Nic., N.Y. (1965).
4. E.S. Amis, "Solvent Effects on Reaction Rates and Mechanism", Academic Press Inc., London. (1966).
5. S.W. Benson, "The foundations of chemical kinetics", McGraw-Hill Book Co., N.Y. (1960).
6. J.E. Leibner, and J. Jacobus, *J. Phys. Chem.,* **81**, 130 (1977).
7. J. H. Fendler, and E. Fendler, *Adv. Phys. Org. Chem.,* **8**, 271 (1970).
8. N. Funasaki, and A. Murata, *Chem. Pharm. Bull.,* **28(3)**, 805 (1980).
9. H. Morawetz, *Adv. in Catalysis,* **20**, 341 (1969).
10. C.A. Bunton, "progress in Solid State Chemistry", 8, 239 (1973).
11. J. Baumrucker, M. Clazadilla, and E.H. Cordes, "Reaction Kinetics in Micelles", Plerum Press, N.Y.
17. T. Higuchi, A. Havinga, and L.W. Busse, *J. Am. Pharm. Associ.* (Sci. Ed.), **39**, 405, 411 (1950).
18. E. Jungermann, "Cationic Surfactants", Vol 4 Surfactant Science Series, Marcel Dekker Inc., N.Y. (1970).
19. E.F.J. Duynstee, and E. Grundwald, *J. Am. Chem. Soc.,* **81**, 4540 and 4524 (1959).
20. P. Mukerjee and K.J. Mysels, *J. Phys. Chem.,* **77**, 2938 (1955).
21. R.G. Bates "Electrometric pH Determination." Chapman and Hall Ltd, London. (1954).
22. I.K. Winterborn, Ph.D. thesis, University of Bath, U.K. (1972).
23. L.R. Romsted, and E.H. Cordes, *J. Am. Chem. Soc.,* **90**, 4404 (1968).
24. A.D. Marcus, and S. Baron, *J. Am. Pharm. Assoc. Sci. Ed.,* **48**, 85 (1959).
(1973).
12. R.B. Dunlap, Ph.D. Thesis, Indiana University, U.S.A. (1968).
13. B.J. Meakin, B.B. Shetewi, and D.J. Davies, *Conf. Proc.* "First International Confe-rence on Pharm Technology, Paris", **1**, 27 (1977).
14. B.J. Meakin, I.K. Winterborn, and D. J. G. Davies, *J. Pharm. Pharmac.,* 23, 258 (1971).
15. I.K. Winterborn, B.J. Meakin, and D.J.G. Davies, *J. Pharm. Sci.,* **63**, 64 (1974).
16. A.E. Beg, B.J. Meakin, and D.J.G. Davies, *Die Pharmazie,* **35**, 161 (1980).