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THE CATALYTIC EFFECT OF CATIONIC AMINO MICELLES ON THE HYDROLYSIS OF SUBSTITUTED PHENYL ESTERS

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Abstract - The catalytic effects of two aminocationic micelles on the hydrolysis of substituted phenyldecanoate esters and a positively charched benzoate ester (CPNBA) were determined. The micellaric catalysts were of the general structure $[CH_3(CH_2)_3N(CH_3)_2(CH_2)_nNH_2]Br$ where n=2 (micelle 1); n=3 (micelle 2). The kinetics followed the expression: $k_{obs}=k_o+k_{cat} \times K_a/(K_a+H^+)+k^c_{OH}[OH^-]$. From the comparison of the k^c_{OH} rates with specific base catalysis rates deduced from reactions in non catalytic micelles, it was concluded that the k^c_{OH} term, is compatible mainly with an aminolysis reaction catalyzed by hydorxide ion. The Hammett and Bronsted correlations (ρ=2.8; β=1.0), in addition to the very small deuterium isotope effect, suggested that k_{cat} corresponded with a nucleophilic mechanism. The Bronsted plot of log k_{cat} vs pKa of the phenolate leaving groups in micelles 1 and 2 showed a biphasic behaviour. The break in the curve occured at pK_o=5.89 and pK_o=6.78 respectively. The partition ratio $k^{\pm}/k_{-a}$ of the zwiterionic tetrahedral intermediate was derived from the experimental data and produced the following correlation: log $k^{\pm}/k_{-a}=-0.92pK_o+0.43pK_N+2.466$. The ester CPNBA exhibited a deuterium isotope effect of 2.1. From product analysis it was concluded that the reaction proceeds via a general base catalysis of aminolysis.

Micelles are known to assist many bimolecular reactions due to the following operating factors: (a) changes in the microenvironment of the reacting species (as medium polarity and its hydrophobic desolvation property), (b) electrostatic interactions such as stabilization or destabilization of transition states and ground states respectively, or changes in the dissociation constants of nucleophiles and, (c) volume and proximity effects resulting from electrostatic and hydrophobic interactions.

The latter effect (c) is associated with entropy losses in the reactants and play a major role in enzyme catalysis. Thus the incorporation of reactants into the micelle is essential for catalysis[1]. In this respect, micellar catalysis depends on the partition coefficient of substrates and catalysts between the bulk and the micellar pseudophase. In order to promote catalysis it is necessary to increase the hydrophobicity of the catalysts and the substrates or, alternatively, to attach the catalyst covalently to the micellar surface.

Indeed many efforts in the last two decades have been directed towards the study of nucleophilic catalysis by monofunctional and bifunctional micelles, together with mixed micelles. This was demonstrated with hydroxy[2-8]

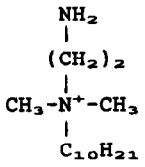
hydroxamic[9-14] carboxy[15,16] thio[17-21] and amino[22-31] surfactants. Bifunctional and mixed micelles composed of imidazole-hydroxyl[22b-23a]; thiol-amine[17,25]; hydroxamate-imidazole[32] head groups have also been reported.

Based on the active site of serine proteinases most of the aminomicellar models were comprised of an imidazolyl group. Esterolysis by this type of micelles exhibited an effective transacylation reaction either with the homocationic imidazolyl micelle or with a cationic comicelle. The apparent catalysis was attributed mainly to the kinetically active imidazolide anion. No evidence of a cooperative effect in the imidazole-hydroxyethyl bifunctional surfactant or in the mixed micelle composed of these catalysts was observed. Similarly, imidazole or amino groups do not demonstrate any cooperativity in thiolate acylation reactions.

Although an appropriate model for the imidazole catalyzed acylation of the hydroxylic group at the interface of micelles (serine protease analogue) has yet to be designed, microenvironmental effects in chiral functional surfactants which leads to a substantial enantioselectivity, stress the importance of micelles as models for enzymatic reactions[33,25,34,35].

An additional aspect of the microenvironmental effect on reactions in micelles is concerned with a possible deviation[36] from the Bronsted correlation for attacking and leaving groups. This can be due to the change in reactivity and basicity of catalysts in cationic micelles.

In an effort to gain a greater insight into this possible effect, we have studied the aminolysis reaction produced by the amino cationic micelles 1 and 2 and the non detergent catalyst 3 on substituted phenyldecanoate esters and the positively charged benzoate ester (CPNBA). The reaction's pathway, Bronsted correlations and the role of the tetrahedral intermediates is herein reported.



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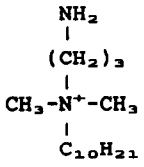

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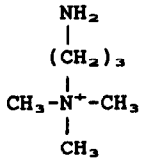

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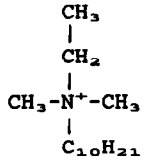

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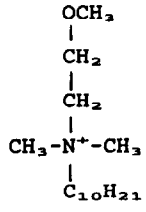

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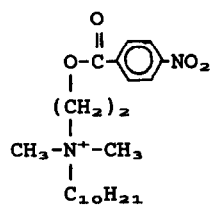
CPNBA



Phenyl esters

2,4-dinitrophenyl decanoate	OPNPD
2,5-dinitrophenyl decanoate	OMNPD
4-nitrophenyl decanoate	PNPD
3-nitrophenyl decanoate	MNPD
Phenyl decanoate	PD
tolyl decanoate	PMePD
4-Nitrophenyl hexanoate	PNPH

EXPERIMENTAL

Materials: N-decyl-N,N-dimethyl-N-(2-aminoethyl)ammonium bromide. HBr (1.HBr). N,N-dimethyl-N-(2-ethoxycarbonyl) ethylamine (A) was prepared by adding 40g (0.45mole) of N,N-dimethyl-N-2-ethylamine to 60g (0.51mole) of diethylcarbonate. The solution was kept at 70°C for 48hr and then distilled under low pressure. Compound (A) was collected at 70°C/0.5 Torr. 44g(0.27mole) of compound (A) were allowed to react with 82g (0.37mole) of decylbromide at room temperature for 7 days. The product N-decyl-N,N-dimethyl- N-(2-N-ethoxycarbonyl ethyl) ammonium bromide (B) was crystallized from acetone-ether. Hydrolysis of the carbamate (B) was carried out in concentrated HBr solution (1:1 diluted with water) for 3 days under reflux. Water was evaporated and the remaining viscous oil was crystallized from ethanol-ether. The white powder obtained has a m.p in the range of 195-220°C. Anal. cal'd. for: $C_{14}H_{34}N_2Br_2$ C,43.07; H,8.72; N,7.18; Br, 41.02; found: C,42,90; H,8.75; N,7.11; Br, 41.30.

N-decyl-N,N-dimethyl-N-(3-aminoethyl)ammonium bromide. HBr(2.HBr)

N,N-dimethyl-N-3-ethoxycarbonylpropylamine (C) was prepared according to the above method bp 90°C/0.5 Torr. N-decyl-N,N- dimethyl-N-(3-ethoxycarbonylpropyl) ammonium bromide (D) was prepared from 70g (0.40 mole) of C and 132g (0.6mole) of decylbromide, as described above (3 days at room temperature). A viscose oil was formed by adding actone followed by ether. The oil was separated and solidified to a white foam after a day in a desicator under high vacuum. Anal. cal'd. for: $C_{18}H_{39}N_2O_2Br$ C,54.68; H,9.87; N,7.08; Br, 20.25; found: C,54.30; H, 9.97; N,7.38; Br, 19.76. ;Hydrolysis of D to the final product II.HBr was accomplished accoridng to the above in HBr solution dilute 1:1 in water by 3 day reflux.

N,N,N -trimethyl-N-3-aminopropyl-ammonium bromide.HBr(3.HBr)

N,N,N-trimethyl-N-(3-N-ethoxycarbonylpropyl) ammonium bromide was prepared by adding compound C to an ice cold solution of methyl bromide. The solid formed was crystallized from ethanol-ether (mp=105°C) and hydrolyzed in HBr/H_2O (1:1) to the final product 3.HBr. Recrystallized from methanol results in white material of m.p. 173°C.

Analysis cal'd for $C_6H_{18}N_2Br_2$: C,25.80; H,6.47; N,10.07; Br, 57.55; found: C,28.88; H,6.46; N,10.10; Br, 57.54.

N-decyl,N,N-dimethyl-N-(3-N-p-nitrobenzoyl-propyl)ammonium bromide (CAI)

5g(0.05 mole) of 3-dimethyl-1-propylamine in dry benzene was added dropwise to a cold solution of 9g (0.05mole) p-nitrobenzoylchloride in benzene. The solution was stirred for 2 hours and the precipitate (E) (N,N-dimethyl, N-3-p-nitro benzoyl propylamine, HCl) was collected, washed with acetone and crystallized from absolute ethanol (m.p=185°C). The amide hydrochloride (E) was dissolved in 1M NaOH solution extracted with ether and dryed over $MgSO_4$. Removal of the ether results in a yellow powder. 3g of the powder were allowed to react with 5g of decyl bromide under reflux for 24h. The final product was crystallized from acetone-ether m.p. 103-105°C. Anal. Cal'd for $C_{22}H_{38}N_3O_3$: C,55.93; H,8.05; N,8.90; Br,16.95; found: C,55.86; H,8.10; N,881; Br,17.04. The detergents: IV and V were available from a previous study[8]. The esters: OPNPD, OMNPD, PNPD, MNPD, PD PMePD and CPNBA were prepared as previously described.

Kinetics: Kinetic measurements were made with a Unicam SP 800 spectrophotometer equipped with a jacketed cell holder. Water was circulated through the cuvette holder at 30°C. The reaction was carried out with 0.1M of catalyst at ionic strength μ=0.8M (KCl). The pH of the kinetic solutions was determined prior to and at the completion of the reactions using a Radiometer Model 26 pH meter. To determine pD the glass electrode correction equation was made [33a]. The rate of phenoxide liberation was determined at the following wavelengths: 2,4-dinitro-325mn; 2,5-dinitro-290mn; 3-nitro-350nm; 4-nitro-350nm; 4-H 277nm; 4-methyl-285nm. The rate of CPNBA hydrolysis was determined at 300 nm. The reactions were initiated by the addition of 5-10 μL of the ester to a cuvette containing the catalyst solution equilibrated at 30°C. At pH=pK_a±0.5 of the catalyst no buffer was used. In other cases 0.01-0.05M of borax and carbonate buffers were employed for the pH range 8-95. and 9.5-10.5 respectively. Rate constants were extrapolated to zero buffer concentration.

A non linear least squares computer program was used to obtain the first order rate constants.

pKa determination: The pKa of 1, 2 and 3 were titrimetrically determined. Solutions of 0.1M of these compounds at 0.8M KCl were titrated with concentrated potassium hydroxide using a microburet. The solutions were thermostated at 30°C and the pH was measured.

Product analysis of CPNBA aminolysis in micelle 2

Product analysis in aminolysis of CPNBA was based on the molar extinction ε of CPNBA (ε(E)=2400); p-nitrobenzoic acid (ε(A)=5600) and CAI (ε(Am=4286) at 300nm pH=9.40, 30°C μ=0.8M(KCl).

The following two experiments were carried out: 1) 7.5 μl of CPNBA stock solution (2.4×10^{-2}M) in acetonitrile were injected to a spectrophotometeric cell containing 3ml of 2 (0.1M) μ=0.8(KCl) pH=9.4. The calculated rate constant k_{obs}

was $48x10^{-3}$ min^{-1} and the OD(1) developed at 300mn was 0.155. 2) The same amount of CPNBA in acetonitrile (7.5µl) was injected into a spectrophotometric cell containing 3ml of micelle 4 (0.1M) kept under identical experimental condition as above. OD(2) developed at 300 nm was 0.190.
According to scheme 2, OD(1) in experiment(1) equals to equation (1):

$$OD(1)=(C_o-C(ii))\ (\varepsilon(A)-\varepsilon(E) + C(ii)\ (\varepsilon(Am) - \varepsilon(E)) \quad (1)$$

and OD(2) correspond to equation (2):

$$OD(2) = C_o(\varepsilon(A) - \varepsilon(E)) \quad (2)$$

where C_o is the initial concentration of the ester CPNBA and C(ii) is the concentration of the esters that formed amide via route (ii). (Route (ii) and Route (i) correspond to Scheme 2).
Equations (1) and (2) lead to equation (3):

$$\frac{OD(2) - OD(1)}{OD(2)} \times \frac{\varepsilon(A) - \varepsilon(E)}{\varepsilon(A) - \varepsilon(Am)} = \frac{C(ii)}{C_o} = \frac{k(ii)}{k_{obs}} \quad (3)$$

where k(ii) is the rate constant for the reaction via pathway(ii) (Scheme 2)
Inserting the experimental values to equation (3) allow the following conclusion.

$$\frac{(0.19 - 0.155)\ (5600 - 2400)}{0.19(5600 - 4286)} = 0.42 = k(ii)/K_{obs}$$

Thus $k(ii)=0.42x48\ 10^{-3}\ min^{-1} = 20.2\ 10^{-3}\ min^{-1}$
Since in addition to the hydrolysis via path(i), specific base catalysis k^{o}_{OH} also contribute to the formation of p-nitrobenzoate k(i) can be deduced:
$k_{obs} = 48.10^{-3}\ min^{-1} = k(ii) + k(i) + k^{o}_{OH}$
at pH=9.4 $k^{o}_{OH}=29.10^{-3}\ min^{-1}$
Thus $k(i)=48.10^{-3}-29.10^{-3}-20.2x10^{-3} \cong 0$
These calculations indicate that pathway (i) (Scheme 2) is not an operative route in the hydrolysis of CPNBA.

RESULTS

In functional micelles it has been demonstrated[14] that the apparent dissociation constant (Kapp) varies with the degree of dissociation α and that titration curve is in accord with the modified Henderson-Hasselbach equation (4) or with the Lindenstam- Lang equation (5):

$$pKa = pH + n \log (1-\alpha)/\alpha \quad (4)$$

where pKa is the pK_{app} at $\alpha = 0.5$

$$pK_{app} = pH + \log (1-\alpha)/\alpha = pK_{int} + S\alpha \quad (5)$$

where S is the slope of the line pK_{app} Vs α and pK_{int} is the intercept of the line at α=0
The electric surface potential ψ can be expressed by equation (6):

$$\psi = S(1-\alpha)\ kT/0.434\ e \quad (6)$$

where e is the elementary charge.
Fig 1 presents the linear correlation observed between the intrinsic pKa of protonated micelles 1 and 2 and their degree of ionization (α). In both micelles the change of pKa_{app} values with α are similar (+0.2 units) and the slope S of both micelles is also approximately the same (0.21 and 0.19 for 1 and 2 respectively).
According to equation (6), this may reflect a closely related effective charge and surface potential in the two systems being compared.

Aminolysis of phenylesters in basic solutions is known[38] to obey equation (7):

$$k_{obs}=k_o + k_{OH}[OH] + k_1[amine] + k_2[amine]^2 + k_3[Amine]\ [OH] \quad (7)$$

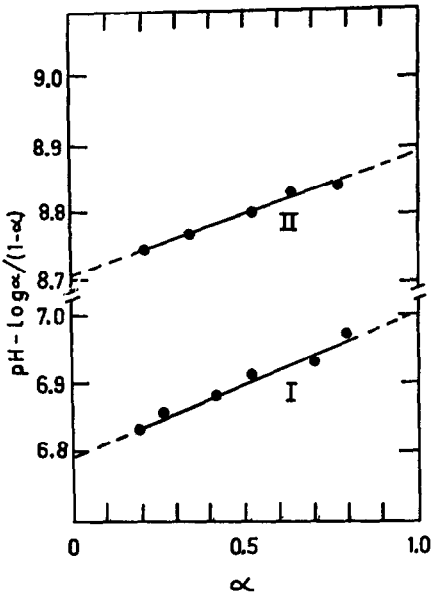


Fig. 1. Dependence of pK_{app} with the degree of dissociation(α) of micelle 1 and 2 pKa(I)=6.9, pKa(II)=8.8, pK_{int}(I)=6.79 pK_{int}(II)=8.71.

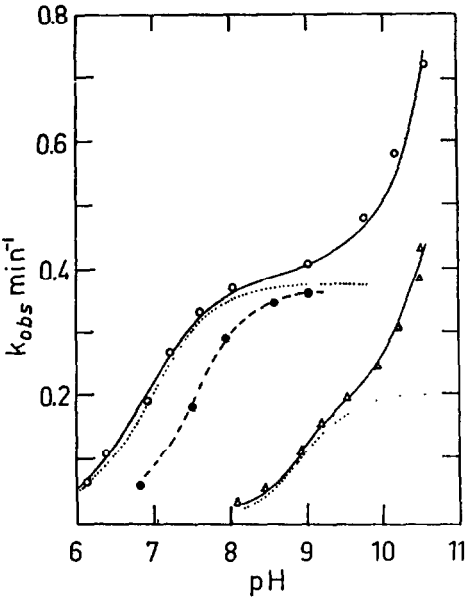


Fig. 2. pH-rate profile of PNPD in micelle 1: O—O (H_2O), O----O (D_2O), and of MNPD in micelle 2, at 30°C and ionic strength of 0.8M (KCl).
The solid lines are caculated from equation (8) using rate constants given in tables I and II. The dot lines are the calculated pH-rate profile after substructing the contribution of k^{o}_{OH}.

In micellar systems, however, as in other intramolecular reactions, the second order rate term k_1 and the third order rate constant k_2 of equation 7 are reduced to first order rates due to the formation of a substrate-micelle intracomplex.

The third order rate term k_3 for the hydroxide ion catalyzed nucleophilic attack of an amine is also reduced to a second order rate constant.

Therefore it appears that the rate law of ester hydrolysis in presence of micelles 1 or 2 as catalysts should follow equation (8) .

$$K_{obs} = k'_{o} + k_{cat}\,\frac{K_a}{K_a+H^+} + k^{o}_{OH}[OH] \qquad (8)$$

where k'_{o} represents, the contribution of the hydrolytic rate constants of the lyate species when all the amino groups are in protonated form (i.e. degree of ionization α=0). The k_{cat} term represents both a nucleophilic (k_n) and an intramolecular general base catalysis (gb) of aminolysis resulting from the amino head groups of the micelles. The k^{o}_{OH} includes: a) the specific base catalysis mode k_{OH} and b) the term assigned to hydroxide ion catalysis. k_{o} was obtained from the plot of k_{obs} Vs α (degree of dissociation for the protonated amine) by extrapolating the observed rate constants to α=0.
The slope of k_{obs} Vs [$^{-}$OH] at a high pH range provides the k^{o}_{OH} value. The intercept of this plot correspond to k'_{o} + k_{cat}. Since in most esters, k'_{o} does not exceed 4% of k_{cat}, the intercept is actually the value of k_{cat}.

In addition, the value of k_{cat} can be determined from the pH independent region of the pH-rate profile (Fig. 2,3) after substracting the contributions of

k'_o and k^c_{OH}. Fig. 2 and Fig. 3 demonstrate the pH-rate profiles of PNPD and MNPD in micelles 1 and 2. With the rate constants being determined as above the expertimental points fit well into equation (8). At high basicity, pH>9, the reaction rates of OPNPD and MNPD were too rapid to be followed. In these cases k_{cat} was determined from the k_{obs} values measured in the pH region of 5-7.5. In this region the contributions of k_o and k^c_{OH} are negligible and the dominante term in equation (8) becomes: k_{cat} Ka/Ka+H^+ = k_{obs}. This expression can be rearranged to expression (9).

$$1/k_{obs} = \frac{1}{k_{cat}.Ka} \times [H^+] + \frac{1}{k_{cat}} \qquad (9)$$

A plot of $1/k_{obs}$ Vs $[H^+]$ result in an intercept=$1/k_{cat}$ and a slope=$1/(k_{cat} \times Ka)$. This is clearly demonstrated in fig 4 for the aminolysis of PNPD in H_2O and D_2O and of OPND in micelle 1 at 30°C μ=0.8M(KCl). In both cases the pKa value of the catalytic amino group I, derived from the linear plot according to

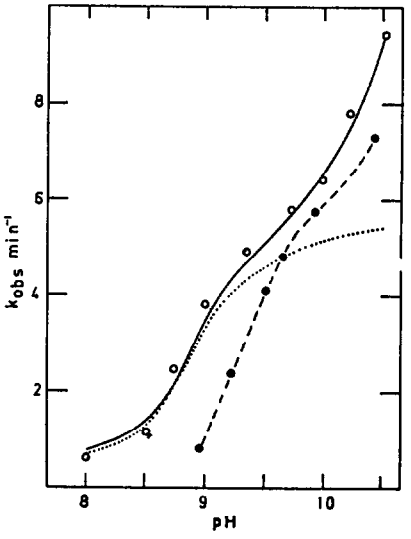


Fig. 3. pH-rate profile of PNPD in micelle 2. O--O (H_2O), ●---● (D_2O) at 30°C and ionic strength of 0.8M KCl. The solid line is caculated from equation (8). The dot line is the caculated curve for k_{cat}.

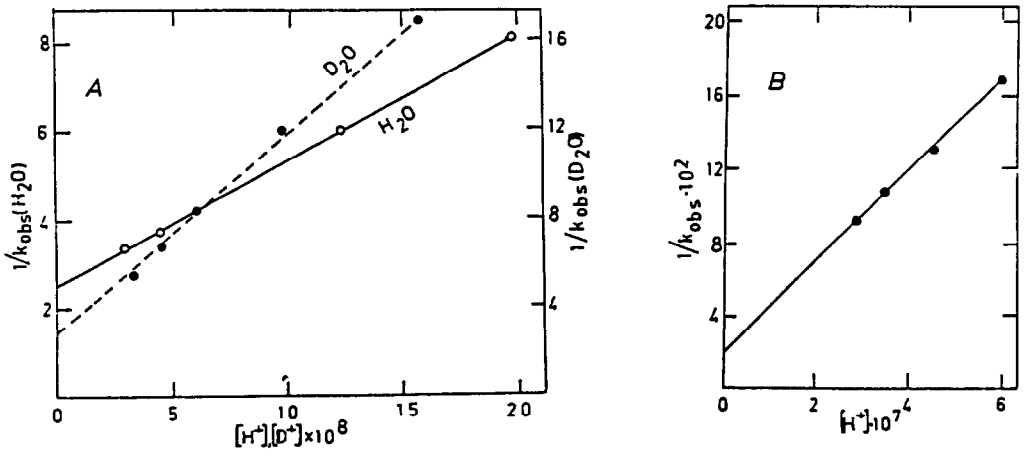


Fig. 4. Linear Dependence of $1/k_{obs}$ on $[H^+]$ or $[D^+]$ (pH(D)=6.5-7.5) in the aminolysis of PNPD (A) and OPND(B) in micelle(1) at 30°C, μ=0.8M (KCl).

equation (9) (7.05), is very close to the value of 6.95 as obtained by the titrimetric method.

In D_2O the pKa value obtained from the kinetic data is 7.5. This is in accordance with the known increase of 0.4 pK units as predicted for the dissociation of D^+.

As preveiously discussed, the k_{cat} value could be also evaluated from the plateau region of the complete pH profile. It can be seen that the values of $k_{cat}=0.38min^{-1}$ resulting from the pH-profile of PNPD in micelle 1 and that derived from equation (9) ($k_{cat}=0.36min^{-1}$) are in close approximation.

The kinetics of amine 2 (pKa=8.8) with esters bearing good leaving groups such as OPND or OMND were extremely repid and could not be monitored, even at 5-10% of amine dissociation. In order to circumvent this problem, we have diluted the catalytic micelle 2 with the non-catalytic micelle 4.

Fig. 5 exhibits a linear correlation between k_{cat} and the concentration of 2 diluted with a non catalytic cationic detergent 4. This correlation was also displayed with some other catalytic detergents and attenuators (cationic micelles), as long as the total concentration of the detergents remains constant. In order to follow the rate of 2,4-dinitrophenol liberation in micelle 2, the catalyst was diluted 10 fold with either micelle 4 or 5. The aminolysis of the ester CPNBA by detergents 1 and 2 was also studied and its pH-rate profile is depicted in Fig. 6.

All the catalytic rate constants for the various esters and micelles are summarized in table I.

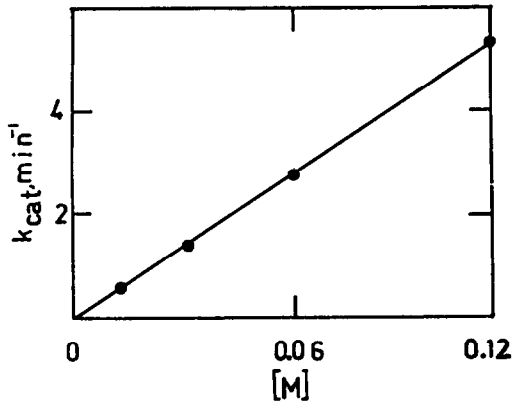


Fig. 5. Dilution effect of non catalytic micelle 4 on the catalytic rate constant of PNPD in micelle 2. The total concentration of 2+4=0.1M.

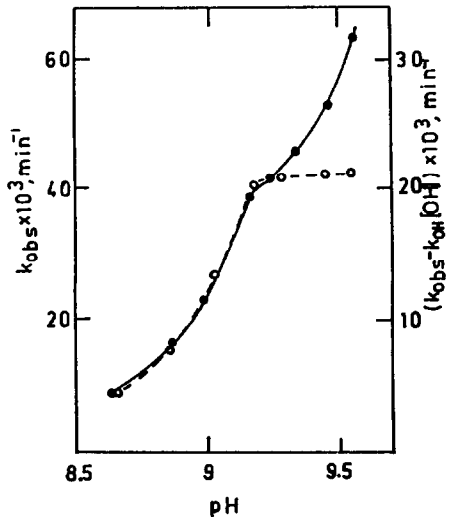


Fig. 6. pH-rate profile of CPNBA in micelle 2 ●---● (left ordinate). Dot line is a calculate curve after substraction of the contribution of $k_{OH}[^-OH]$ (right Ordinate).

Table I. Rate constants for reactions of phenyl decanoate esters phenyl hexanoate and CPNBA in micelles 1 and 2 at 30°C and ionic strength=0.8M(KCl).

Esters	pKa(l.g)[a]	k^{c}_{OH} $min^{-1}M^{-1}$	k_{OH} in micelle 5,($min^{-1}M^{-1}$)	k_{OH}-NH_2 $min^{-1}M^{-1}$	k_{cat} min^{-1}	k_o min^{-1}
Micelle 1 pKa=6.95						
OPNPD	4.1		1200		34	0.25
OMNPD	5.4	27500	645	26855	7.5	0.1
PNPD	7.1	800	176	624	0.38(0.35[b])	0.01
MNPD	8.4	75	47	28	0.01	0.004
PD	10	3	3.5		0.001	
CPNBA	13.4	830	780		$4.0(0.5^{b})10^{-3}$	
Micelle 2 pKa=8.8						
OPNPD	4.1		1200		130	
OMNPD	5.4		645		40	
PNPD	7.1	9000	176	8824	5.5(4.7[b])	
MNPD	8.4	550	47	503	0.208	
PMePD	10.2	1.3			0.0011	
CPNBA	13.4	830	780		$21(10^{b})10^{-3}$	
PNPH[c]	7.1				$8.8^{d}(6.8^{b})$	

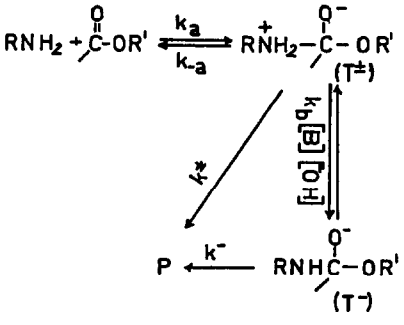
a. pKa of leaving groups; b. rate constant in D_2O;
c. with compound 3 as catalyst (pKa=9.2); d. second order rate constant. (in 0.1M of catalyst 3 rate is 0.88 min^{-1}).

DISCUSSION

Substituted phenyl esters

The pH-profile of the phenyl esters in amino micelles 1 and 2 involves (equation 8) three kinetic terms: k^{c}_{OH}, k_{cat} and k_o. k^{c}_{OH} is attributed to a specific base catalysis since the rate constants (Table I) measured in the non catalytic cationic micelle (k_{OH} in micelle 5) are of much lower magnitude. However, in analogous with known pathways of aminolysis reactions, it is plausible to assume that k^{c}_{OH} term is compatible with aminolysis reaction catalysed by hydroxide ion. The correct rate constant which corresponds to the hydroxide ion catalysis, is k_{OH}-NH_2=k^{c}_{OH}-k_{OH}(5). A simple route for phenyl esters aminolysis is shown in scheme 1.

scheme 1



According to the proposed mechanism the reaction may proceed either by: (a) rate limiting amine attack (ka), b) rate limiting expulsion of the phenolate ion (k^{*}) and c) rate determining proton removal from $T^{\pm}$ by a base ($k_b[B]$; $k_b[OH]$).

The return reaction of $T^{\pm}$ (k_{-a}) to the starting material is assumed to be in the range of 10^{7}-10^{9} sec^{-1}. On the other hand proton transfer from $T^{\pm}$ to hydroxide ion (k_b) is thermodynamically favored process, with a rate of $k_b=10^{+10}M^{-1}$ sec^{-1}. At a pH range of 9.5-10.5 (experimental region), the collapse of $T^{\pm}$ to the starting material is faster then the proton transfer reaction ($k_b[^{-}OH]$ and the observed rate constant can be given by equation 10.

$$k_{OH}\text{-}NH_2 = \frac{k_a}{k_{-a}} \times k_b = K_a^{\pm} k_b \qquad (10)$$

It seems, therefore, reasonable that the substituent effect on the observed rate constant (k_{OH}-NH_2) is mainly due to the effect on $K_a^{\pm}$. The values of the equilibrium constant $K_a^{\pm}$ were estimated to be: 4.5 10^{-7}, 1.10^{-9} and 4.6 10^{-11} M^{-1} for OMPND, PNPD and MNPD in 1 respectively and 1.48 10^{-8} and 7.55 10^{-10} M^{-1} for PNPD and MNPD in micelle 2 respectively.

The contribution of k'_o (water rate) to the kinetic rate in all cases is relatively small. The k'_o presumably does not correlate to a general acid catalysis involving the assistence of protonated amine to aminolysis, but probably can be assigned to the water attack reaction in the protonated micelle. This suggestion is supported by the data given in Table I where it is apparent that, in spite of the 2 pK unit difference between 1 and 2, the k'_o values in both micelles are similar.

The relatively high water rates (k'_o in 1 and 2) were also noticed also in our previous studies with other cationic micelles. This was explained on the basis of transition state stabilization by the positively charged cations. Mechanistically, k_{cat} can be associated with a) a nucleophilic pathway; b) a general base catalysis of ester aminolysis by the amino micelle or, c) an amine catalyzed ester hydrolysis.

The deuterium isotope effect for PNPD in micelle 1 and 2 is 1.08 and 1.17 respectively and for MNPD, in the above corresponding micelle is 1.17 and 1.2. Therefore, it seems that a water molecule does not participate in the transition state of the reaction and that the amine catalyzed ester hydrolysis pathway can be ruled out. Although the deuterium isotope effect value is very small, the exclusion of a possible general aminolysis mechanism have to be considered with care. This is based upon several observations reported in the literature that general base catalyzed aryl esters aminolysis do not show a significant deuterium isotope effect[39].

In the light of the general kinetic correlations as indicated below, it seems that k_{cat} represents a nucleophilic catalysis rather than a general base catalytic reaction.

a) It is a well known phenomenon that the reactions of esters containing good leaving groups, with strong nucleophiles proceed via a nucleophilic mechanism . As the leaving group becomes poorer the contribution of a general base mechanism is revealed. Indeed, in the aminolysis (pKa=9.60) and the hydrazonolysis (pKa=8.6) of substituted phenylacetate esters a general base term was not experimentally detected with p-nitro and m-nitro phenyl acetates. However, with p-Cl-phenyl, phenyl and tolyl-acetate, a general base mechanism prevails. Since the pKa of protonated amine in micelle 2 is 8.8, it can be assumed that, at least, OPNPD, OMNPD, PNPD and MNPD are hydrolyzed through a nucleophilic mechanism.

b) Current studies demonstrate that the sensitivity to polar effects in nucleophilic reactions are considerably much higher than in general base or general acid reactions.
The $\sigma\rho$ plot displayed in Fig. 7 (ρ=2.8), supports a nucleophilic mechanism for both detergents 1 and 2. It should be noted that the Hammett correlation includes the esters phenylacetate and tolylacetate.
c) Bronsted plots for nucleophilic catalysis have in general higher slopes than those for general base catalysis. For amines and phenyl acetates the ß value for the variation of leaving groups in a nucleophilic reaction consists of β_o=1±0.2, for the rate determining leaving group expulsion and ß=0.3 for the rate detemining nucleophilic attack. The Bronsted correlation shown in Fig. 8 is again in accordance with a nucleophilic mechanism.

The solid lines in Fig. 8 were calculated from equation (11):

$$\log k_1 = \log k_a = -0.3pK(lg) + C_1 \qquad (11a)$$

$$\log k_2 = \log \frac{k_a k^*}{k_{-a}} = -1.22pK(lg) + C_2 \qquad (11b)$$

$$k_{obs} = \frac{k_a k^*}{k_{-a}+k^*} = \frac{k_1 k_2}{k_1+k_2} \qquad (11c)$$

For micelle 1, C_1 and C_2 are 0.329 and 8.163 respectively and for micelle 2 the corresponding values are 3.319 and 9.561.
The plots in Fig. 8 show a clear cut biphasic behaviour. The two parts of the curves are assigned to a rate limiting nucleophilic attack, with ß(lg) =-0.3, for the upper line and a rate limiting break down of tetrahedral intermediate, with ß(lg)=-1.22, for the lower line.

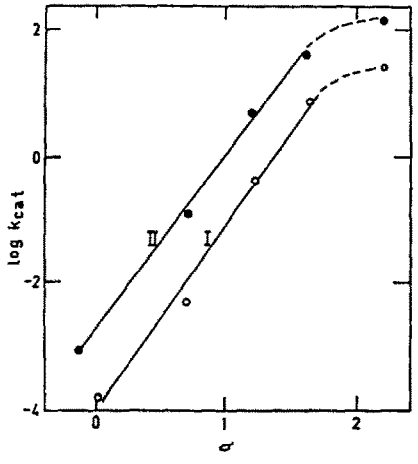


Fig. 7. Hammett correlation of substituted phenyl decanoate esters in micelles 1 and 2.

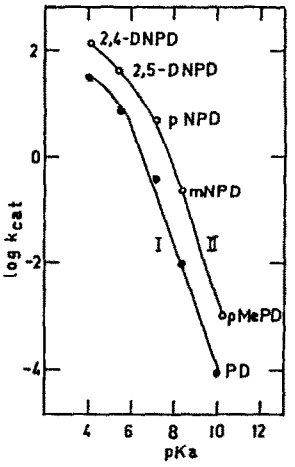


Fig. 8. Bronsted plot of log k_{cat} Vs pKa of substituted phenoxides leaving groups in the hydrolysis of phenyl- decanoate esters in micelles 1 and 2.

The break in the curve, which corresponds to the change in the rate limiting step, occurs with micelle 1 and 2 at pK_o=5.89 and 6.78 respectively.
This result is somewhat surprising in view of the fact that in aminolysis of

aryl esters, an equal partition of the amine and the aryloxide from the tetrahedral intermediate occurs when the phenolate ion is 4-5 pK units less basic than the attacking amine[40] as is derived from equation (12):

$$\log \frac{k^{\pm}}{k_{-a}} = -0.9pK_{o} + 0.7\ pK_{N} - 2.4 \qquad (12)$$

where pK_{o} is the pKa of the leaving group and pK_{N} is the pKa of the amine.

Based on equations 11a-11c and the pKa values of 1 and 2, a similar relationship can be derived for the partition ratio of the tetrahedral intermediate in the above micelles.

$$\log k^{\pm}/k_{a} = -0.92pK_{o} + 0.43\ pK_{N} + 2.466 \qquad (13)$$

Indeed, inserting a value of pK_{N}=6.9 (micelle 1) or pK_{N}=8.8 (micelle 2) in equation 13 results in an equal partition of the tetrahedral intermediate at pK_{o}=5.9 and 6.79 respectively.

A comparison of equations (12) and (13) reveals that the effective charge on the phenolate leaving group in the transition state for the rate determining attack and for the rate determining breakdown of the tetrahedral intermediate is almost identical in the micellar and the non micellar systems. However, the effective charge on the nitrogen, in the corresponding transition states, is not equal in both systems. In the non micellar system, the effective charge on the nitrogen was predicted to be 0.2 and 0.9 for the rate limiting attack and the leaving group expulsion respectively, while the respective values in the micellar system are 0.3 and 0.73.

This difference in the effective charge, together with the difference in the C_{ϵ} sign, reflects the difference of the interconversion position in the rate determining step of the above systems.

The linear correlation obtained for pK_{o} Vs pK_{N} (of the attacking nucleophiles) was calculated and displayed in Fig. 9. It can be seen that with the non micellar system (aryloxide esters), the pK_{o} value of the leaving group at the transition point from the rate determining amine attack to the rate determining phenoxide expulsion is continually smaller than the pK_{N} value of the

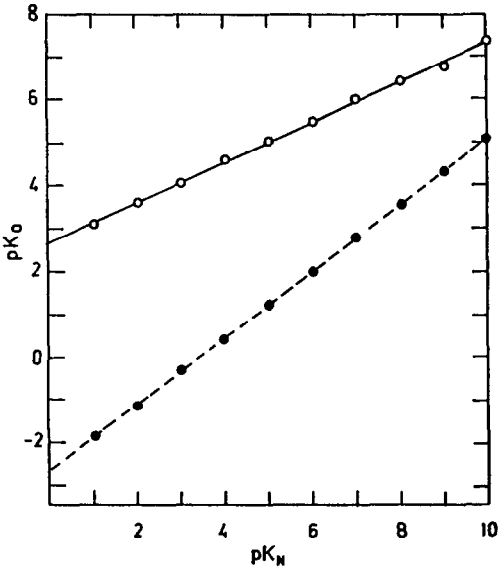


Fig. 9. A linear correlation between pK of leaving groups (pK_{o}) and pK of attacking amino nucleophiles (pK_{N}) at equal partition ratio of the tetrahedral intermediate. For non micellar systems the line was calculated from equation (12) (0----0). For micellar systems the line was derived from equation 10 (0---0).

attacking nucleophile. This is ascribed to a better leaving ability of the positively charged amine from the zwitterionic intermediate $T^{\pm}$. On the other hand, Fig. 9 demonstrates that in the case of the micellar system at $pK_N<5$, $pK_o>pK_N$, while at $pK_N>5$, $pK_N>pK_o$ and at $pK_N=5$, $pK_N=pK_o$.

It seems that the effect of cationic micelles on the partition ratio can most likely be attributed to the electrostatic stabilization of both product-like and reactant-like transition states or, alternatively, to the increase in leaving ability of the phenolate ion and the decrease in amine nucleophilicity. Indeed, several reports have showed that cationic micelles increase the ionization of many functional groups[41]. The balance between these two opperative effects may probably account for the transition position between the two transition states. Thus, at a $pK_N<5$, stabilization of the product like transition state is the predominant factor, while at $pK_N>5$, the reactant like transition state prevails.

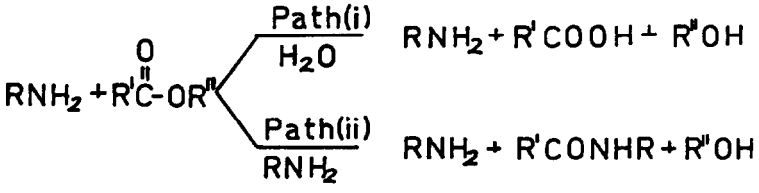
The second order rate constant of PNPH in the non micellar catalyst 3 (pKa=9.2) is: $k_{cat}=8.8M^{-1}min^{-1}$. On using a ß Bronsted value of 0.9, the rate constant at pKa=8.8 is calculated to be $k_{cat}=8.44M^{-1}min^{-1}$ and at 0.1M of catalyst 3, $k_{cat}=0.84min^{-1}$. A comparison of this value with the first order rate constant value (k_{cat}) of PNPD in 0.1M of micelle 2, reveals that the micellar system is more effective than its bemolecular analogue by a factor of 5.5/0.84 = 6.5. This value, together with other assembled data in the literature [8b,a], indicates that catalysis displayed by micelles is, in general, greater that its bimolecular counter part, but much smaller than in known intramolecular systems.

Hydrolysis of CPNBA

The kinetics of aminolysis of CPNBA fit well with equation (8). The hydroxide ion rate (k^c_{OH}) is not consistent with aminolysis catalyzed by ^-OH but to a specific base catalysis. This is inferred from: a) the equal rate constants k^c_{OH} of CPNBA in micelles 1 and 2, b) the hydrolytic rate constant (k^c_{OH}) of CPNBA in the non catalytic micelle (4) ($780min^{-1}$) is very close to that observed in 1 and 2. From the isotope effect of k_{cat} (H_2O)/k_{cat}(D_2O)=21.10^{-3}/ 10.10^{-3}=2.1 it can be concluded that the aminolysis reaction is subject to a general base catalysis.

Plausible pathways are: a general base catalysis of hydrolysis-path (i), or a general base catalysis of aminolysis- path (ii).

Scheme 2



Distinguishing between the two routes (in micelle 2) can be carried out on the basis of a products analysis according to the method outlined in the experimental section. The formation of an amide indicates that the reaction proceeds via pathway ii rather than i.

REFERENCES

1. For general review see: a) Kunitake, T., Shinkai, S., Adv. Phys. Org. Chem., 1980, 17, 435; b) Brown, J.M., in colloid Science, Specialist Periadical Report, The Chemical Society, London, 1979, vol. 3 P 253; c) Bunton, C.A., Catal. Rev. Sci. Eng., 1979, 20 1; d) Fendler, J.H., "Membrane mimetic chemistry" Wiley-Interscience, New York 1981; e) O'connor, C.J. Ramage, R.E., Porter. A.J., J. Adv. Colloid interface Sci., 1981, 15, 25.
2. a) Biresaw, G., Bunton, C.A., Quan.C., Yang, Z-Y., J. Amer. Chem. Soc., 1984, 106, 7178; b) Bunton, C.A., McAneny, M., J. Org. Chem., 1976, 41 36; c) Bunton, C.A., Diaz, S., J. Amer. Chem. Soc., 1976, 98, 5663; d) Bunton, C.A., Robinson, L., Stam, M., J. Amer. Chem. Soc., 1970, 92 7393; e) Bunton, C.A., Ionescu, L.G., J. Amer. Chem. soc., 1973, 95, 2912.
3. a) Meyer, G., Viout, P., Tetrahderon, 1977, 33, 1959; b) Tetrahedron Lett., 1972, 4581.
4. Menger, F.M., Whitesell, L.G., J. Amer. Chem. Soc., 1985, 107, 707.
5. Eckert, T., Zander, M., Arch. Pharm., 1977, 310, 136.
6. Martinek, K., Levashov, A.V., Berezin, I.V., Tetrahedron Lett., 1975, 1275.
7. Moss, R.A., Nahas, R.C., Rawaswami, S., Sanders, W.J., Tetrahedron Lett., 1975, 3379.
8. a. Pillersdorf, A., Katzhendler, J., J. Org. Chem., 1979, 44, 934; b) Pillersdorf, A., Katzhendler, J., Isr. J. Chem., 1979, 18, 330. c) Wexler, D., Pillersdorf, A., Shiffman, R., Katzhendler, J., Sarel, S., J. Chem. Perkin Trans. 2, 1978, 479; d) Shiffman, R., Chevion, M., Katzhendler, J., Rav-Acha, C., Sarel, S., J. Org. chem., 1977, 42, 856; e) Chevion, M., Katzhendler, J., Sarel, S., Isr. J. Chem., 1972, 10, 975.
9. a. Kunitake, T., Shinikai, S., Hiratsu, S., Biopolymers., 1976, 15, 1143; b) Kunitake, T., Shinikai, S., Okahata, Y., Bull. Chem. Soc. Jap., 1976, 49, 540; c) Kunitake, T., Okahata, Y., Sakamoto, T., Chem. Lett., 1975, 459.
10. Ueoka, R., Kato, M., Ohkulo, K., Tetrahedron Lett., 1977, 2163.
11. Epstein, J., Kaminski, J.J., Bodov, N., Enever, R., Sowa, J., Higuchi, T., J. Org. Chem., 1978, 43, 2816.
12. Tabushi, I., Kuroda, Y., Tetrahedron Lett., 1974, 3613.
13. Yetsimirski, A.K., Martinek, K., Berezin, I.V., Tetrahedron, 1971, 27, 2855.
14. Pillersdorf, A., Katzhendler, J., J. Org. Chem., 1979, 44, 549.
15. Kunitake, T., Sakamoto, T., Bull. Chem. Soc., Jap., 1979, 52, 2624.
16. a. Rav-Acha, Ch., Chevion, M., Katzhendler, J., Sarel, S., J. Org. Chem., 1978, 43, 591. b) Shiffman, R., Rav-Acha, Ch., Chevion, M., Katzhendler, J., Sarel., S., J. Org. Chem., 1977, 42, 3279.
17. a. Moss, R.A., Hendrickson, T.F., Bizigotti, G.O., J. Amer. Chem. Soc., 1986, 108, 5520; b) Moss, R.A., Bizzigotti, G.O., Huang, Ch. W., ibid., 1980, 102, 754; c) Moss, R. A., Bizzigotti, G.O., Lukas, T.J., Sanders, W.J., Tetrahedron Lett., 1978, 3661.
18. a. Shinikai, S., Kunitake, T., Makromol. Chem., 1977, 178, 1613; b) Bull. Chem. Soc. Jap., 1976, 49, 3219.
19. Murakami, Y., Nakano, A., Matsumoto, K., Wamoto, K.I., Bull. Chem. Soc. Jap., 1979, 52, 3573.
20. Tagaki, W., Amada, T., Yamashita, Y., Yano, Y., J. Chem. Soc. Chem. Commun., 1972, 219.
21. Hietman, P., Eur. J. Biochem., 1968, 5, 305.
22. a. Fornasier, R., Tonellata, U., J. Chem. Soc., Perkin 2, 1984, 1313; b) Tonellato, U., ibid., 1977, 821; c) ibid, 1976, 771; d) Formaisier, R., Tonellato, U., J. Chem. Soc. Faraday I, 1980, 76, 1301.
23. a. Tagakai, W., Fukushima, D., Eiki, T., Yano, Y., J. Org. Chem., 1979, 44, 555; b) W. Tagakai, G. Kagaku, 1977, 74, 12.
24. Martinek, K., Osipov, A.P., Yotsimirsky, A.K., Berezin, I.V., Tetrahedron, 1975, 31, 709.
25. a. Moss, R.A., Nahas, R.C., Lukas., T.J., Tetrahedron Lett., 1978, 507; b) J. Amer. Chem. soc., 1978, 100, 5920.
26. Okahata, Y., Ando, R., Kunitake, T., J. Amer. Chem. Soc., 1977, 99, 3067.
27. Bunton, C.A., McAneny, M., J. Org. Chem., 1977, 42, 475.
28. a) Okenfull, D., J. Chem. Soc., Perkin 2, 1973, 1006. b) Okenfull, D., Fenwick, D.E., Austral, J. Chem. 1975, 28, 715.
29. Gitler, C., Ochoa-Solano, A., ibid., 1968, 90, 5004.
30. Shorenstein, R.G., Pratt, C.S., Hsu. C-J., Wagner, T.E., J. Amer. Chem. Soc., 1968, 90, 6199.
31. Bruice, T.C., Katzhendler, J., Fedor, L.R., J. Amer. Chem. soc., 1968, 90, 1333.
32. a. Kunitake, T., Okahata, Y., Sakamoto, T., J. Amer. Chem. Soc., 1976, 98, 7799. b. Kunitake, T., Sakamoto, T., Polymer. J., 1979, 11, 871.
33. Brwon, J.M, Bunton, C.A., J.C.S. Chem. Commun. 1974, 969.
34. a. Moss, R.A., Chiang, Y-CH. P., Hui, Y., J. Amer. Chem. Soc., 1984, 106, 7506; b) Moss, R.A., Lee, Y.S., Luka, T.J., ibid., 1979, 101, 2499; c) Moss, R.A., Lee, Y.S., Alwis, K.W., Tetrahedron Lett., 1981, 22, 283, d) Ueoka,

R., Moss, R.A., Swarup, S., Matsumoto, Y., Strauss, G., Murakami, Y., J. Amer. Chem. Soc., 1985, 107, 2185.
35. a. Ihara, Y., J.C.S. Chem. commun., 1978, 984; b) Yamada, K., Shosenji, H., Ihara, H., Chem. Lett., 1979; c) Yamada, K., Shosenji, H., Ihara, H., Otsulo, Y., Tetrahedron Lett., 1979, 2529.
36. Okahato, Y., Ando, P., Kunitake, T., Bull. Chem. Soc. Jap., 1979, 52, 3647.
37. Linderstrom-Lang, K.C.R., Trav. Lab. Carlsberg Ser. Chim., 1924, 15, 17.
38. Bruice, T.C., Danzel, A., Huffman, R.W., Butler., A.R., J. Amer. Chem. Soc., 1967, 89, 2106.
39. a. Bruice, T.C., Benkovic, S.J., "Bioorganic Mechanisms" vol. I p. 72, W.A. Benjamin, New York 1966. b. Bender, M.C., Bergeron, R.J., Kamijama, M., Bioorganic Chemistry of Enzymatic Catalysis" p. 96, John Wiley New York 1984.
40. Gresser, M.J., Jencks, W.P., 1977, 99, 6963.
41. a) Behme, M.T.A., Cordes, E.H., J. Amer. Chem. Soc. 1965, 87, 260. b) Bunton, C.A.. Minch, M.J., J. Phys. Chem. 1974, 78, 1490. c) Fendler, E.J., Fendler, J.H., Adv. Phys. Org. Chem., 1970, 8, 271.