Transition state stabilization by micelles: thiolysis of *p*-nitrophenyl alkanoates in cetyltrimethylammonium bromide micelles

Oswald S. Tee and Ogaritte J. Yazbeck

Abstract: Thiolysis of *p*-nitrophenyl esters (acetate to decanoate) by the anion of 2-mercaptoethanol (ME) is catalyzed by micelles of cetyltrimethylammonium bromide (CTAB) in aqueous solution. At fixed [ME], the observed rate constants (k_{obs}) show saturation with respect to added [CTAB], consistent with ester binding in the micelles. Plots of k_{obs} vs. [ME] are linear in the absence and in the presence of the CTAB, and analysis of the slopes of the plots afford rates constants for thiolate ion attack on the esters in the aqueous phase (k_N) and in the micellar phase (k_{cN}). The strengths of substrate binding and transition state binding to the micelles are strongly correlated, with a slope of *unity,* because they have the same dependence on the ester chain. Consequently, the catalytic ratios (k_{cN}/k_N) are independent of the length of the ester. Similar behaviour is found for thiolysis by the dianions of mercaptoacetic acid, 3-mercaptopropionic acid, and cysteine, and also for ester cleavage by the anions of glycine and 2,2,2-trifluoroethanol, as earlier for cleavage by hydroxide ion. The results are consistent with Kirby's dissection of transition state binding into "passive" and "dynamic" components. The passive component involves hydrophobic binding of the ester chain which is more or less the same as in the substrate binding. The dynamic component is associated with reaction in the Stern layer of the micelle, and its magnitude varies with the nucleophiles because of differences in their ease of exchange between the aqueous medium and the Stern layer.

Key words: catalysis, esters, thiolysis, micelles.

Résumé : La thiolyse des esters (acétate à décanoate) de *p*-nitrophényle, par l'anion 2-mercaptoéthanol (ME) en solution aqueuse, est catalysée par les micelles de bromure de cétyltriméthylammonium (« CTAB »). À des valeurs fixes de [ME], les constantes de vitesse observées (k_{obs}) présentent une saturation par rapport à la [CTAB] ajoutée et cette observation est en accord avec une fixation dans les micelles. Les courbes de k_{obs} en fonction de [ME] sont linéaires tant en absence qu'en présence de CTAB et une analyse des pentes de ces courbes permet de déterminer les constantes de vitesse pour l'attaque de l'ion thiolate sur les esters en phase aqueuse (k_N) et en phase micellaire (k_{cN}). Il existe une grande corrélation entre les forces de fixation des micelles avec le substrat ou de l'état de transition; la pente est égale à l'unité en raison du fait qu'elles dépendent toutes les deux de la même chaîne ester. En conséquence, les rapports catalytiques (k_{cN}/k_N) sont indépendants de la longueur de l'ester. On observe un comportement semblable lors de la thiolyse par les anions de l'acide mercaptoacétique, de l'acide 3-mercaptopropionique et de la cystéine ainsi que lors du clivage des esters par les anions de la glycine et du 2,2,2-trifluoroéthanol; antérieurement, on avait observé le même résultat avec l'ion hydroxyde. Les résultats sont en accord avec la dissection de Kirby de la fixation de l'état de transition en des composantes « passive » et « dynamique ». La composante passive implique une fixation hydrophobe de la chaîne de l'ester qui est à peu près semblable à la fixation du substrat; la composante dynamique est associée à la réaction dans la couche de Stern de la micelle et son amplitude varie avec les nucléophiles en raison des différences dans leur facilité d'échange entre le milieu aqueux et la couche de Stern.

Mots clés: catalyse, esters, thiolyse, micelles.

[Traduit par la Rédaction]

Introduction

Over the last forty years, the effects of micelles on organic reactions have been studied extensively (1). One of the first reactions to be studied in detail was the cleavage of aryl esters by hydroxide ion, which is retarded by anionic micelles but catalyzed by cationic ones (for example see ref. (2)). Since the catalytic effects of cationic micelles are more evident for esters with long chains, it was reasonable for authors to conclude that the acceleration is chain length

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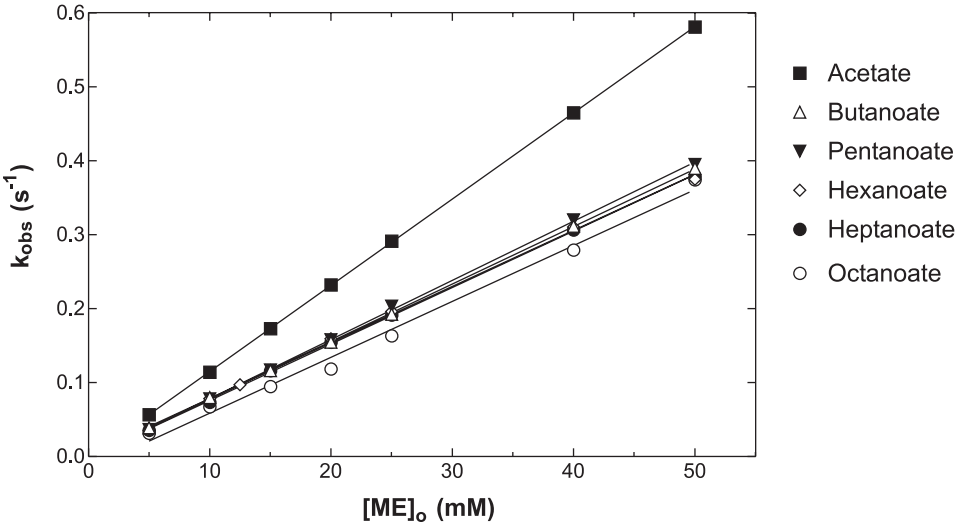
Fig. 1. Variation of k_{obs} for ester cleavage with [ME] in the presence of 5.00 mM NaBr, but no CTAB, at pH 10.60. The data are for the esters acetate, butanoate, pentanoate, hexanoate, heptanoate, and octanoate, as indicated. The slopes of the plots provide k_N values (Table 1).



dependent, presumably because an ester with a longer acyl chain is more readily incorporated into the micelle.

The origin of the micellar catalysis of ester cleavage was ascribed to concentration of the reactants in the restricted volume of the micelle: hydroxide ion in the Stern layer, and the ester in the hydrophobic core but with its carbonyl group accessible to the aqueous environment of the Stern layer (1, 2). Consistent with this interpretation, Al-Awadi and Williams (3) found that the Hammett ρ value for basic cleavage of substituted phenyl dodecanoate esters in CTAB micelles is the same as the value for reaction in aqueous solution. Subsequently, one of us pointed out (4) that this finding means that the transition state stabilization by CTAB micelles is independent of the aryloxy leaving group of the ester, and so, presumably, it depends on the acyl chain length of the ester.

Recently, we tested this suggestion by studying the basic hydrolysis of *p*-nitrophenyl alkanoates (acetate to octanoate) in CTAB micelles (5). Remarkably, we found that the chain length dependence of the transition state binding, and thus of the transition state stabilization, is exactly the same as that for the substrate binding. As a result, the limiting acceleration is independent of the ester chain length, although it is more evident for longer esters because they bind to the micelles more strongly. The work described below was carried out to see if these features carry over to reactions of aryl esters with thiolate anion nucleophiles. There have been a few previous studies of the effect of cationic surfactants on ester thiolysis (6) but none of them focussed on a series of alkanoates, which is the case here.

Results

We have studied the effect of CTAB micelles on the thiolysis of *p*-nitrophenyl alkanoate esters: acetate, butanoate, pentanoate, hexanoate, heptanoate, octanoate, and in some cases the decanoate. The reaction medium was an aqueous 0.10 M carbonate buffer of pH 10.60. To be consistent with previous work (3, 5), and to avoid the complications arising from variable bromide ion exchange into the micelles (2*c*, 2*d*, 2*h*, 3, 7), the total bromide ion concentration was kept constant at 5.0 mM.

Our first series of experiments involved the anion of 2-mercaptoethanol (ME) as the thiolate nucleophile (Nuc). In the aqueous buffer with no CTAB, the dependence of k_{obs} on added nucleophile is strictly linear (Fig. 1), as expected from previous work (8). For reaction in the presence of a fixed concentration of CTAB, the dependence of k_{obs} on [Nuc] is also linear (Fig. 2), which indicates that even though thiolate ions exchange into the Stern layers of micelles, the effect does not approach saturation. At a fixed concentration of the nucleophile, the variation of k_{obs} with [CTAB] shows saturation behaviour (Fig. 3) due to binding of the ester substrates in the micelles.

Following the approach developed previously for bimolecular reactions mediated by cyclodextrins (8, 9), analysis of the data is based on consideration of four competing processes: (*i*) basic hydrolysis of the ester (Es) in the medium (eq. [1]); (*ii*) basic hydrolysis within the micelles (eq. [2]); (*iii*) nucleophilic attack in the medium (eq. [3]); and (*iv*) nucleophilic attack within the micelles (eq. [4]). Together, these four processes require the variation of the rate constant for ester cleavage with surfactant concentration, [Surf], which is given in eq. [5], assuming that the concentration of ester is low enough not to affect micellization. Note that binding of the ester to the micelle is characterized by a dissociation constant, K_S = [Es][Surf]/[Es/Surf].

[1] $$\mathrm{Es} \xrightarrow{k_u} \text{products}$$

[2] $$\mathrm{Es} + \mathrm{Surf} \underset{K_S}{\rightleftharpoons} \mathrm{Es{\cdot}Surf} \xrightarrow{k_c} \text{products}$$

[3] $$\mathrm{Es} + \mathrm{Nuc} \xrightarrow{k_N} \text{products}$$

[4] $$\mathrm{Es{\cdot}Surf} + \mathrm{Nuc} \xrightarrow{k_{cN}} \text{products}$$

[5] $$k_{obs} = \frac{(k_u K_S + k_c[\mathrm{Surf}]) + (k_N K_S + k_{cN}[\mathrm{Surf}])[\mathrm{Nuc}]}{(K_S + [\mathrm{Surf}])}$$

Fig. 2. Variation of k_{obs} for ester cleavage with [ME] in the presence of 5.00 mM of CTAB, but no NaBr, at pH 10.60. The data are for the esters indicated on the graph. Analysis of the slopes (see text) gives values of k_{cN}. Note that, because of micellar catalysis, the vertical scale here is 10 times that in Fig. 1.

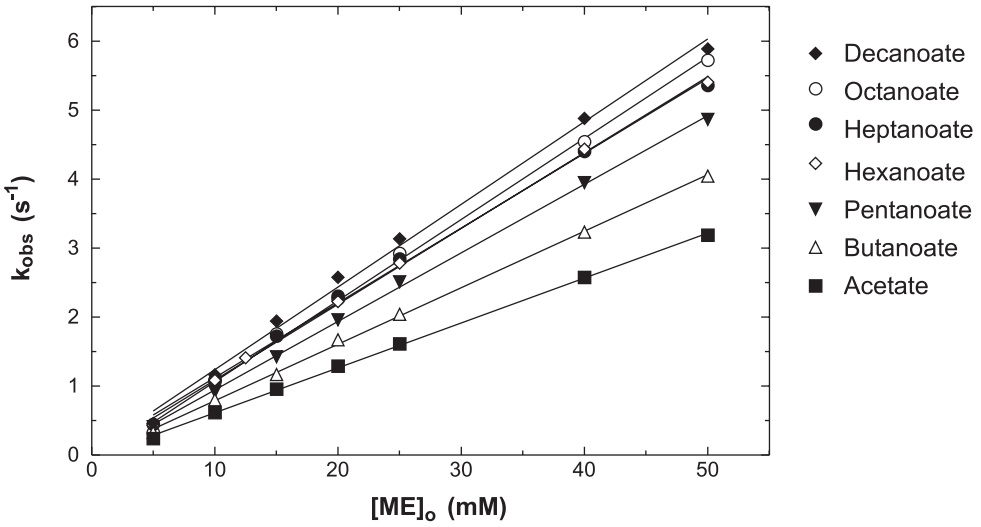
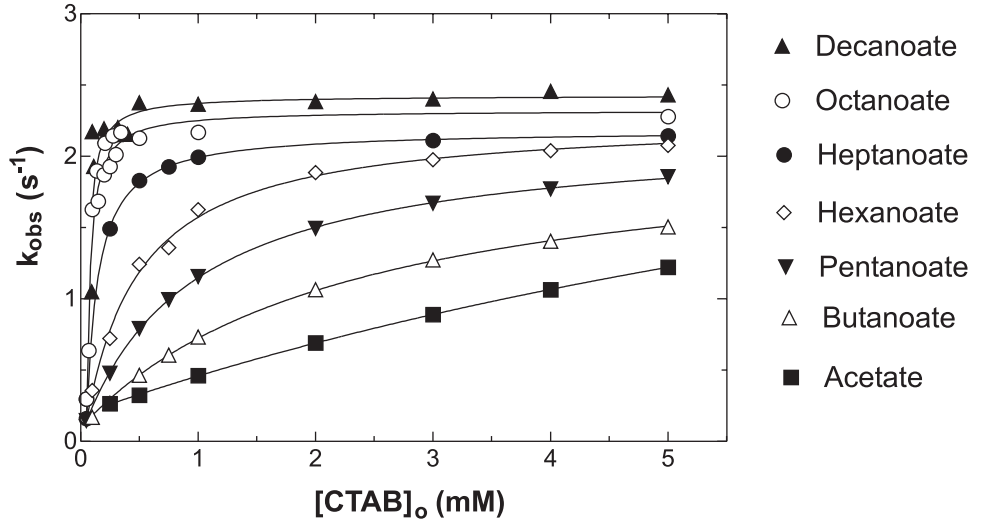


Fig. 3. Variation of k_{obs} for ester cleavage with [CTAB] in the presence of 20 mM mercaptoethanol, and total bromide ion = 5.00 mM, at pH 10.60. The data are for the esters indicated. Fitting eq. [6] to the data, with [Surf] = ([Surf]$_o$- cmc), provide values of K_S for the esters. See Experimental section.



Values of k_N are obtained from the linear plots found for experiments with no added surfactant, when $k_{obs} = k_u + k_N[Nuc]$ (e.g., Fig. 1). With varying [Surf], but constant [Nuc], and assuming that the added nucleophile does not alter K_S or [Surf], eq. [5] simplifies to eq. [6], where $k_u' = (k_u + k_N[Nuc])$ and $k_c' = (k_c + k_{cN}[Nuc])$. Equation [6] corresponds to simple saturation kinetics, as is observed (Fig. 3), and nonlinear regression of the data affords estimates of K_S, as well as of k_u' and k_c'.[2]

$$[6] \qquad k_{obs} = \frac{(k_u' K_S + k_c'[Surf])}{(K_S + [Surf])}$$

For the experiments with constant [Surf], eq. [5] requires a linear dependence of k_{obs} on [Nuc], as observed for ME (Fig. 2), with a slope of $(k_N K_S + k_{cN}[Surf])/(K_S + [Surf])$. Knowing k_N and K_S from the analyses of the other experiments, values of k_{cN} can be estimated from such slopes. Table 1 collects the values of k_N, k_{cN}, and K_S for reaction between the anion of ME and the series of esters, deduced from the kinetic data shown in Figs. 1, 2, and 3.

Analogous experiments with the dianion of mercaptoacetic acid (MAA) gave results similar to those found for the anion of ME. The slopes of the linear plots of k_{obs} vs. [Nuc] in the absence of CTAB provided k_N, and the saturation behaviour of k_{obs} with [CTAB], at fixed [Nuc],

[2] As explained in the Experimental Section, we have taken [Surf] = [Surf]$_o$ – cmc, with the critical micellar concentration (cmc) fixed at 0.05 mM.

Table 1. Constants for the reaction of thiolate ions and other nucleophiles with *p*-nitrophenyl alkanoates in the presence of CTAB micelles.[a]

Ester	k_N (M^{-1} s^{-1})	k_{cN} (M^{-1} s^{-1})	K_S (mM)	k_{cN}/k_N	K_{TS} (mM)
(*a*) Anion of 2-mercaptoethanol (ME)					
Acetate	11.7 ± 0.02	202 ± 3	12.7 ± 0.5	17.3	0.736
Butanoate	7.77 ± 0.04	117 ± 2	2.34 ± 0.10	15.1	0.155
Pentanoate	7.99 ± 0.08	118 ± 2	0.975 ± 0.015	14.8	0.0660
Hexanoate	7.59 ± 0.13	120 ± 2	0.465 ± 0.030	15.8	0.0294
Heptanoate	7.64 ± 0.06	110 ± 3	0.0995 ± 0.0040	14.4	0.00691
Octanoate	7.56 ± 0.31	118 ± 3	0.0323 ± 0.0065	15.6	0.00207
Decanoate	7.56[b]	120 ± 4	0.00585[c]	15.9	0.000369
(*b*) Dianion of mercaptoacetic acid (MAA)					
Acetate	15.6 ± 0.2	1780 ± 100	24.6 ± 4.0	114	0.216
Butanoate	10.4 ± 0.2	774 ± 26	2.60 ± 0.23	74.4	0.0349
Pentanoate	10.9 ± 0.2	776 ± 39	1.06 ± 0.07	71.2	0.0149
Hexanoate	11.0 ± 0.2	776 ± 24	0.374 ± 0.009	70.5	0.00530
Heptanoate	11.2 ± 0.2	915 ± 20	0.141 ± 0.009	81.7	0.00173
Octanoate	10.1 ± 0.1	886 ± 7	0.0539 ± 0.0032	87.7	0.000614
Decanoate	10.1[b]	867 ± 14	0.00664[c]	85.8	0.0000774
(*c*) Dianion of 3-mercaptopropionic acid (MPA)[d]					
Acetate	11.8 ± 0.2	786 ± 96	24.6	66.8	0.368
Butanoate	8.64 ± 0.07	453 ± 25	2.60	52.4	0.0497
Pentanoate	8.44 ± 0.19	435 ± 24	1.08	51.5	0.0205
Hexanoate	8.08 ± 0.25	462 ± 16	0.374	57.2	0.00654
Heptanoate	8.11 ± 0.11	421 ± 18	0.141	51.9	0.00271
Octanoate	7.62 ± 0.39	395 ± 25	0.0539	51.8	0.00104
(*d*) Dianion of cysteine (CYST)[d]					
Acetate	9.78 ± 0.08	812 ± 17	24.6	83.0	0.296
Butanoate	6.01 ± 0.07	362 ± 16	2.60	60.3	0.0431
Hexanoate	5.70 ± 0.03	364 ± 16	0.374	63.8	0.00586
Octanoate	6.91 ± 0.01	370 ± 9	0.0539	53.5	0.00101
(*e*) Anion of glycine (GLY)[d]					
Acetate	1.51 ± 0.03	2.55 ± 0.05	24.6	1.69	14.6
Butanoate	0.561 ± 0.025	0.711 ± 0.12	2.60	1.27	2.05
Hexanoate	0.573 ± 0.007	0.856 ± 0.068	0.374	1.49	0.250
Octanoate	0.477 ± 0.041	0.639 ± 0.055	0.0539	1.34	0.0402
(*f*) Anion of 2,2,2-trifluoroethanol (TFE)[e]					
Acetate	13.1 ± 0.08	531 ± 19	11.4	40.5	0.282
Butanoate	7.25 ± 0.09	196 ± 3	1.96	27.1	0.0723
Hexanoate	7.67 ± 0.02	178 ± 5	0.257	23.2	0.0111
Octanoate	7.00 ± 0.21	176 ± 2	0.0423	25.4	0.00167

[a]At 25°C, in an aqueous carbonate buffer of pH 10.60, with the total bromide concentration ([CTAB] + [NaBr]) kept at 5.00 mM. The actual data for ME are shown in Figs. 1, 2, and 3.

[b]Difficult to determine accurately and so assumed to be the same as for the octanoate.

[c]Obtained by extrapolation of the linear plot of pK_S vs. *N*.

[d]For the experiments with the anions of MPA, CYST, and GLY the values of K_S were to be taken to be the same as those found with the mercaptoacetate dianion.[4]

[e]For the experiments with the anion of TFE, the values of K_S were to be taken to be the same as those found earlier with hydroxide ion (5), under the same conditions.

was analyzed in terms of eq. [6] to find K_S. Plots of k_{obs} vs. [MAA] at fixed [CTAB] show very slight downward curvature[3] at the high end of the range of [MAA] = 0–25.0 mM, and to minimize its effect values of k_{cN} were estimated from the data points in the concentration range 0–15.0 mM, where the variation in k_{obs} is essentially linear.

[3]This curvature may indicate the onset of saturation of the micelles with the thiolate dianions which probably bind stronger than the monoanion of ME — see Discussion. Alternatively, high thiolate concentrations may start to alter the micellization parameters.

[4]The K_S values found with the anions of ME and MAA (Table 1) differ little from those found earlier with hydroxide ion (5), despite differences in pH, buffer, and ionic strength.

Experiments were also carried out with the dianions of 3-mercaptopropionic acid (MPA) and cysteine (CYST), and, for comparison, with the anion of glycine (GLY), an amine nucleophile, and the anion of 2,2,2-trifluoroethanol (TFE), an oxyanion. For the experiments with TFE, the medium was a 0.20 M phosphate buffer of pH 11.60, as used for previous studies of ester cleavage by hydroxide ion (5). Again, the plots of k_{obs} against [Nuc], at constant [CTAB], showed slight curvature at the high [Nuc], and so k_{cN} values were estimated from the linear dependence in the range [Nuc] = 0–15.0 mM. Since the values of K_S do not appear to be significantly sensitive to the nucleophile,[4] the values found from the experiments with MAA were used in the analyses to find k_{cN} values for the anions of MPA, CYST, and GLY. For the anion of TFE, the values of K_S that were found from reaction with hydroxide ion in the same phosphate buffer (5) were used.

Values of k_N and k_{cN} obtained for the anions of MAA, MPA, CYST, GLY, and TFE are also collected in Table 1, along with apparent "equilibrium constants," K_{TS}. Such constants are useful measures of transition state stabilization in catalyzed reactions (4). For the present purposes, K_{TS} is defined in eq. [7] to be the dissociation constant of the transition state for the micelle-catalyzed cleavage (TS·Surf) into the transition state of normal cleavage (TS) and the micellized surfactant (Surf). We have used analogous constants extensively in work on the effects of cyclodextrins on reactions (4, 8, 9, and references therein), as have other authors for various catalysts (10), including enzymes (11), enzyme mimics (12), and micelles (13).

$$[7] \qquad K_{TS} = [TS][Surf]/[TS\cdot Surf] = k_N/k_3 = k_N K_S/k_{cN}$$

Note that in eq. [7], k_3 is the third order rate constant corresponding to the overall process shown below in eq. [8] which is kinetically equivalent to that shown in eq. [4]. Hence, $k_3 = k_{cN}/K_S$.

$$[8] \qquad Es + Surf + Nuc \xrightarrow{k_3} products$$

Discussion

Two features of the rate and equilibrium constants in Table 1 are immediately apparent. First, beyond the acetate, the rate constants k_N and k_{cN} both show almost no variation with ester chain length and so the limiting accelerations, k_{cN}/k_N, are virtually constant for each nucleophile. Second, and in sharp contrast, the equilibrium constants K_S and K_{TS} vary appreciably with chain length. Consequently, the third order rate constants, $k_3 = k_{cN}/K_S$ (eq. [8]), increase substantially: (*i*) 1300-fold for the anion of ME and 1800 for the dianion of MAA (going from the acetate to the decanoate ester); (*ii*) 200-fold for the dianions of MPA and CYST, and (*iii*) 100-fold for the anions of GLY and TFE (going from the acetate to the octanoate). Similar behaviour was found earlier for cleavage of the same series of esters by hydroxide ion (5).

According to eq. [7], the "catalytic" ratio, $k_{cN}/k_N = K_S/K_{TS}$, is determined by the relative strengths of transition state binding and substrate binding (4, 12). Seen from this point of view, the nearly constant k_{cN}/k_N ratios for each nucleophile (Table 1) arise because the substrate binding and transition state binding have exactly the same sensitivity to elongation of the ester chain. This is precisely the case, as shown by the correlations summarised in Table 2, some of which are plotted in Fig. 4. For each thiolate nucleophile, the slopes of the plots of pK_{TS} vs. chain length (N) and pK_S vs. N, are all essentially the same ($\approx 0.43 \pm 0.02$),[5] and they are barely different for the other three nucleophiles: glycinate ion, the TFE anion, and hydroxide ion. Even more to the point, pK_{TS} values (for transition state binding) are very strongly correlated with pK_S values (for substrate binding), and the slopes are very close to *unity* (Table 2), suggesting that transition state binding and substrate binding are governed by the same structural feature(s) of the esters.

Kirby (12) has proposed that transition state binding can be divided into two, conceptually distinct components: (*i*) *passive binding*, which arises from noncovalent interactions, such as those involved in host–guest complexation; (*ii*) *dynamic binding*, which is due to interactions between the catalyst and the substrate(s) at the reaction centre. At first sight, this division may seem artificial or even naive, especially for catalysts as complex as enzymes and catalytic antibodies (12), but it does provide a useful framework for discussion. Moreover, the division seems entirely appropriate for the present results for micelles.

For micellar catalysis of ester cleavage by nucleophiles, transition state binding closely parallels substrate binding (Fig. 4 and Table 2). This behaviour suggests that the passive binding component is more or less totally hydrophobic in origin, since the slopes of the plots of pK_{TS} vs. N, and pK_S vs. N, of 0.4 (Table 2) are perfectly consistent with dominant hydrophobic interactions (5). Conceivably, then, the passive component of the transition state binding is little different from the initial state binding of the esters. The dynamic component, of course, is associated with nucleophilic attack on the micelle-bound ester and it will be greatly influenced by the exchange of nucleophiles into the micelles. The nearly constant ratios, k_{cN}/k_N, for each nucleophile (Table 1 and ref. (5)) are quite understandable if they are determined almost solely by the accessibility of the nucleophile to the micelle-bound ester.

A key feature of current models of the effects of micelles on reactivity is the exchange of ions between the Stern layer of the micelle and the bulk aqueous medium (1, 7). To quote Bunton et al. (1*f*), for cationic micelles, "large, weakly hydrated polarizable anions displace hydrophilic anions." Among other things, this factor explains why added bromide ion depresses the rate of CTAB-catalyzed hydroxide ion attack on esters (and other substrates) and why high concentrations of CTAB are less catalytic than moderate ones (2, 7). Also, it explains why cetyltrimethylammonium chloride micelles are better catalysts for hydroxide ion attack on esters than are CTAB micelles (for example see ref.(2)). With

[5] The cleavage of *p*-nitrophenyl alkanoates by hydroxide ion is strongly retarded by sodium dodecylsulfate (SDS) micelles (1, 2). Analysis of inhibition curves gives K_S values for binding of the esters to SDS micelles, and the slope of the plot of pK_S vs. N is 0.40 ± 0.01 ($r = 0.9986$, 5 points, for acetate to hexanoate) (A.A. Fedortchenko and O.S. Tee. Unpublished work).

Table 2. Least-squares correlations of substrate binding ($pK_S = -\log K_S$) and transition state binding ($pK_{TS} = -\log K_{TS}$) with acyl chain length (*N*), and with each other, for the reaction of nucleophiles with *p*-nitrophenyl alkanoates in the presence of CTAB micelles.[a]

Nucleophile	Plot	Slope	*r*	*n*
Anion of ME	pK_S vs. *N*	0.43 ± 0.03	0.9924	6
	pK_{TS} vs. *N*	0.43 ± 0.02	0.9950	7
	pK_{TS} vs. pK_S	0.99 ± 0.01	0.9998	7
Dianion of MAA	pK_S vs. *N*	0.44 ± 0.01	0.9994	6
	pK_{TS} vs. *N*	0.43 ± 0.01	0.9990	7
	pK_{TS} vs. pK_S	0.98 ± 0.03	0.9981	7
Dianion of MPA	pK_S vs. *N*	0.44 ± 0.01	0.9994	6[b]
	pK_{TS} vs. *N*	0.43 ± 0.01	0.9996	6
	pK_{TS} vs. pK_S	0.97 ± 0.02	0.9995	6[b]
Dianion of CYST	pK_S vs. *N*	0.44 ± 0.01	0.9993	4[b]
	pK_{TS} vs. *N*	0.41 ± 0.01	0.9997	4
	pK_{TS} vs. pK_S	0.94 ± 0.02	0.9994	4[b]
Anion of GLY	pK_S vs. *N*	0.44 ± 0.01	0.9993	4[b]
	pK_{TS} vs. *N*	0.43 ± 0.01	0.9997	4
	pK_{TS} vs. pK_S	0.97 ± 0.03	0.9992	4[b]
Anion of TFE	pK_S vs. *N*	0.41 ± 0.01	0.9996	4[c]
	pK_{TS} vs. *N*	0.38 ± 0.02	0.9972	4
	pK_{TS} vs. pK_S	0.92 ± 0.04	0.9980	4[c]
Hydroxide ion[d]	pK_S vs. *N*	0.42 ± 0.01	0.9983	7
	pK_{TS} vs. *N*	0.42 ± 0.02	0.9963	7
	pK_{TS} vs. pK_S	1.00 ± 0.02	0.9994	7

[a]Using the values of K_S and K_{TS} presented in Table 1, except for hydroxide ion where they are taken from ref. (5). "Slope" is the slope of the least squares line, "*r*" is the correlation coefficient, and *n* is the number of data points in the analysis.

[b]The values of K_S were taken to be the same as those found with the mercaptoacetate dianion.[4]

[c]The values of K_S were taken to be the same as those found with hydroxide ion under the same conditions (5).

[d]From previous experiments carried out in an aqueous phosphate buffer of pH 11.60 (5).

respect to the present results, replacement of bromide ions, as well as of hydroxide ion and buffer anions, in the Stern layer by less hydrophilic thiolate anions can explain the catalysis of thiolysis, and also the observation that the catalytic ratios k_{cN}/k_N are independent of the ester.

Hydroxide ion is a small, "hard" anion that is strongly solvated in water, and for its CTAB-catalyzed reaction with *p*-nitrophenyl esters the catalytic ratio k_{cN}/k_N is only 2.4 ± 0.3, when the total bromide ion is kept at 5.0 mM (5). This ratio is low because the heavily hydrated hydroxide ion does not compete well with bromide ion in the Stern layer (7). Thiolate ions, which are "softer," more polarizable, and less strongly solvated, interact more strongly with CTAB micelles, and so they exchange much more readily with bromide ions (6*d*). Consequently, CTAB catalysis of ester thiolysis is appreciably stronger. For the anion of 2-mercaptoethanol, the catalytic ratio is larger than for hydroxide ion and remarkably constant at 15.3 ± 0.6, for esters beyond the acetate (Table 1). For the mercaptoacetate dianion this ratio is larger still, at 79 ± 7, presumably because the double negative charge on the nucleophile enhances its ion exchange. The catalytic ratio is not quite as big for the 3-mercaptopropionate dianion (53 ± 2) or the cysteine dianion (59 ± 4), perhaps because in these larger ions the double negative charge is more spread-out or because they are hydrated slightly more strongly than the dianion of MAA.

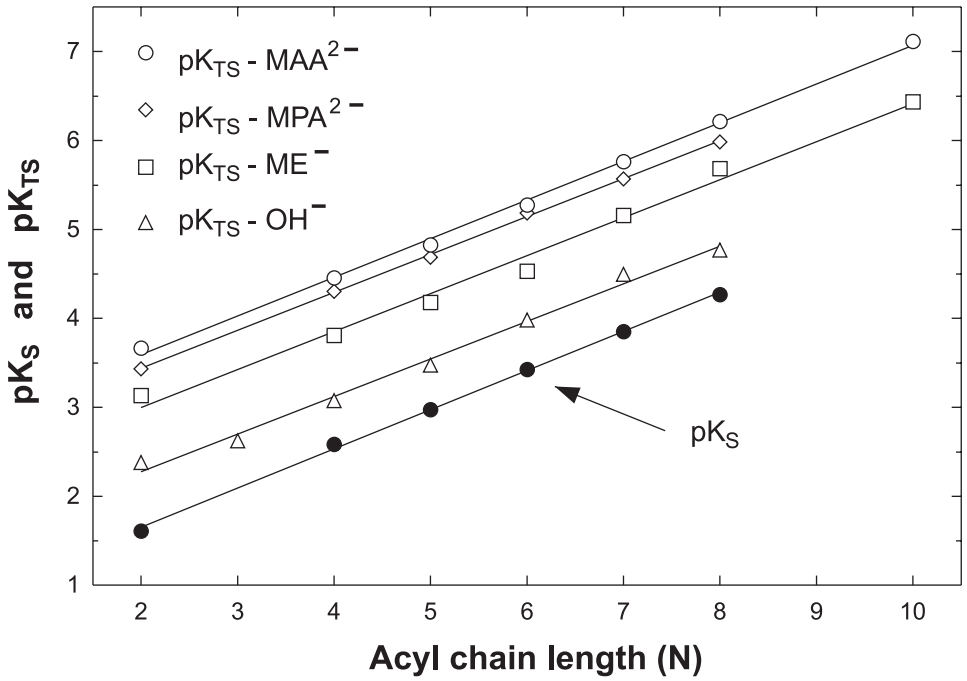
By contrast to the high ratios found for the thiolate dianions, for the glycinate anion, which is an amine nucleophile, the catalytic ratio is barely greater than one, at ~1.4 (Table 2). This much lower value is presumably due to a combination of factors: (*i*) the lower overall charge, *(ii)* the harder, nitrogen nucleophile, and (*iii*) stronger hydration in the bulk aqueous medium. Interestingly, the TFE anion has a much higher catalytic ratio (~25) than hydroxide ion (~2.4), even though both are oxyanions. Almost certainly, the TFE anion is appreciably more hydrophobic and less strongly hydrated than hydroxide ion, so that it exchanges into the CTAB micelles more readily.

Catalysis of thiolate attack by cationic micelles has been observed before (6, 14, 15). Moreover, spectral measurements have shown that there are very strong interactions between thiophenoxide ions and CTAB micelles (14). Correspondingly, CTAB micelles catalyze the reaction of thiophenoxide ion with *p*-nitrophenyl acetate by 50-fold (15) and its reaction with 2,4-dinitrofluorobenzene even more so (14). Obviously in this latter case there are additional factors, besides ion exchange, contributing to the dynamic component of transition state stabilization.

Conclusions

On the face of it, Kirby's (12) dissection of transition state binding into passive binding and dynamic binding seems simplistic, and yet it appears to be particularly suitable for the cleavage of *p*-nitrophenyl alkanoates by thiolate ions and other nucleophilic anions in CTAB micelles. From the results discussed above, it is concluded that: (*i*) the passive component of the transition state binding involves hydrophobic binding of the acyl chain of the esters in the micelles that is more or less the same as that involved in the substrate

Fig. 4. The dependence of transition state binding (pK_{TS}) and substrate binding (pK_S) to CTAB micelles on the ester chain length (N) of *p*-nitrophenyl alkanoates. The values of pK_{TS} (open symbols) are for various nucleophiles, as indicated; the values of pK_S (●) are those found with MAA. The pK_{TS} points for CYST and TFE (not shown) are close to those for MPA, and those for GLY are barely different from pK_S because k_{cN}/k_N values are almost one (Table 1). The slopes of the graphs are all about 0.43 (Table 2). The corresponding plots of pK_{TS} against pK_S are linear, with slopes very close to one (Table 2).



binding (Fig. 4); (*ii*) the dynamic component is essentially constant for a given nucleophile because it is primarily determined by the interactions associated with acyl transfer in the Stern layer of the micelle; (*iii*) it varies with the nucleophiles because of differences in their ease of exchange into the Stern Layer, due to their hard and (or) soft character, solvation, and charge.

Support for our first conclusion, (*i*) above, is provided by a recent paper from Buurma et al. (13*c*). These authors probed the nature of the Stern region of micelles (cationic, anionic, and non-ionic) using the kinetics of two pH-independent hydrolysis reactions. From their findings they concluded "…. that the stabilisation by the hydrophobic parts of the micelle is similar for the reactant state and for the activated complex." Obviously, this conclusion is essentially the same as the one we have arrived at from the data in Table 2 and Fig. 4.

Experimental

The *p*-nitrophenyl esters were purchased from Sigma Chemical Co., except for the heptanoate which was synthesized as previously (16). Cetyltrimethylammonium bromide (hexadecyltrimethyl-ammonium bromide, CTAB) was obtained from ICN Biochemicals and purified by extraction with diethyl ether in a Soxhlet apparatus for 4 h to remove any residual amines (17), followed by drying overnight. The other chemicals were the best grades available from the Aldrich Chemical Co.mpany, except for standard NaOH solutions which were obtained from A & C Chemicals (Montreal).

The kinetics of the ester cleavage were followed by monitoring the pseudo-first order appearance of the *p*-nitrophenolate ion at 405 nm, using an Applied Photophysics Ltd. SX17MV Stopped-flow Spectrophotometer, with the cell temperature kept at 25.0 ± 0.1°C. From five to 10 absorbance traces were acquired and computer averaged before estimation of k_{obs} by nonlinear least-squares fitting of an exponential growth curve.

As outlined in the main text, three basic types of kinetics experiments were carried out: (*i*) to find k_N, determine k_{obs} vs. [Nuc], with no CTAB (Fig. 1); (*ii*) to find K_S, determine k_{obs} vs. [CTAB], with fixed [Nuc] (Fig. 2); (*iii*) to find k_{cN}, determine k_{obs} vs. [Nuc], with fixed [CTAB] (Fig. 3). Aliquots of stock ester solutions (0.1 M in spectral grade acetonitrile) were added to solutions of NaBr + requisite amount of CTAB in distilled water to give ester solutions of twice the desired final concentrations. The ester + CTAB solutions were sonicated for 10–20 min to facilitate complete solubilization of the ester and dispersal of the surfactant. The dilute substrate solution was mixed 1:1 with a solution containing carbonate buffer + Nuc, brought to pH 10.60. The final reacting solutions, after mixing in the stopped-flow machine, contained 0.10 M carbonate buffer, CTAB (0–5.00 mM), NaBr (5.00 mM – $[CTAB]_o$), and ester concentrations as follows: (*i*) acetate to pentanoate, 50 μM; (*ii*) hexanoate, 25 μM; (*iii*) heptanoate, 5 μM; (*iv*) octanoate, 2.5 μM; and (*v*) decanoate, 1.5 μM. Note that generally [ester] << $[CTAB]_o$, so the micelles would not be significantly affected by the presence of the esters (1). Experiments with TFE were carried out with a 0.20 M phosphate buffer, at pH 11.60, in place of the carbonate buffer.

Nonlinear fitting of eq. [6] was carried out with GraphPad Prism software. When using eqs. [5] and [6] in data analysis, one has to decide how to handle the concentration of surfactant [Surf] involved in micelles. This quantity is reduced from the total surfactant by the amount of the critical micellar concentration (cmc): [Surf] = ([Surf]$_o$ – cmc) (1). For CTAB, cmc is 0.92 mM at *zero* ionic strength, but it is appreciably lower at high salt concentrations (18) and the lowering effect is greater still for less hydrophilic anions like thiolate ions (19). For example, the addition of only 40 μM thiophenolate ion, in a 0.010 M borate buffer at pH 10, lowers the cmc of CTAB to 0.08 mM (14). In the present work, taking [Surf] = ([Surf]$_o$ – cmc), and treating cmc as a fitting parameter in eq. [6] for the data obtained for each of the seven esters reacting with 20 mM ME in 0.10 M carbonate buffer, gave values of cmc that were close to an average of 0.05 mM. Accordingly, for consistency we have taken the cmc to be equal to this value throughout.

According to the literature, the pK_as of the thiols at zero ionic strength are: (*i*) cysteine, 8.39 (20); (*ii*) 2-mercaptoethanol, 9.72 (21); (*iii*) mercaptoacetic acid, 10.56 (20);[6] (*iv*) 3-mercaptopropionic acid, 10.84 (21), but they are lower at high ionic strength. For example, at μ = 1.0 M, the pK_a of ME is 9.61 (22), and at μ = 0.2 M, the second pK_a of MAA drops from 10.56 to 9.84 (20). Thus, at the working pH of 10.60, in the 0.10 M carbonate buffer, the thiols will exist to a considerable extent as their reactive thiolate anions. The exact fractions of the anions are not important to the discussion above because they are the same for all the esters in the series, and they cancel out in the ratios k_{cN}/k_N and in $K_{TS} = k_N K_S/k_{cN}$ (eq. [7]). The relevant pK_a of glycine is 9.78 (23), and that of TFE is 12.4 (22, 24).

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References

1. (*a*) I.V. Berezin, K. Martinek, and A.K. Yatsimirski. Russ. Chem. Rev. Eng. Transla. **42**, 787 (1973); (*b*) J.H. Fendler and E.J. Fendler. Catalysis in micellar and macromolecular systems. Academic Press, New York, 1975; (*c*) C.A. Bunton. Pure Appl. Chem. **49**, 969 (1977); (*d*) E.J.R. Südholter, G.B. van de Langkruis, and J.B.F.N. Engberts. Recl. Trav. Chim. Pays-Bas Belg. **99**, 73 (1980); (*e*) C.A. Bunton and G. Savelli. Adv. Phys. Org. Chem. **22**, 21 (1986); (*f*) C.A. Bunton, F. Nome, F.H. Quina, and L.S. Romsted. Acc. Chem. Res. **24**, 357 (1991); (*g*) J.B.F.N. Engberts. Pure Appl. Chem. **64**, 1653 (1992); (*h*) S. Tascioglu. Tetrahedron, **52**, 11113 (1996); (*i*) M.-F. Ruasse. Pure Appl. Chem. **69**, 1923 (1997).
2. (*a*) M.T.A. Behme, J.G. Fullington, R. Noel, and E.H. Cordes. J. Am. Chem. Soc. **87**, 265 (1965); (*b*) F.M. Menger and C.E. Portnoy. J. Am. Chem. Soc. **89**, 4698 (1967); (*c*) L.R. Romsted and E.H. Cordes. J. Am. Chem. Soc. **90**, 4404 (1968); (*d*) M. Almgren and R. Rydholm. J. Phys.Chem. **83**, 360 (1979); (*e*) N. Funasaki. J. Phys. Chem. **83**, 237 (1979); (*f*) N. Funasaki and A. Murata. Chem. Pharm. Bull. **28**, 805 (1980); (*g*) T.J. Broxton. Aust. J. Chem. **35**, 1357 (1982); (*h*) E. Rodenas and S. Vera. J. Phys. Chem. **89**, 513 (1985).
3. N. Al-Awadi and A. Williams. J. Org. Chem. **55**, 2001 (1990).
4. O.S. Tee. Adv. Phys. Org. Chem. **29**, 1 (1994).
5. O.S. Tee and A.A. Fedortchenko. Can. J. Chem. **75**, 1434 (1997).
6. (*a*) W. Tagaki, T. Amada, Y. Yamashita, and Y. Yano. J. Chem. Soc. Chem. Commun. 1131 (1972); (*b*) I.M. Cuccovia, E.M. Schroter, P.M. Monteiro, and H. Chaimovich. J. Org. Chem. **43**, 2248 (1978); (*c*) M.K. Kawamuro, H. Chaimovich, E.B. Aubin, E.A. Lissi, and I.M. Cuccovia. J. Phys. Chem. **95**, 1458 (1991); (*d*) V.R Correia, I.M. Cuccovia, and H. Chaimovich. J. Phys. Org. Chem. **6**, 7 (1993).
7. (*a*) N. Funasaki. J. Phys. Chem. **83**, 1998 (1979); (*b*) H. Chaimovich, J.B.S. Bonihla, M.J. Politi, and F.H. Quina. J. Phys. Chem. **83**, 1851 (1979); (*c*) D. Bartet, C. Gamboa, and L. Sepulveda. J. Phys. Chem. **84**, 272 (1980); (*d*) F.H. Quina, M.J. Politi, I.M. Cuccovia, E. Baumgarten, S.M. Martins-Frachetti, and H. Chaimovich. J. Phys. Chem. **84**, 361 (1980); (*e*) C.A. Bunton and J.R. Moffat. J. Phys. Chem. **92**, 2896 (1988).
8. (*a*) O.S. Tee and T.A. Gadosy. J. Chem. Soc. Perkin Trans. 2, 2307 (1994); (*b*) T.A. Gadosy and O.S. Tee. J. Chem. Soc. Perkin Trans. 2, 71 (1995).
9. (*a*) O.S. Tee, T.A. Gadosy, and J.B. Giorgi. Can. J. Chem. **75**, 83 (1997); (*b*) O.S. Tee and M.J. Boyd. Can. J. Chem. **77**, 950 (1999).
10. For example: (*a*) M.J. Pregel, E.J.Dunn, and E.J. Buncel. J. Am. Chem. Soc. **113**, 3545 (1991); (*b*) R. Cacciapaglia and L. Mandolini. Chem. Soc. Rev. **22**, 221 (1993); (*c*) D.M. Davies, G.A. Garner, and J.R. Savage. J. Chem. Soc., Perkin Trans. 2, 1525 (1994); (*d*) D.R.J. Palmer, E. Buncel, and G.R.J. Thatcher. J. Org. Chem. **59**, 5286 (1994); (*e*) M.J. Pregel, E.J. Dunn, R. Nagelkerke, G.R.J. Thatcher, and E. Buncel. Chem. Soc. Rev. **24**, 449 (1995); (*f*) N. Pirrinccioiglu and A. Williams. J. Chem. Soc. Perkin Trans. 2, 37 (1998); (*g*) D.M. Davies, S.J. Foggo, and P.M. Paradis. J. Chem. Soc. Perkin Trans. 2, 1597 (1998); (*h*) D.M. Davies and M.E. Dreary. J. Chem. Soc. Perkin Trans. 2, 1027 (1999).
11. (*a*) R. Wolfenden. Acc. Chem. Res. **5**, 10 (1972); (*b*) G.E. Leinhard. Science (Washington, D.C.), **180**, 149 (1973); (*c*) W.P. Jencks. Adv. Enzymol. **43**, 219 (1975); (*d*) R.L. Schowen. *In* Transition states in biochemical processes. *Edited by* R.D. Gandour and R.L. Schowen. Plenum, New York, 1978; (*e*) J. Kraut. Science (Washington, D.C.), **242**, 533 (1988); (*f*) R. Wolfenden and W.M. Kati. Acc. Chem. Res. **24**, 209 (1991).
12. A.J. Kirby. Acta Chem. Scand. **50**, 203 (1996); Angew. Chem. Int. Ed. Engl. **35**, 707 (1996).
13. (*a*) D.M. Davies, N.D. Gillitt, and P.M. Paradis. J. Chem. Soc. Perkin Trans. 2, 659 (1996); (*b*) D.M. Davies and S.J. Foggo. J. Chem. Soc. Perkin Trans. 2, 247 (1998); (*c*) N.J. Buurma, A.M. Herranz, and J.F.B.N. Engberts. J. Chem. Soc. Perkin Trans. 2, 113 (1999); (*d*) N. Pirrinccioglu, F. Zuman, and A. Williams. J. Org. Chem. **65**, 2537 (2000).
14. H. Chaimovich, A. Blanco, L. Chayet, L.M. Costa, P.M. Monteiro, C.A. Bunton, and C. Paik. Tetrahedron, **31**, 1139 (1975).

[6] Irving et al. (21) determined a value of 10.68.

15. I.M. Cuccovia, E.H. Shroter, P.M. Monteiro, and H. Chaimovich. J. Org. Chem. **43**, 2248 (1978).
16. O.S. Tee and T.A. Gadosy. J. Chem. Soc. Perkin Trans. 2, 715 (1994).
17. D.D. Perrin, W.L.F. Armarego, and D.R. Perrin. Purification of laboratory chemicals. 2nd ed. Pergamon Press, Oxford. 1980.
18. M.J. Rosen. Surfactants and interfacial phenomena. 2nd ed., John Wiley and Sons, New York. 1989.
19. E.J.R. Südholter and J.B.F.N. Engberts. J. Phys. Chem. **83**, 1854 (1979).
20. D.P. Wrathall, R.M. Izatt, and J.J. Christiansen. J. Am. Chem. Soc. **86**, 4779 (1964).
21. R.J. Irving, L. Nelander, and I. Wadso. Acta Chem. Scand. **18**, 769 (1964).
22. D.J. Hupe and W.P. Jencks. J. Am. Chem. Soc. **99**, 454 (1977).
23. E.J. King. J. Am. Chem. Soc. **73**, 155 (1951).
24. C.H. Arrowsmith, A.J. Kresge, and Y.C. Tang. J. Am. Chem. Soc. **113**, 179 (1991).