J. Chem. Sci., Vol. 120, No. 5, September 2008, pp. 475–480.

Micellar catalysis in the retro-Knoevenagel reaction of ethyl-α-cyanocinnamates

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MS received 23 November 2007; revised 19 March 2008

Abstract. Kinetics of base catalysed hydrolytic cleavage of ethyl α-cyanocinnamate (ECC) and several *para*-substituted ECC have been investigated spectrophotometrically in the presence of anionic surfactant sodium laurylsulphate (NaLS). The rate of cleavage of ECC was retarded by NaLS. The pseudo-first order rate constants, k_{obs}, correlate with the Hammett σ_p^+ – constants. The ρ+ value (0·86) in aqueous medium is less than ρ^+ value (1·11) in 0·02 M NaLS. Kinetic data were analysed by Menger–Portnoy and Piszkiwicz model. The substrate-micelle binding constants, K_s, correlate with the Hammett σ-constants and Hansch hydrophobicity constants – π of the substituents.

Keywords. Ethyl α-cyanocinnamate; micellar catalysis; retro-Knoevenagel reaction; hydrophobicity.

1. Introduction

The design of microscopic molecular assemblies which mimic the micro environment present in biological system can contribute to a great deal in the understanding of the naturally occurring process. Micelles are good examples of organized assemblies. Micellar catalysis are useful biochemical models for numerous processes which occur on or involve amphiphilic surface. Therefore the micellar catalysis and inhibition have received considerable attention in view of the analogies between the micellar and enzyme catalysis.[1–7] The effects of micelles on the rates of organic reactions are explicable in terms of the differences in the reactivity of the substrate in the micellar phase and in bulk solution and the degree and nature of substrate-micelle binding. Basically these effects can be attributed to electrostatic and hydrophobic interaction between the substrate and surfactant aggregates.

Olefinic compounds containing electron withdrawing substituents in α-position of >C=C< bond undergo facile hydrolytic cleavage in the presence of base in aqueous medium.[8–11] For such organic reactions involving nucleophilic anion and neutral substrate, based on electrostatic consideration one may expect rate acceleration by cationic micelles and rate retardation by anionic micelles. In the present work, the effect of the anionic surfactant sodium laurylsulphate (NaLS) on the rates of base catalysed hydrolytic cleavage of Knoevenagel reaction of ethyl α-cyanocinnamate (ECC) and several *para*-substituted ethyl α-cyanocinnamates has been investigated. Attempts made to measure the effect of cationic surfactant, cetyltrimethylammonium bromide, on the rate of the title reaction was unsuccessful due to the high acceleration of the rate caused by cationic micelle under the experimental condition.

2. Experimental

Ethyl α-cyanocinnamate and all the *para*-substituted ethyl α-cyanocinnamates (ECC) were prepared by the literature method.[12] An equimolar ethanolic solution (0·1 M) of appropriate benzaldehyde and ethylcyano acetate containing few drops of pyridine was refluxed for 4–6 h on a water bath. The solvent was removed, the residue filtered and purified by recrystallisation from ethanol. Acetonitrile was refluxed for 5 h over phosphorous pentoxide and then distilled through a fractionating column. Sodium laurylsulphate (NaLS) is a commercial sample (Fluka) and used as such. Carbonate free sodium hydroxide solution was prepared by washing the pellets of sodium hydroxide with doubly distilled water and rejecting

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the supernatant liquid and it was standardized using standard potassium hydrogen phthalate.

The base catalysed cleavage of ECC was investigated in 10% acetonitrile (v/v) water mixture at 30°C. Concentration of ester in the reaction medium is ca. $2–7 \times 10^{-5}$ M. The course of the reaction was monitored by measuring the decrease in absorbance of ECC employing Hitachi 200-20 UV-Visible spectrophotometer attached with a thermostatic cell holder. The wave length values at which measurements were made are: 432, 345, 321, 305, 309, 314 and 316 nm respectively for the substituents *p*-$N(CH_3)_2$, *p*-OCH_3, *p*-CH_3, *p*-H, *p*-F, *p*-Cl and *p*-Br. The pseudo-first order rate constants, k_{obs}, were evaluated from the slopes of linear plot of log OD versus time by the method of least squares.

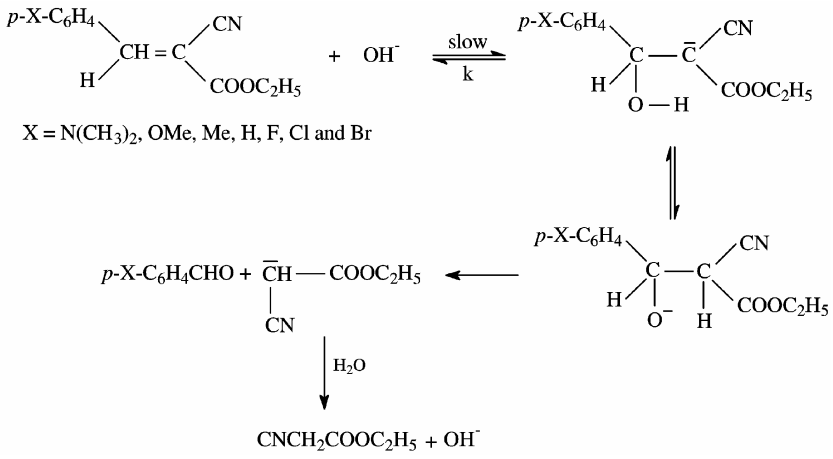
3. Results and discussion

3.1 *Mechanism in the absence of NaLS*

In the absence of surfactant, the pseudo-first order rate constant for the base catalysed retro-Knoevenagel reaction of ECC was measured in the presence of various amount of [OH^-]. The plot of k_{obs} vs [OH^-] is linear ($r = 0{\cdot}996$) with negligible intercept. The plot of log[OH^-] vs logk_{obs} is also linear with unit slope. This shows that the order of the reaction with respect to [OH^-] is one. The reaction proceeds as shown in the scheme 1.

3.2 *Substituent effect*

The pseudo-first order rate constant, k_{obs}, was measured in 0·001 M NaOH at 30°C for several *para*-substituted ECC (table 1). Applicability of the Hammett equation, ($\log k = \rho\sigma + \log k_o$) was tested by plotting logk_{obs} values of substituted ECC versus the respective Hammett σ_p – constants (figure 1). The electron donating substituents (–OCH_3, –$N(CH_3)_2$) deviate considerably from the Hammett plot. Correlation of k_{obs} with σ_p^+ – constants gave fairly good correlation ($r = 0{\cdot}986$) with ρ^+ value of 0·86. The positive value of rho is in accordance with the mechanism involving the formation of negatively charged transition state.



Scheme 1.

Table 1. Effect of NaLS on the rate of hydrolytic cleavage of substituted ECC.

[NaOH] = 0·001 M	$10^4\ k_{obs}/s^{-1}$				Temp. = 30°C		
[NaLS]/M	*p*-$N(CH_3)_2$	*p*-OCH_3	*p*-CH_3	*p*-H	*p*-F	*p*-Cl	*p*-Br
0·000	1·43	16·0	27·0	41·0	51·6	52·5	62·5
0·010	0·25	4·7	6·6	22·0	16·1	13·5	23·7
0·015	0·15	3·2	4·0	12·7	13·6	7·7	14·5
0·020	0·10	2·0	3·0	10·7	9·0	5·3	11·2
0·025	0·09	1·8	2·3	7·2	7·6	4·1	8·3
0·030	–	1·4	1·7	5·2	6·2	4·0	7·3
0·040	–	0·8	1·2	4·9	5·0	2·5	5·9
0·060	–	0·6	0·9	3·7	3·5	1·3	3·6

3.3 *Effect of NaLS*

Addition of anionic surfactant NaLS decreases the rate of cleavage. Figure 2 shows the variation of k_{obs} with [NaLS] for ethyl α-cyanocinnamate. The plot is typical for reactions inhibited by micelles. Similar rate retardation was observed for all the substituted ECC (table 1). For micellar inhibited reactions, the extent of rate retardation is usually obtained by the ratio k_{min}/k_w, where k_{min} is the minimum rate constant in the saturation limit in the presence of high concentration of surfactant and k_w is the rate constant in

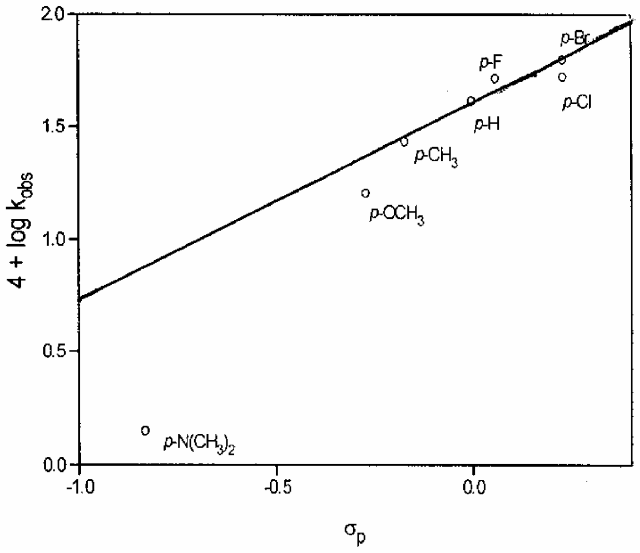


Figure 1. Hammett plot for the base catalysed cleavage of *para*-substituted ECC in the absence of surfactant (temperature = 30°C; [NaOH] = 0·001 M).

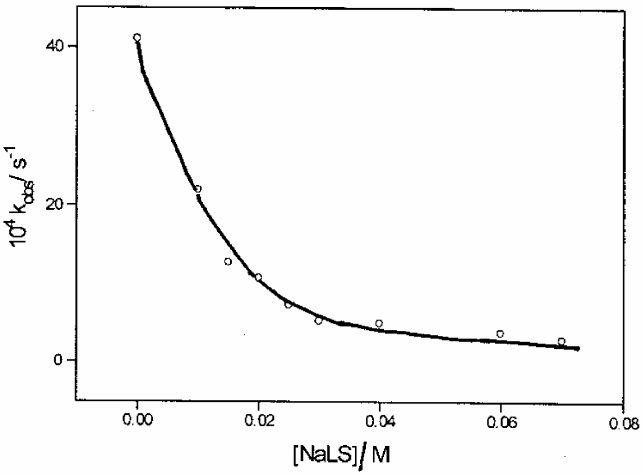


Figure 2. Effect of [NaLS] on the rate of base catalysed hydrolytic cleavage of ethyl α-cyanocinnamate (temperature = 30°C; [NaOH] = 0·001 M).

the absence of surfactant. In the present study, for all the substrates no saturation limit of the rate was reached under the experimental conditions employed. A rough estimate of the rate retardation in 0·06 M NaLS is evaluated by the ratio k_{obs}^{NaLS}/k_w where k_{obs}^{NaLS} is the rate constant in the presence of 0·06 M NaLS and k_w is the rate constant in the absence of NaLS (table 2). The extent of rate retardation varies from substituent to substituent and it is in the range of 10–40 times.

Rate retardations caused by micelles can be explained in terms of electrostatic interactions, distribution of the substrate between micellar phase and aqueous phase, relative first order rate constants in micellar phase and aqueous phase.

In the presence of surfactant, ECC is distributed between the micellar phase and aqueous phase. In micellar phase, probably the reaction takes place in the shear surface by the attack of OH^- ions present in bulk aqueous phase. Due to electrostatic repulsion between the polar head group of the micelle formed from NaLS and the anionic nucleophile OH^-, the concentration of OH^- ion in this region will be depleted leading to rate retardation.

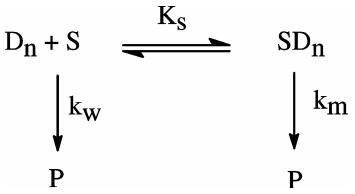
In the present reaction, there is a development of negative charge in the transition state (scheme 1). Such a transition state will be electrostatically destabilized. Since the micellar surface is less polar than water, the solvation of transition state in the micellar phase will be less when compared to the polar aqueous phase. As a result, the rate of reaction in micellar phase is decreased. Increase in [NaLS] causes more solubilisation of the substrate into micelle which results in decrease of k_{obs} with an increase of [NaLS].

3.4 *Substituent effect in the presence of NaLS*

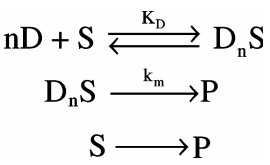
The applicability of Hammett equation has been reported for micelle catalysed reactions. The ρ value for the micelle catalysed reactions are slightly different from the corresponding value for uncatalysed reaction.[13,14] The k_{obs} values in 0·02 M NaLS, at 0·001 M NaOH were correlated with the Hammett σ_p^+ – constants. The ρ^+ value was found to be 1·11 (r = 0·986) which is slightly higher than the ρ^+ value in the absence of surfactants. Since the rate of reaction in micellar phase is less than that in aqueous phase, according to the Reactivity-Selectivity Principle, the reaction in micellar phase will be more sensitive to substituent effect and hence ρ value in micellar phase is higher than in aqueous phase.

Table 2. Rate retardation in 0·06 M NaLS for hydrolytic cleavage of substituted ECC.

Substituent	*p*-OCH_3	*p*-CH_3	*p*-H	*p*-F	*p*-Cl	*p*-Br
k^{NaLS}/k_w	0·04	0·03	0·09	0·07	0·03	0·06



Scheme 2.



Scheme 3.

3.5 *Rate law and mechanism in presence of NaLS*

3.5a *Menger–Portnoy model:* To interpret the kinetic data, the pseudo-phase kinetic model proposed by Menger and Portnoy[15] may be considered. The base catalysed cleavage of ECC occurs in bulk aqueous phase and the micellar pseudo-phase (scheme 2).

Here k_w and k_m are pseudo-first order rate constants in aqueous and micellar phase respectively, K_s is the substrate-micelle binding constant and $[D_n] = \{[D]_t - \text{CMC}\}$. ($[D]t$ is the total concentration of surfactant: CMC is the critical micelle concentration). For the calculation of $[D_n]$, CMC of NaLS is taken as $8{\cdot}1 \times 10^{-3}$ M.

For the above scheme, the rate law is

$$k_{obs} = \frac{k_w + k_m K_s[D_n]}{1 + K_s[D_n]}. \quad (1)$$

which may be rearranged to (2).

$$\frac{1}{(k_w - k_{obs})} = \frac{1}{(k_w - k_m)} + \frac{1}{(k_w - k_m)}\left[\frac{1}{K_s[D_n]}\right]. \quad (2)$$

In this model, double reciprocal plot is involved and there will be some uncertainty in the intercept. In order to remove this uncertainty, the (2) was modified as (3).

$$(k_{obs} - k_w) = -\frac{1}{K_s}\frac{(k_{obs} - k_w)}{[D_n]} + (k_m - k_w). \quad (3)$$

The plot of $(k_{obs} - k_w)$ vs $(k_{obs} - k_w)/[D_n]$ is linear and from the slope and intercept of such plots, the rate constants, k_m, for the micellar phase and the substrate-micelle binding constants, K_s, for substituted ECC were evaluated and presented in table 3.

3.5b *Piszkiewicz model:* A number of micellar catalysed reaction have also been explained by the model developed by Piszkiewicz,[16] in analogy with the model used to explain the enzyme catalysis by Hill.[17] For a sigmoid type of catalysis, Piszkiewicz proposed the scheme 3.

K_D is the dissociation constant of the micelle-substrate complex, k_m is the rate of the reaction within micelle, k_w is the rate of the reaction in aqueous medium and n is the index of cooperativity.

For such a scheme, the observed rate constant, k_{obs}, can be expressed as a function of the concentration of surfactant as in (4).

$$k_{obs} = \frac{k_m[D]^n + K_D k_w}{K_D + [D]^n}. \quad (4)$$

The above (4) can be rearranged to

$$\log\left(\frac{k_{obs} - k_w}{k_m - k_{obs}}\right) = n\log[D] - \log K_D. \quad (5)$$

The advantage of (5) is that it does not require the knowledge of CMC of the surfactant. Although this model was developed for micelle catalysed reactions showing a maximum rate followed by inhibition, the model has been applied by several workers[18,19] to explain micellar effect in which the reaction is inhibited/catalysed by the micelle over the whole range as observed in the present study.

Since NaLS retards the rate at very high concentration of NaLS, the substrate will be completely solubilised in micelles and hence $k_m \cong 0$. From the plot of $\log(k_{obs} - k_w/k_{obs})$ vs log[NaLS}, values of n,

Table 3. Parameters evaluated employing Menger–Portnoy model.

Substituent	*p*-$N(CH_3)_2$	*p*-OCH_3	*p*-CH_3	*p*-H	*p*-F	*p*-Cl	*p*-Br
K_s/mol dm^{-3}	3472 ± 350	606 ± 55	1856 ± 190	341 ± 39	470 ± 19	1728 ± 200	1770 ± 190
$10^4\ k_m$/s^{-1}	0·07	0·17	1·4	1·4	1·7	1·8	1·6

Table 4. Parameters evaluated employing Piszkiewicz model.

Substituent	*p*-CH_3	*p*-H	*p*-F	*p*-Cl	*p*-Br
K_s/mol dm^{-3}	1779 ± 53	281 ± 15	324 ± 17	1587 ± 82	1770 ± 90
N	1·4	1·3	1·1	1·3	1·2
log$[D]_{50}$	–2·37	–1·88	–2·28	–2·41	–2·09

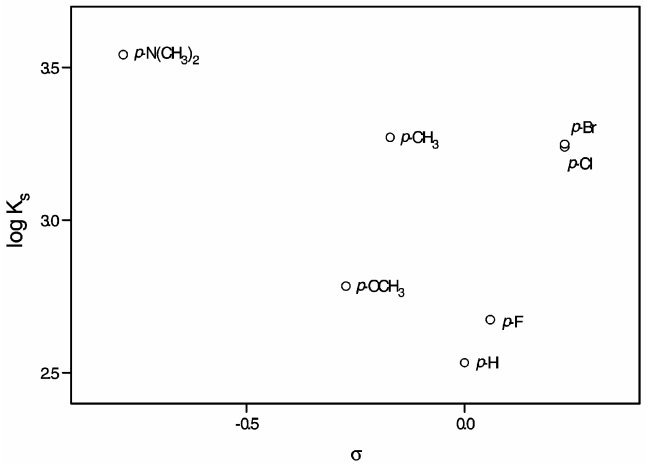


Figure 3. Plot of substrate-micelle binding constants of *para*-substituted ethyl α-cyanocinnamates evaluated by Menger–Portnoy model vs Hammett σ-constants.

K_D and log$[D]_{50}$ for several substituted ECC were evaluated and presented in table 4. ($[D]_{50}$ is the concentration of surfactant needed to retard the rate of the reaction by 50%).

3.6 *Quantitative analysis of substrate-micelle binding constants*

The substrate-micelle binding constants, K_s evaluated by Menger–Portnoy model for substituted ECC was plotted against the Hammett σ-constants (figure 3). The plot is scattered indicating that electronic effects of the substituents alone cannot account for the substrate-micelle binding. It has been well established that the hydrophobic interaction plays an important role in the substrate-micelle binding.[3,4,15] NMR studies show that non-polar aromatic compounds are incorporated into the hydrophobic interior core of the micelle[20–22] and the micelle-substrate binding increases with an increase in hydrophobicity of substrate/micelle. The K_s value for substituted ECC is sensitive to the nature of the substituents present in the aromatic ring. Therefore it appears that the micellar site of ECC is the stern layer with a part of aromatic ring penetrating into the hydrophobic core of the micelle as shown in figure 4.

Hydrophobic interaction between micelle and the substrate alters the magnitude of binding. Biologically active compounds exert a rate-controlling effect on chemical/physical process. The biological effects resulting from the structural changes can be correlated by regression analysis employing the two parameters namely σ and π. The σ-constants are measure of electronic effect. The π-constants are measure of hydrophobicity and it is defined as follows:

$$\pi = \log(P_X/P_H), \tag{6}$$

where P_H is the partition coefficient of a parent compound and P_X is that of a derivative (in octanol–water system) i.e. π is a measure of the relative free energy change resulting in moving a derivative from one phase to another phase and hence it is a useful parameter to account for biological activity.

In some cases, the biological activity (1/*C*) of closely related substrates is correlated[23] with the electronic effect and hydrophobicity of the substituents using the Hammett σ-constants and Hansch hydrophobic constants π.

$$\log\left(\frac{1}{C}\right) = a\pi + \rho\sigma + k. \tag{7}$$

The parameters '*a*' and ρ are measure of the sensitivity of electronic effect and hydrophobic effect of the substituents for the biological effect studied.

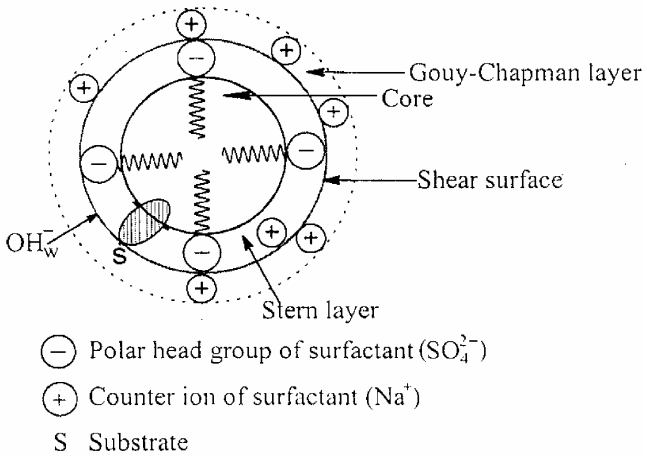


Figure 4. Site of occupation of ECC in the micelle.

Table 5. Hammett σ-constants and Hansch hydrophobicity constants – π.

Substituent	π	σ
p-$N(CH_3)_2$	0·14	–0·83
p-OCH_3	–0·02	–0·27
p-CH_3	0·52	–0·17
p-H	0	0
p-F	0·14	0·06
p-Cl	0·71	0·23
p-Br	0·86	0·23

The σ- and π-constants of selected substituents are presented in table 5. Multiple linear regression analysis of $\log K_s$ with σ-constants and π-constants gave the regression (8).

$$\log K_s = 1{\cdot}14\pi - 0{\cdot}97\sigma + 2{\cdot}55 \ (R = 0{\cdot}990). \qquad (8)$$

Excellent correlation obtained with σ- and π-constants shows that both the electronic effect of the substituents and its hydrophobicity play an important role in the micelle-substrate binding. Positive value of 'a' implies that as the hydrophobicity of the substituent increases, the substrate-micelle binding also increases. Thus micellar catalysed reactions are useful biological models.

4. Conclusion

Base catalysed hydrolytic cleavage of ECC is retarded by the anionic surfactant NaLS and ρ^+ value in presence of NaLS is slightly higher than the ρ^+ value in aqueous medium. A part of the aromatic ring of ECC is incorporated into the hydrophobic interior of the micelles. The substrate-micelle binding constant is sensitive to the electronic effect and hydrophobicity of substituent present in aryl ring. Micellar catalysis is a useful biological model.

Acknowledgement

The authors thank the Managing Board of VHNSN College, Virudhunagar for financial assistance and for providing infra-structural facilities.

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