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The Effect of Hydrophobic–Lipophilic Interactions on Chemical Reactivity. 1. New Evidence for Intermolecular Aggregation and Self-Coiling

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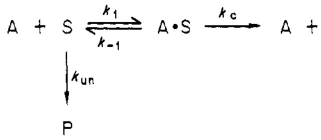
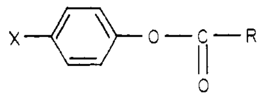
Abstract: The hydrolytic behavior of 21 para-substituted phenyl esters of *n*-alkanoic acids (**n**-X) with various chain lengths in 60:40 ($\Phi = 0.60$), 50:50 ($\Phi = 0.50$), and 40:60 v/v ($\Phi = 0.40$) Me_2SO–H_2O mixtures was studied. Four new sets of experimental results which include departure from Hammett correlation for *n*-hexadecanoates (**16**-X), substantial differences in activation parameters, and effects of amylose on the kinetic parameters and on the activation parameters are presented along lines of reasoning mentioned by previous authors. These data establish that the aggregation and self-coiling of the *n*-alkanoate chain actually exist under experimental conditions.

Hydrophobic–lipophilic interactions play important roles in bioprocesses and are also the basic force that incorporates substrates into micelles or macrocyclophanes in which they may further undergo catalyzed reactions.[1-5] However, it seems that the effects of hydrophobic forces on chemical reactivity of organic substrates have not yet received enough attention, and relatively few papers dealing directly with this subject have been published.[6-10]

Menger first reported that intermolecular aggregation is the cause of the rate retardation of the hydrolysis of *p*-nitrophenyl dodecanoate in aqueous solution.[7] Later, Knowles suggested that such rate retardations could also be attributed to the coiling-up of the long alkyl chains.[8] More recently, Murakami also rationalized his results in terms of these two effects, and he has specifically suggested that only monomeric species are sufficiently reactive.[9] However, although six lines of evidence can be summed up from these previous works,[11] the array of facts cited to support their conclusions still seems to be limited in scope and depth, and presentation of new facts and other detailed studies should be a welcome addition to this interesting field. Therefore, we investigated the hydrolytic behavior of 21 para-substituted phenyl esters of straight-chain carboxylic acids (**n**-X) with various chain lengths in 60:40 v/v ($\Phi = 0.6$), 50:50 ($\Phi = 0.5$), and 40:60 ($\Phi = 0.4$) Me_2SO–H_2O solvent mixtures. On the basis of these investigations we can now present ten lines of evidence for the fact that both the phenomenon of aggregation and the phenomenon of self-coiling actually exist and they can join force and greatly slow down the hydrolysis of long-chain substrates. Four of these lines of evidence are new, and particularly noteworthy and pleasing is the fact that strong support is provided by experimental results when amylose is used as a host, a macromolecule with the singular capability of wrapping up these long-chain substrates as single pieces in their straightened-up conformations.

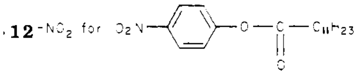
Scheme I





X = NO_2, CN, Cl, COOH, CH_3, OCH_3, H
R = CH_3, *n*-$C_{11}H_{23}$, *n*-$C_{15}H_{31}$

e.g. **12**-NO_2 for



Experimental Section

Substrates. Various para-substituted phenyl carboxylates were synthesized by the method described below: A substituted phenol was refluxed with an excess of acyl chloride in dry benzene for 1–4 h and cooled, the product was extracted by ether, and the ethereal solution was washed with water and saturated aqueous $NaHCO_3$ and finally dried. After removal of the solvent the product was recrystallized from EtOH or distilled.

Solvent. Me_2SO and water were purified as previously described.[12] All experiments were performed in mixtures of Me_2SO and aqueous 0.02 M carbonate buffer solution (pH 10.13). The pH value of the final mixture is 13.12 for $\Phi = 0.50$, 12.46 for $\Phi = 0.40$, and 13.54 for $\Phi = 0.60$.

Solubility Measurement. The solubility of the long-chain substrate **16**-Cl was measured by the method described below: *p*-chlorophenyl hexadecanoate dissolved in ethanol was diluted with a 1:1 (v/v) Me_2SO:H_2O mixture solution, and the ϵ value ($\log \epsilon = 3.67$) was obtained by measuring the absorptions at different substrate concentrations at 268 nm. Then, excess substrate was added to the solvent mixture and thermally equilibrated for 8 h at 50 °C, and the saturated solution was cooled to 35 °C and filtered. On the basis of the above-mentioned ϵ value, the concentration of this saturated solution at 35 °C was calculated to be 2×10^{-4} M.

Kinetics. Kinetic measurements were made by using a modified Model 710 recording spectrophotometer with a constant-temperature bath connected to a cell holder. A 1.0-cm cell was filled with 3.00 mL of solution and thermally equilibrated for 15 min. An ethanol solution of the substrate (30 μL) was injected into the cell with a microsyringe. The increase in absorbance of phenolate was then traced as a function

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(11) Six lines of evidence presented by previous workers correspond in nature to discussions under the headings I, II, III, IV, V, and VIII of this paper. Another type of evidence, the effects of added ureas, etc.,[7] is not discussed in the present work.

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Table I. The Rate Constants k_{obsd} (10^{-3} s^{-1}) and Their Ratios for the Hydrolysis of the Substrates at 35 °C in $\Phi = 0.50$ Me_2SO-H_2O Solution

	R			ratios		
X	CH_3	$C_{11}H_{23}$	$C_{15}H_{31}$[a]	k_2/k_{12}	k_{12}/k_{16}	k_2/k_{16}
NO_2	32.2	11.7	0.41	2.76	28.7	79
CN	19.6	6.77		2.86		
Cl	4.66	0.68	0.018[b]	6.76	38.1	258
COO^-	3.05	0.70	0.71	4.4	0.99	4.3
H	2.31	0.36	0.019[b]	6.36	19.4	124
CH_3	1.47	0.21	0.007[b]	7.3	30	200
OCH_3	1.39	0.43	0.051[b]	3.22	8.4	27.2

[a] The rate constants of **2**-X and **12**-X are independent of their initial concentrations; the concentrations of **16**-X (10^{-5} M) are as follows: NO_2 2.43; Cl 4.97; CH_3 4.49; H 4.83; and OCH_3 4.81, respectively. [b] The values are obtained by extrapolating from the data determined at higher temperatures.

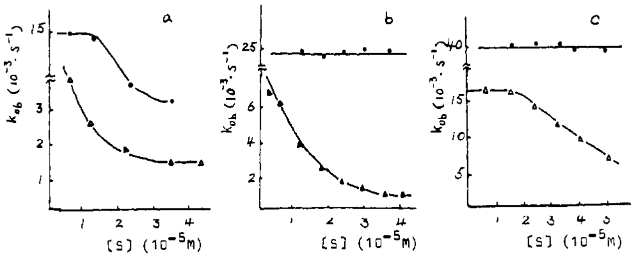

Figure 1. The dependence of k_{ob} on the concentrations of **16**-NO_2 and **12**-NO_2 at 45 °C: (a) $\Phi = 0.40$; (b) $\Phi = 0.50$; (c) $\Phi = 0.60$; (•) for **12**-NO_2; (△) for **16**-NO_2.

of time. Pseudo-first-order rate constants (k_{ob}) were obtained in the normal manner in all cases. For **16**-X, however, there were positive deviations after 50% conversion of the esters, so the pseudo-first-order rate constants of **16**-X were obtained from the linear portion of the curves for the initial stage of the reaction.[13] For monitoring the production of para-substituted phenoxide ions, different wavelengths were used for the different substrates, viz., nitro 410 nm; cyano 280 nm; chloro 310 nm; carboxlate 295 nm; methyl 305 nm; methoxy 310 nm; and unsubstituted 280 nm. All of the rate constants are accurate to within ±5%, except for **16**-X (±10%).

Different modes of catalysis were affected by amylose in the hydrolysis of esters with different chain lengths. The acetates (**2**-X) followed second-order kinetics, but saturation behavior was shown by the dodecanoates (**12**-X) and hexadecanoates (**16**-X). As shown in Scheme I, A, S, P, and A·S respectively represent amylose, substrate, product, and the amylose–substrate complex, and $k_{-1}/k_1 = K_d$. As done previously, from the rate constants in the presence or absence of amylose, i.e., k_{ob} and k_{un}, the k_c and K_d values were obtained by Lineweaver–Burk plots.[14]

Results

The pseudo-first-order rate constants (k_{ob}) of the hydrolysis of all of substrates in the absence of amylose and their ratios, e.g., the ratio of the rate constants of **12**-X to that of **16**-X, k_{12}/k_{16}, are summarized in Table I.

In solutions of $\Phi = 0.50$, the effects of substrate concentrations on the rate constants of hydrolysis are summarized in Table II. All of rate constants are independent of substrate concentrations except those of **16**-NO_2. The concentration dependence of **16**-NO_2 is shown in Figure 1b.

In solutions of $\Phi = 0.40$, the rate constants of hydrolysis for both **12**-NO_2 and **16**-NO_2 are dependent on substrate concentrations, whereas those of **2**-NO_2 and **8**-NO_2 are not; the results are shown in Table II and Figure 1a.

In solutions of $\Phi = 0.60$, the rate constants of hydrolysis are independent of substrate concentrations for all four esters except for those of **16**-NO_2 in the high-concentration region (above 2.50 × 10^{-5} M). The results are shown in Table II and Figure 1c.

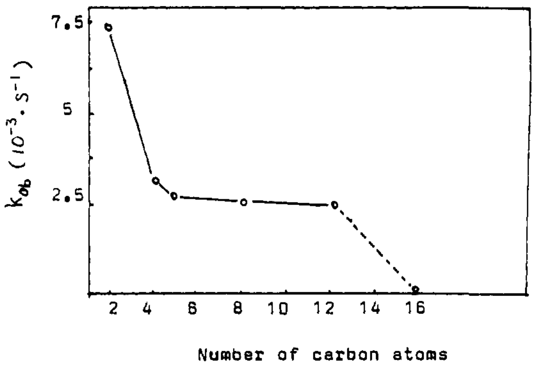

Figure 2. Effect of chain length on hydrolysis rate, at 35 °C, $\Phi = 0.50$; k_{un} of **5**-NO_2 is from previous work.[17]

From the temperature dependcence of rate constants (k_{ob} at $\Phi = 0.5$) measured in the range of 35 to 60 °C, the activation parameters for the hydrolysis of substrates in the absence of amylose were calculated and are shown in Table III. The substrates were chosen with the objective of obtaining information concerning chain-length and substituent effects on the rates.

After the addition of various concentrations of amylose, the hydrolytic rate profiles of substrates **12**-Cl, **16**-Cl, **12**-COO^-, and **16**-COO^- followed Michaelis–Menten kinetics. Lineweaver–Burk plots yielded k_c and K_d values listed in Table IV.

The dependence of the rate constants on the pH values of solvent with $\Phi = 0.50$ was measured, and the data are shown in Table V. Plotting the k_{ob} values against the concentrations of the OH^- ion yields a straight line.

Discussion

Hydrolysis of carboxylic esters under alkaline conditions usually proceeds via the addition–elimination mechanism involving tetrahedral intermediates. For *n*-alkanoic esters with a good leaving group on their carbonyl, the first step is usually rate determining, and the steric effect expresses itself by slowing down the hydrolysis rate 2–4 times if a methyl group of the alkanoyl moiety is replaced by a *n*-propyl or a *n*-butyl; further lengthening of the straight hydrocarbon chain normally produces much less or very little rate retardation, and Taft's Es parameters characterizing such steric effects also approach a constant value.[15-17] This generalization is certainly valid for substrates with straight-chain lengths of less than 12 carbons studied in this work (cf. Table I), as well as those in previous works.[18] However, in the present $\Phi = 0.50$ Me_2SO-H_2O system, when this chain lengthens to 16 carbons, i.e., for the esters **16**-X, there are exceptionally large decreases in the rate constants which do not conform to this generalization. As mentioned in the introduction, such large rate retardations have been rationalized by the proposition that they are consequences of the phenomena of aggregation and coiling-up.[7-9,19] Since we believe that a thorough investigation of all the effects of hydrophobic–lipophilic interactions on the chemical and physical properties of organic molecules is a worthy endeavor, in the first part of our efforts we embarked upon a systematic study of the hydrolytic behavior of 21 carboxylates, (*n*-X). For clarity of presentation, we will discuss and group our results or lines of evidence under nine headings listed below.

I. Unusual Effects of Lengthening the Chain. For the type of straight-chain substrates discussed above with an alkyl group of more than 3 or 4 carbons, the usual effects of further lengthening the alkyl chain are the bringing about of a gradual change in some

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Table II. Rate Constant Dependence on Substrate Concentrations for the Hydrolysis of *p*-Nitrophenyl Esters at $\Phi = 0.40$, 0.50, and 0.60 (45 °C, k_{obsd}s in Units of 10^{-3} s^{-1})

		concentration of substrates (10^{-5} M)								
Φ	ester	5.03	4.24	3.63	3.03	2.42	1.82	1.21	0.85	0.36
0.40	**2**-NO_2	46.2		46.4			46.8		46.0	
	8-NO_2	18.0		17.7			17.7		17.5	
	12-NO_2	4.95		7.04			14.4		14.7	
	16-NO_2	0.14		0.13			0.24		0.34	
0.50	**2**-NO_2			72.9	71.8	72.1		72.7		
	8-NO_2		25.6	25.5		24.9	25.1	25.0		
	12-NO_2			24.5	24.0	23.9	23.4	23.5		
	16-NO_2		0.62	0.95	1.17	1.66	2.27	3.49	5.06	6.94
0.60	**2**-NO_2	125		122		127	126			
	8-NO_2	41.5	41.2	42.0		41.5	41.8			
	12-NO_2	39.5	39.8	40.8		41.1	40.4			
	16-NO_2	6.60	9.11	11.3		14.2	16.3		16.5	

Table III. Chain-Length and Substituent Effects on the Activation Parameters for the Hydrolysis of the Substrates, $\Phi =$ 0.50

substrate	$\Delta H^{\ddagger}$,[b,c] kcal/mol	$\delta\Delta H^{\ddagger}$,[a] kcal/mol	$\Delta S^{\ddagger}$,[b,c] eu	$\delta\Delta S^{\ddagger}$, eu
2-NO_2	13.1		−22.1	
12-NO_2	13.8	13.1	−22.7	38
16-NO_2	27.1		+15.3	
2-Cl	13.5		−24.9	
12-Cl	18.1	11.3	−13.8	29
16-Cl	29.4		+15.1	
2-COO^-	13.7		−25.7	
12-COO^-	15.5	0.4	−22.6	1.3
16-COO^-	15.9		−21.3	
2-H	14.2		−24.4	
12-H	16.5	10.7	−20.8	29.1
16-H	27.2		+8.3	
2-CH_3	15.1		−21.4	
12-CH_3	19.7	22.3	−11.1	31.3
16-CH_3	32.0		+20.3	
2-OCH_3	15.1		−22.1	
12-OCH_3	15.9	5.9	−22.4	15.1
16-OCH_3	21.8		−7.3	

[a] $\delta\Delta H^{\ddagger} = \Delta H^{\ddagger}_{(16-X)} - \Delta H^{\ddagger}_{(12-X)}$; $\delta\Delta S^{\ddagger} = \Delta S^{\ddagger}_{(16-X)} - \Delta S^{\ddagger}_{(12-X)}$. [b] Experimental error: **16**-X, ±20%, others, ±10%. [c] Calculated at $T = 35 + 273$ °C.

Table IV. Kinetic Parameters of the Amylose-Catalyzed Hydrolysis of Some Substrates at 35 °C, $\Phi = 0.50$

substrate	$10^3 k_{un}$,[a] s^{-1}	$10^3 k_c$, s^{-1}	K_d, mM	k_c/k_{un}
12-Cl	0.69	12.6	0.048	18.3
16-Cl	0.018	4.16[b]	0.021[b]	230
12-COO^-	0.70	9.25	0.088	13.2
16-COO^-	0.71	4.01	0.018	5.63

[a] The k_{un} is the same as the k_{ob} used in previous tables. [b] Experimental uncertainty is ±20%, other k_c and K_d, ±10%.

Table V. Rate Constant Dependence of the Hydrolysis of Some Esters on the pH Values (k_{ob}'s in Units of 10^{-3} s^{-1}, $\Phi = 0.50$, 45 °C)

	pH values				
substrate	12.34	12.60	12.88	13.18	13.64
12-NO_2	5.48	8.20	10.1	24.4	49.0
16-NO_2	0.205	0.309	0.480	1.02	1.97

Table VI. The Ratios of Rate Constants of *p*-Nitrophenyl Esters with Different Chain Lengths in Various Solvent Systems, 45 °C

Φ	k_2/k_8	k_8/k_{12}	k_{12}/k_{16}
0.60	3.01	1.04	2.4,[a] 6.0[b]
0.50	2.86	1.05	79[b]
0.40	2.62	1.22,[a] 3.4[b]	43.4[b]

[a] The rate constant that is independent of concentrations was used. [b] The concentration of ester is 2.43×10^{-5} M.

of their properties, e.g., hydrolytic rate constants and activation parameters. If an abrupt change is produced by just adding a few more carbons, we will coin these effects as "unusual". In the preceeding paragraph we have already described such an unusual effect on hydrolytic rate (cf. Figure 2), but in the present work these unusual chain-length effects are almost ubiquitous and will be discussed separately under the following headings (relevant data can be found in Tables I, II, and III and Figures 1 and 2). However, no matter how many ways they can manifest themselves, we deem it necessary to present them as one unifying notion which serves as a undeniably strong evidence for the phenomena of aggregation and self-coiling.

II. Rate Constant Dependence on Initial Substrate Concentrations. As mentioned, the dependence of hydrolysis rates on initial concentrations as strong evidence for aggregation has been presented by various authors, whereas self-coiling, as an intramolecular process, is relatively independent of these concentrations. Previously, most of these works were done in aqueous solutions,[7,8,17] but the present work makes use of binary systems so that effects of solvent composition can also be investigated. Results of this study of rate dependence in Me_2SO-H_2O systems of $\Phi = 0.40$, 0.50, and 0.60 are tabulated in Table II (cf. Figure 1, a, b, and c). As indicated, the rate constants of not only the short-chain **2**-NO_2 but also the **8**-NO_2 with medium chain length are independent of the initial concentrations in all three of these solvents. On the contrary, the rate constants of **16**-NO_2 are strongly dependent on the substrate concentration in all of these solvent mixtures of different compositions, i.e., hydrolysis rates increase upon dilution. In fact, the rates start to deviate positively from first-order kinetics at about the first half-life, and pseudo-first-order constants were obtained from the earlier part of the rate vs. time plots.[9] For the $\Phi = 0.50$ and 0.40 systems, k increases continuously upon dilution, but in the $\Phi = 0.60$ curve, a "plateau" corresponding to the disappearance of aggregates appears at concentrations $<2.4 \times 10^{-5}$ M, indicating that the $\Phi = 0.60$ system is a better solvent than the other two mixtures. All of these facts conform with expectations based on the notion of aggregation. Notably, further support for the above statement is provided by the "border-line" behavior of **12**-NO_2, which has a chain length in between those of **8**-NO_2 and **16**-NO_2. Its profile in the $\Phi = 0.40$ solvent looks very similar to that of **16**-NO_2 in $\Phi = 0.60$. In other words, **12**-NO_2 does not aggregate in the $\Phi = 0.50$ and 0.60 solvents as well as in the $[S] < 1.68 \times 10^{-5}$ M region of the $\Phi = 0.40$ solvent.

III. Exceptionally Large Rate Retardations. To provide substance to our section I statement linking abrupt changes to unusual effects of lengthening the chain, we present Table I, in which k_{ob} values represent rate constants of ***n***-X in the $\Phi = 0.50$ system. Obviously, for all the X substituents, the k_2/k_{12} values remain in the range of roughly 3–7, indicating that a 12-carbon chain

Table VII. Ratios of Rate Constants[a] of Hydrolysis of *p*-Nitrophenyl Esters in Solvents of Various Compositions

ratio	**2**-NO$_2$	**8**-NO$_2$	**12**-NO$_2$	**16**-NO$_2$
$k(\Phi = 0.60)/k(\Phi = 0.50)$	1.74	1.66	1.71	14.1[b]
$k(\Phi = 0.50)/k(\Phi = 0.40)$	1.57	1.44	4.0[c]	5.0[c]

[a] k(average) used except if otherwise specified. [b] Concentration 4.24×10^{-5} M. [c] Concentration 5.03×10^{-5} M.

Table VIII. Ratios of Rate Constants Measured in Solvents of Different pH

substrate	k(pH 13.54)[a]/ k(pH 13.12)	k(pH 13.12)/ k(pH 12.46)[a]
12-NO$_2$	2.3	2.5
16-NO$_2$	2.4	2.7

[a] The k values at pH 13.54 and 12.46 are obtained from the straight-line plot based on data listed in Table VII.

induces no abrupt change in hydrolysis rates over those of shorter-chain substrates. Similar conclusions can be drawn from data in Table VI, in which ratios are tabulated in mediums of Φ = 0.60, 0.50, and 0.40. On the other hand, and back to Table I, either the k_2/k_{16} or the k_{12}/k_{16} values are remarkable in their variations both in range and magnitude. Especially noteworthy here are the k_{12}/k_{16} values—any deviation of them much from unity indicates an unusual chain-lengthening effect. Indeed, a glaring value of almost unity stands out singularly for X = COO$^-$, species with hydrophilic end groups (cf. section VIII). We believe these ratios can actually be used as indicators of the degree of aggregation, as the k_8/k_{16} ratios are used in separate works.[19]

IV. Evidence for Self-Coiling. Murakami's work indicates a rate-retarding factor of 12–13 caused by self-coiling of **12**-NO$_2$ when it is compared with **6**-NO$_2$ in 1.0% (v/v) aqueous dioxane. This factor is arrived at by comparing his rate constant derived from the plateau region of the rate profile of **12**-NO$_2$ with the concentration-independent k_2 of **6**-NO$_2$.[9] Such a method seems to be justifiable because we have found that the k_{12}/k_{16} ratio for **12**-COO$^-$ and **16**-COO$^-$ is unity. Thus the present work yields a coiling-retarded factor of 2.4 for **16**-NO$_2$ when it is compared with the concentration-independent k_{12} of **12**-NO$_2$ in the Φ = 0.60 solvent (cf. Table II). Greater retarding factors are expected in poorer solvent systems, e.g., either the Φ = 0.50 or 0.40. Finally, a decisive proof for self-coiling will be presented in a future communication,[20] in which we forced some long-chain molecules to be engaged in very-large-ring "neighboring-group participation".

V. Effects of Changing the Solvent Composition. With our Me$_2$SO–H$_2$O system, increasing the Φ value (or organic component) will make a better solvent for long-chain substrates because of the reduced hydrophobic and increased lipophilic interactions. In fact, as far as the observed rate constants are concerned, we may anticipate that the effect of increasing Φ will bring about similar changes as that of reducing the substrate chain length or concentration. These expectations are nicely borne out by the curves in Figure 1. For **16**-NO$_2$, its curve in the Φ = 0.60 medium may be visualized as the low-concentration part of its Φ = 0.50 curve plus an extension (plateau) to the left, and its Φ = 0.40 curve might be looked at as part of the high-concentration part of its Φ = 0.50 curve plus an extension to the right. For **12**-NO$_2$, the same solvent-composition effect now expresses itself in a somewhat different way. Reducing the value to 0.40 now produces a curve which closely resembles that of the **16**-NO$_2$ in the Φ = 0.60 medium.

A different approach to link the composition effect on rate changes with molecular aggregation is to compare the ratios of the rate constants from mediums of different Φ values for the same substrates at specified concentrations. This is done for each of the four esters in Table VII. Clearly, five of the eight values are roughly in the range of 1.5–1.7, and this factor can be accounted for by the effect of pH changes illustrated in Table VIII, in which the pH 13.54 value corresponds to the Φ = 0.60 solvent used, and the value of 12.46 corresponds to Φ = 0.40. Thus the 4.0 value in Table VII for **12**-NO$_2$ signifies aggregation, just as the two values for **16**-NO$_2$ do. Interestingly, the lower-row value (5.0) is smaller than the upper-row value (14.1), implicating that the change in the degree of aggregation and coiling-up in going from the Φ = 0.50 to the Φ = 0.40 system is smaller than that in going from Φ = 0.60 to Φ = 0.50.

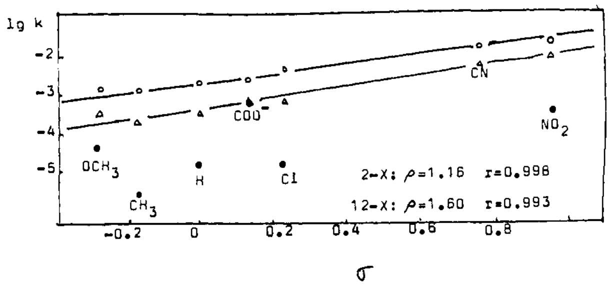
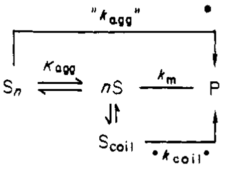


Figure 3. Hammett correlation diagram of k_{ob} at 35 °C, Φ = 0.50: (○) for **2**-X, (△) for **12**-X, and (•) for **16**-X.

Scheme II



VI. Departure from Hammett Correlation for 16-X. On the basis of the rate data in the Φ = 0.50 medium for 21 substrates with three chain lengths tabulated in Table I, Hammett correlations were attempted. As expected, good correlations were found for the normally behaving esters, **2**-X with ρ = 1.16, r = 0.998 and **12**-X with ρ = 1.60, r = 0.993, if the Leffler–Grunwald modification (eq 1) was employed for the para nitro and cyano groups.[21,22] In the present case, r was found to be 0.35, and the

$$\log (k/k_0) = \rho[\sigma + r(\sigma^- - \sigma)] \qquad (1)$$

substituent constants for *p*-NO$_2$ and *p*-CN were 0.95 and 0.78, respectively. If a similar correlation were found for **16**-X, one might be tempted to believe that for hydrolysis of long-chain substrates nucleophilic attack on the carbonyl carbon of the monomeric ester species was also the rate-determining step. Such was found not to be the case; as Figure 3 clearly shows, the correlation is very poor (r = 0.574) for the **16**-X esters. Even without the two substituents which depart most, i.e., COO$^-$ and OCH$_3$, the correlation is still not very good (n = 4, r = 0.979). The involvement of aggregation and coiling-up and the possibility of more than one slow step will certainly complicate matters formidably,[23] as Scheme II may suggest. At present, we are satisfied with the observation that, on this count of substituent effect, **16**-X esters are totally different from their shorter counterparts, thus they could not possibly follow the same "simple" path taken up by the latter esters. In short, aggregation and coiling remain the most plausible rationale.

VII. Substantial Differences in Activation Parameters. On account of the fact that the aggregation number n in Scheme II is not a constant and there is a whole array of conformations that affect the rate of nucleophilic attack to different extents, the complexity of the problem defies rigorous kinetic analysis and detailed rationalization. Thus along the same line of reasoning mentioned in the preceding section, we deem it good supporting

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Table IX. The Different Hydrolytic Behavior of **16**-COO$^-$ and **16**-Cl

substrate	k_{12}/k_{16}	$\delta\Delta H^{\ddagger}$,[a] kcal/mol	$\delta\Delta S^{\ddagger}$,[b] eu	k_c/k_{un}
16-Cl	38.1	10.3	22.5	230
16-COO$^-$	0.99	0.4	1.3	5.63

[a] $\delta\Delta H^{\ddagger} = \Delta H^{\ddagger}_{16} - \Delta H^{\ddagger}_{12}$. [b] $\delta\Delta S^{\ddagger} = \Delta S^{\ddagger}_{16} - \Delta S^{\ddagger}_{12}$.

Table X. Activation Parameters[a,b] of Amylose-Catalyzed Hydrolysis, in Comparison with the Uncatalyzed Hydrolysis, $\Phi = 0.50$

substrate	$\Delta H^{\ddagger}_c$, kcal/mol	$\Delta H^{\ddagger}_{un}$, kcal/mol	$\delta\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}_c$, eu	$\Delta S^{\ddagger}_{un}$, eu	$\delta\Delta S^{\ddagger}$, eu
12-Cl	18.2	18.1	0.1	−6.7	−13.8	7.1
16-Cl	19.1	29.4	−10.3	−7.4	15.1	−22.5
12-COO$^-$	17.7	15.5	2.2	−10.9	−22.6	11.7
16-COO$^-$	17.6	15.9	1.7	−12.1	−21.3	9.2

[a] $\Delta H^{\ddagger}_c$ and $\Delta S^{\ddagger}_c$ values are calculated at $T = 273 + 35$ °C and cited from ref 19; their uncertainties are ±15%. [b] $\delta\Delta H^{\ddagger} = \Delta H^{\ddagger}_c - \Delta H^{\ddagger}_{un}$. $\delta\Delta S^{\ddagger} = \Delta S^{\ddagger}_c - \Delta S^{\ddagger}_{un}$.

evidence for aggregation of any sizeable difference in activation parameters between **16**-X esters and their shorter counterparts. Data in Table III can speak for themselves; nevertheless, one may notice that the positive $\Delta H^{\ddagger}$ values and negative $\Delta S^{\ddagger}$ values for **2**-X and **12**-X conform to conventional wisdom and that **16**-COO$^-$ again preferred to behave as if it were a short molecule.

VIII. A Welcome Role Played by the Carboxylate End Group. Among the six substituents studied, the carboxylate group stands out unique in being charged and hydrophilic or solubilized in aqueous solvent mixtures. Thus it may be able to thwart the tendency of long-chain molecules to aggregate and coil-up in poor solvents.[15,24] Alternatively speaking, if our notions about aggregation and coiling are valid, and if the driving force of these phenomena is the hydrophobic–lipophilic interaction, we should expect **16**-COO$^-$ to behave differently from all other **16**-X substrates but similarly to the shorter substrates. Gratifyingly, all our data aggree with such an expectation. To enumerate: (1) In contrast to **16**-NO$_2$ described in section II, the hydrolytic rate of **16**-COO$^-$ was found to be independent of its initial concentration. (2) As mentioned in section III, unlike all five other **16**-X esters, **16**-COO$^-$ shows no rate retardation when compared with **12**-COO$^-$. (3) As Table III indicates, unlike all the other five trios, the $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ values for **16**-COO$^-$, **12**-COO$^-$, and **2**-COO$^-$ are very close in magnitude (cf. section VII). (4) As discussed in section IX, **16**-COO$^-$ also lived up to our expectations if amylose is added to the system. Table IX is a brief summary of the above observations. To conclude, we believe the carboxylate or other solubilizing groups can play important future roles in the evaluation of the many effects caused by aggregation and coiling.

IX. Effects of Amylose on (1) the Kinetic Parameters and (2) the Activation Parameters. Having presented all the abovementioned observations bearing witness to the phenomena of aggregation and self-coiling, we now call in our new host molecule amylose for a final decisive proof. On the basis of the knowledge that amylose possesses a special clout of wrapping up long-chain guest molecules as single pieces in their straightened-up forms,[12,18,25] we suspect it will not tolerate such things as aggregation and coiling in aqueous solutions. Thus hydrophobic long-chain esters are expected to readjust their manners in the presence of this "host", and indeed they did, as borne out by the data in Tables IV and X.

Four substrates can be grouped into two pairs. Members of each pair differ by four carbons. But for the first pair, one of the two members (**16**-Cl) will aggregate and coil-up, whereas for the second pair, none of the two will aggregate. Comparison both between the members and between the pairs will lead to interesting observations. For instance, members of the second pair, **12**-COO$^-$ and **16**-COO$^-$, have identical k_{un}'s as expected and their k_c's differ by a factor of 2.3. The latter piece of information is valuable because it indicates how a difference in 4-carbon chain length might be reflected in the k_c values. Now for the first pair, in starting with a k_{un} difference of 38.2-fold, after the addition of amylose it ends up with a k_c difference of only 3-fold, fairly close to the 2.3-fold value for the second pair. Certainly this demonstrates that in the presence of amylose the originally aggregating **16**-Cl molecules have readjusted to a catalyzed hydrolytic path very similar to that of the other three members. Close examination of the k_c/k_{un} data shows that there is a 12.6-fold difference between members of the first pair and a 0.43-fold difference between members of the second pair. Thus comparison between the pairs will yield a difference factor of around 30, again adding support to our previous arguments.

Finally, a close look at Table X. The $\delta\Delta H^{\ddagger}$ is defined as the difference between the activation enthalpies of uncatalyzed and amylose-catalyzed reactions, and $\delta\Delta S^{\ddagger}$ is similarly defined. First, one may note that members of the second pair possess very close $\Delta H^{\ddagger}_{un}$, $\Delta H^{\ddagger}_c$, $\Delta S^{\ddagger}_{un}$, and $\Delta S^{\ddagger}_c$ values, but members of the first pair have greatly different $\Delta H^{\ddagger}_{un}$ and $\Delta S^{\ddagger}_{un}$ values but similar $\Delta H^{\ddagger}_c$ and $\Delta S^{\ddagger}_c$ values. Second, members of the second pair also have close $\delta\Delta H^{\ddagger}$ and $\delta\Delta S^{\ddagger}$ values, but these values are way apart for members of the first pair. Undoubtedly, only arguments in the perceding paragraph are consistent with these findings.

Acknowledgment. We express our thanks to Mrs. Shujing Wang for providing some substrates.

Registry No. $O_2NC_6H_4$-*p*-OAc, 830-03-5; NCC_6H_4-*p*-OAc, 13031-41-9; ClC_6H_4-*p*-OAc, 876-27-7; $HO_2CC_6H_4$-*p*-OAc, 2345-34-8; PhOAc, 122-79-2; MeC_6H_4-*p*-OAc, 140-39-6; $MeOC_6H_4$-*p*-OAc, 1200-06-2; $O_2NC_6H_4$-*p*-$OCO(CH_2)_{10}CH_3$, 1956-11-2; NCC_6H_4-*p*-$OCO(CH_2)_{10}CH_3$, 90149-61-4; ClC_6H_4-*p*-$OCO(CH_2)_{10}CH_3$, 83491-06-9; $HO_2CC_6H_4$-*p*-$OCO(CH_2)_{10}CH_3$, 56670-30-5; $PhOCO(CH_2)_{10}CH_3$, 4228-00-6; MeC_6H_4-*p*-$OCO(CH_2)_{10}CH_3$, 10024-57-4; $MeOC_6H_4$-*p*-$OCO(CH_2)_{10}CH_3$, 55250-82-3; $O_2NC_6H_4$-*p*-$OCO(CH_2)_{14}CH_3$, 1492-30-4; ClC_6H_4-*p*-$OCO(CH_2)_{14}CH_3$, 83491-07-0; $HO_2CC_6H_4$-*p*-$OCO(CH_2)_{14}CH_3$, 86960-47-6; $PhOCO(CH_2)_{14}CH_3$, 24632-92-6; MeC_6H_4-*p*-$OCO(CH_2)_{14}CH_3$, 4907-37-3; $MeOC_6H_4$-*p*-$OCO(CH_2)_{14}CH_3$, 90149-62-5; amylose, 9005-82-7.

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