Secondary Valence Force Catalysis. VI. Catalysis of Hydrolysis of Methyl Orthobenzoate by Sodium Dodecyl Sulfate[1]

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Abstract: The acidic hydrolysis of methyl orthobenzoate is subject to marked catalysis by sodium dodecyl sulfate. Below the critical micelle concentration (cmc) for this surfactant, second-order rate constants for this reaction are independent of surfactant concentration; above the cmc, these rate constants increase rapidly, level off, and finally decrease slowly with increasing surfactant concentration. The surfactant-dependent hydrolysis of methyl orthobenzoate is subject to marked inhibition by cations. For example, 0.09 *M* sodium ion decreases the second-order rate constant 4-fold, 0.01 *M* dimethylammonium ion decreases it 25-fold, and 0.001 *M* tetrapropylammonium ion decreases it 20-fold when the reaction is conducted in the presence of 0.01 *M* sodium dodecyl sulfate. Inhibition by alkali metal cations increases with increasing hydrated radius of the cation, that by alkaline earth cations is rather independent of the nature of the cation, and that by ammonium ions increases with increasing hydrophobic character of the cation. Chromatography of methyl orthobenzoate on Sephadex G-15 in the presence of various concentrations of sodium dodecyl sulfate yields an approximate equilibrium constant for association of ortho ester with micelles derived from this surfactant of 73 M^{-1} in dilute aqueous solutions of carbonate buffer, pH 9.2. This value seems not to be substantially altered by addition of 0.24 *M* ammonium or sodium ions but is decreased by the addition of 0.24 *M* tetramethylammonium ion or 0.12 *M* tetraethylammonium ion. The maximum rate increase for the hydrolysis of methyl orthobenzoate elicited by a series of alkyl sulfates increases with increasing alkyl chain length and decreases with increasing temperature.

Interest in the kinetics and mechanism for organic reactions occurring on the surface of micelles formed from ionic detergents has been sharpened by the realization of a relationship between these processes and those which are enzymatic in nature.[3-28] While it is certainly possible to overdraw the analogy, points of similarity between enzyme-catalyzed and micelle-catalyzed reactions include the following. First, the catalysts are structurally related in terms of their molecular weights and the relative dispositions of their hydrophobic and hydrophilic portions with respect to the aqueous solvent. Second, micelle-catalyzed reactions, like their enzymatic counterparts, exhibit substrate specificity. Thus, the hydrolysis of methyl orthobenzoate but not that of methyl orthoformate is subject to catalysis by sodium dodecyl sulfate[4,5] and the hydroxide ion dependent hydrolysis of *p*-nitrophenyl hexanoate is more sensitive to catalysis by tetradecyltrimethylammonium bromide than is that of *p*-nitrophenyl acetate.[5] Third, both enzymatic and micellar reactions exhibit kinetic behavior characterized by saturation of substrate with catalyst and saturation of catalyst with substrate.[5] Fourth, certain nucleophilic groups known to occur on the surface of enzymes prove to exhibit enhanced nucleophilicities when present on the surface of suitably constituted micelles.[7,8] These results, together with the purely organochemical interest in such reactions in both mechanistic and synthetic terms, have prompted us to further develop our earlier studies of certain reactions by attempting to illuminate the scope of catalysis in terms of variation in substrate and detergent structure and to define the dependence of such catalysis on additional parameters including ionic strength and temperature. Such studies ought to both shed light on the source of the catalytic activity and more closely define the relationship between those reactions which occur on the surface of proteins and on the surface of micelles.

In this work, attention is directed specifically toward the sodium alkyl sulfate catalyzed hydrolysis of methyl orthobenzoate and is an extension of our previous studies of this reaction.[4,5] A preliminary report concerning a portion of this work has appeared.[23]

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(2) Career Development Awardee of the National Institutes of Health.

(3) For leading references to the kinetics of nonenzymatic reactions in micellar systems, see ref 4–28. For related properties of enzymatic reactions, we suggest consulting the following: H. R. Mahler and E. H. Cordes, "Biological Chemistry," Harper and Row, New York, N. Y., 1966; M. Dixon and E. C. Webb, "Enzymes," 2nd ed, Academic Press Inc., New York, N. Y., 1964; W. P. Jencks, *Ann. Rev. Biochem.*, **32**, 639 (1963).

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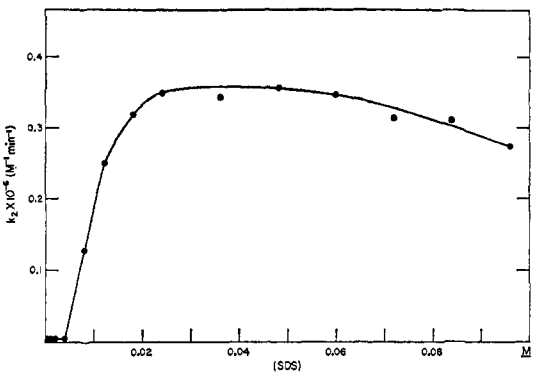

Figure 1. Second-order rate constants for hydrolysis of methyl orthobenzoate in aqueous solution at 25° plotted against the concentration of sodium dodecyl sulfate. Values of pH were maintained through the addition of 0.01 *M* acetate buffers.

Experimental Section

Materials. Methyl orthobenzoate was synthesized from benzotrichloride (α,α,α-trichlorotoluene) as previously described.[29] The product was further purified by careful distillation at reduced pressure on a spinning-band column in order to remove remaining traces of starting material. Elemental analysis and infrared and proton magnetic resonance spectra established that the product was essentially pure and specifically free of contamination by starting material and carboxylic ester. Sodium dodecyl sulfate was the best grade available from Distillation Products Industries and was employed without further purification. Surface tension measurements, spectrophotometric studies of the change in the visible absorption spectrum of pinacyanol chloride, and studies of the kinetics of surfactant-dependent hydrolysis of methyl orthobenzoate yielded values of the critical micelle concentration (cmc) that compared favorably with accepted values under similar conditions.[30] A highly purified sample of sodium dodecyl sulfate was kindly provided by the Miami Valley Laboratories of Proctor & Gamble, Inc. Selected kinetic measurements of methyl orthobenzoate hydrolysis employing this sample as catalyst yielded results in good agreement with those obtained employing the Distillation Products Industries material. Other sodium alkyl sulfates employed were obtained in a purified state from the Mann Research Laboratories. Sephadex G-15 was a product of Pharmacia Inc. All inorganic salts employed were of reagent grade and were used without further purification. Glass-distilled water was employed throughout.

Kinetic measurements were carried out spectrophotometrically with a Zeiss PMQ II spectrophotometer equipped with a cell holder through which water from a thermostated bath was continuously circulated.[4,5] All hydrolyses were followed by observing the appearance of methyl benzoate at 228 mμ;[31] initial methyl orthobenzoate concentration was 5×10^{-5} *M*. First-order rate constants were obtained from plots of log ($OD_\infty - OD_t$) against time in the usual fashion; second-order rate constants were obtained by dividing the first-order constants by the activity of the hydrated proton. Values of pH were determined with a Radiometer PHM 4c pH meter utilizing an internal glass electrode for measurements at 25° and a thermostated external glass electrode for those at 40°.

Equilibrium constant measurements for association of methyl orthobenzoate with micelles derived from sodium dodecyl sulfate were performed by employing molecular sieve filtration on Sephadex G-15 according to the method of Herries, *et al.*[11] A column of dimensions 2.5 × 33.6 cm (total volume V_t = 164.8 cm^3) was employed for all measurements. Using Blue Dextran 2000, the void volume, V_0, of the packed column was determined to be 60.5 cm^3. The imbibed volume, V_i, was calculated to be 74.5 cm^3 from the equation

$$V_i = \frac{w_r d}{w_r + 1}(V_t - V_0)$$

in which w_r and d are the water regain and wet density for Sephadex G-15, respectively. Before each run the column was equilibrated with 1500 ml of 0.042 *M* carbonate buffer, pH 9.3, the appropriate concentration of sodium dodecyl sulfate, and added salt (if any). The runs were initiated by the addition of 1 ml of 0.01 *M* methyl orthobenzoate in the appropriate buffer to the column with a sample applicator. Elution with the same buffer followed. Fractions (1 ml) were collected employing an automatic fraction collector and these were analyzed spectrophotometrically for methyl orthobenzoate at 261 and 267 mμ, and, following acidification, for methyl benzoate at 273 mμ. The use of the surfactant caused some difficulties in that ultraviolet absorbing materials were continuously eluted from the column. Although these provided some interference in our assays for methyl orthobenzoate they did not prevent a reasonably accurate assessment of the results. The necessary equilibrium constant was evaluated from plots of $V_i/(V_e - V_0)$ against C_m as described by Herries, *et al.*;[11] V_e is the effluent volume for washing methyl orthobenzoate off the column (see Table II, Results) and C_m is the total concentration of surfactant in the eluting fluid less the cmc value for the surfactant. The partial specific volume of sodium dodecyl micelles was taken to be 0.9 ml/g.[32]

Results

In Figure 1, second-order rate constants for hydrolysis of methyl orthobenzoate in aqueous solution at 25° are plotted as a function of sodium dodecyl sulfate concentration. Values of pH were maintained near 5.40 with 0.01 *M* acetate buffers. Catalysis of this hydrolysis reaction is initiated at concentrations of surfactant very near the cmc.[30] At higher concentrations of surfactant, a maximum catalysis near 80-fold is achieved following which the rate constants decrease slowly with further increases in surfactant concentration. In terms of the magnitude of the catalysis and the over-all shape of the curve, these results are similar to those previously reported for this reaction employing a less highly purified sample of sodium dodecyl sulfate.[4,5] However, our earlier reports claimed considerable catalysis below the cmc. It now seems clear that this behavior is a consequence of lowering of the cmc by impurities in the surfactant and is not a consequence of substrate-induced micelle formation below the cmc.

In Table I, second-order rate constants for hydrolysis of methyl orthobenzoate in 0.01 *M* solutions of sodium dodecyl sulfate are collected as a function of the concentration of 21 cations of various types. These studies were carried out at 25° where possible or at 40° in those cases in which the surfactant salts were not soluble at the lower temperature. In the case of each cation, marked inhibition of the surfactant-dependent hydrolysis is observed. That this is the effect of the cation and not the anion is demonstrated by the finding that sodium chloride and sodium perchlorate behave similarly in this system (Table I). We now wish to present the results for each class of cation graphically in Figures 2 through 6. The abbreviations employed in these figures are those identified in Table I.

The five classes into which the cationic inhibitors have been divided are as follows: alkali metal cations (Figure 2), alkaline earth cations (Figure 3), methylammonium ions (Figure 4), monosubstituted *n*-alkylammonium ions (Figure 5), and tetrasubstituted *n*-alkylammonium ions (Figure 6). Examination of these figures clearly reveals the following three facts: for alkali metal cations, inhibitory effectiveness decreases with increasing size of the hydrated ion;[33] for alkaline

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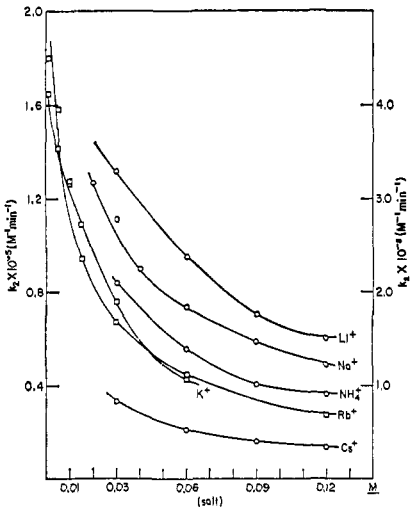

Figure 2. Second-order rate constants for methyl orthobenzoate hydrolysis in aqueous solutions containing 0.01 *M* sodium dodecyl sulfate plotted against the concentration of several alkali metal ions and ammonium ion. See Table I for details.

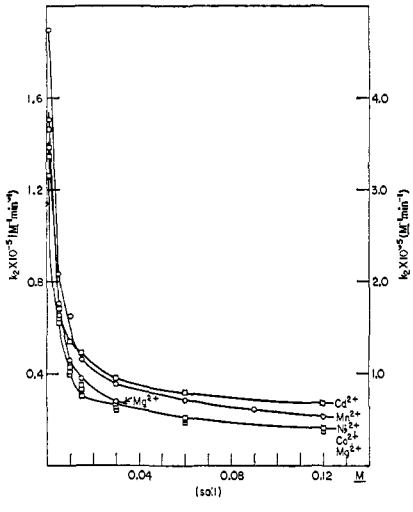

Figure 3. Second-order rate constants for methyl orthobenzoate hydrolysis in aqueous solutions containing 0.01 *M* sodium dodecyl sulfate plotted against the concentration of several alkaline earth cations. See Table I for details.

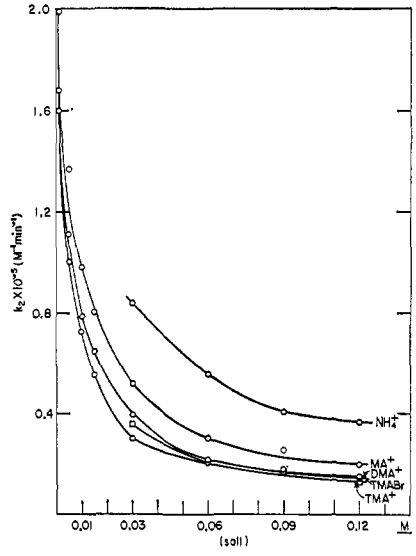

Figure 4. Second-order rate constants for methyl orthobenzoate hydrolysis in aqueous solutions containing 0.01 *M* sodium dodecyl sulfate plotted against the concentration of a series of methyl ammonium ions. See Table I for details and abbreviations.

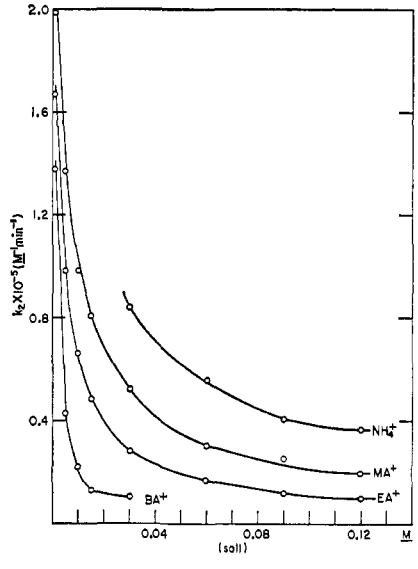

Figure 5. Second-order rate constants for methyl orthobenzoate hydrolysis in aqueous solutions containing 0.01*M* sodium dodecyl sulfate plotted as a function of the concentration of a series of monosubstituted *n*-alkylammonium ions. See Table I for details and abbreviations.

earth cations, inhibitory effectiveness is largely independent of the nature of the cation; and, for ammonium ions of all types, inhibitory properties increase with increasing hydrophobic character of the ion. Note that, due to differences in the temperature at which the kinetics were carried out, not all curves in some of the figures are directly comparable. Table I may be consulted for complete details. Note also that inhibition by these cations never causes the rate constants to be substantially less than those obtained in the absence of surfactant: the second-order rate constant for methyl orthobenzoate hydrolysis at 25° below the cmc is near $4.5 \times 10^3\ M^{-1}\ \text{min}^{-1}$, a value close to that previously reported for this reaction in the absence of surfactant and at ionic strength 0.50.[34] For example, although a concentration of tetra-*n*-butylammonium ion of 0.01 *M* is sufficient to reduce the second-order rate constant almost to the value characteristic of surfactant-free solutions (a rate decrease of 33-fold), increasing the concentration by more than an order of magnitude has little further effect on the rate constant (Table I).

The equilibrium constant for association of methyl orthobenzoate with micelles derived from sodium dodecyl sulfate was evaluated from molecular sieve chromatography on Sephadex G-15 in 0.042 *M* carbonate buffer, pH 9.3 (see Experimental Section and ref 11). Use of this buffer prevented significant hydrolysis of the ortho ester during the time period necessary for development of the columns. In Table II, the effluent volume for methyl orthobenzoate from the Sephadex G-15 column is tabulated as a function of the concentration of sodium dodecyl sulfate both in the presence and absence of added salts. From the first three entries

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Table I. Second-Order Rate Constants for the Hydrolysis of Methyl Orthobenzoate in 0.01 *M* Solutions of Sodium Dodecyl Sulfate as a Function of the Concentration of Several Salts[a]

Salt	Temp,[b] °C	Concn, *M*	$k_2 \times 10^{-5}$, M^{-1} min^{-1}
1. Sodium chloride (Na^+)	25	0	2.13
		0.020	1.27
		0.030	1.11
		0.040	0.9
		0.060	0.743
		0.090	0.59
		0.120	0.494
		0.150	0.435
		0.180	0.316
		0.210	0.304
		0.240	0.280
2. Sodium perchlorate	25	0	2.06
		0.030	1.08
		0.060	0.83
		0.12	0.456
		0.18	0.350
		0.24	0.294
3. Lithium chloride (Li^+)	25	0.03	1.32
		0.06	0.954
		0.09	0.708
		0.12	0.607
		0.18	0.45
		0.24	0.382
4. Ammonium chloride (NH_4^+)	25	0.03	0.84
		0.06	0.56
		0.09	0.408
		0.12	0.368
		0.18	0.281
		0.24	0.229
5. Potassium chloride (K^+)	40	0	4.25
		0.001	4.12
		0.005	3.54
		0.010	3.16
		0.015	2.72
		0.030	1.90
		0.060	1.07
6. Rubidium chloride (Rb^+)	40	0	4.42
		0.001	4.51
		0.005	3.96
		0.010	3.18
		0.015	2.36
		0.030	1.68
		0.060	1.12
		0.12	0.69
7. Cesium chloride (Cs^+)	25	0.03	0.334
		0.06	0.213
		0.09	0.162
		0.12	0.139
		0.18	0.119
8. Methylamine hydrochloride (MA^+)	25	0.001	1.99
		0.005	1.37
		0.010	0.985
		0.015	0.808
		0.030	0.522
		0.060	0.303
		0.090	0.254
		0.12	0.198
		0.18	0.154
		0.24	0.119
9. Dimethylamine hydrochloride (DMA^+)	25	0.001	1.68
		0.005	1.14
		0.010	0.79
		0.015	0.65
		0.030	0.395
		0.060	0.218
		0.090	0.179
		0.12	0.148
		0.18	0.107
		0.24	0.09
10. Trimethylamine hydrochloride (TMA^+)	25	0.001	1.60
		0.005	1.03
		0.010	0.726
		0.015	0.558
		0.030	0.301
		0.060	0.209
		0.090	0.179
		0.120	0.128
		0.180	0.096
		0.240	0.086
11. Tetramethylammonium chloride (TMACl)	25	0.03	0.356
		0.06	0.21
		0.09	0.167
		0.12	0.146
		0.18	0.108
		0.24	0.092
12. Tetraethylammonium bromide (TEABr)	25	0.001	1.18
		0.005	0.501
		0.010	0.324
		0.015	0.263
		0.030	0.158
		0.060	0.104
		0.090	0.090
		0.120	0.081
		0.180	0.082
		0.240	0.052
13. Tetrapropylammonium bromide (TPABr)	25	0.001	0.957
		0.005	0.207
		0.010	0.116
		0.015	0.081
		0.030	0.060
		0.060	0.047
		0.090	0.041
		0.12	0.042
14. Tetra-*n*-butylammonium bromide (TBABr)	25	0.001	0.748
		0.005	0.113
		0.01	0.064
		0.015	0.053
		0.03	0.040
		0.06	0.035
		0.09	0.034
		0.12	0.038
15. Ethylamine hydrochloride (EA^+)	25	0.001	1.67
		0.005	0.985
		0.010	0.662
		0.015	0.488
		0.030	0.282
		0.060	0.170
		0.080	0.121
		0.120	0.099
		0.180	0.083
		0.240	0.071
16. *n*-Butylamine hydrochloride (BA^+)	25	0.001	1.38
		0.005	0.432
		0.010	0.222
		0.015	0.131
		0.030	0.104
17. Manganous chloride (Mn^{2+})	25	0.001	1.90
		0.005	0.835
		0.010	0.65
		0.015	0.464
		0.030	0.358
		0.060	0.286
		0.090	0.246
		0.120	0.214
		0.18	0.186
18. Magnesium chloride (Mg^{2+})	25	0.001	1.52
		0.005	0.705
		0.010	0.458
		0.015	0.380
		0.030	0.279
	40	0.001	3.16
		0.005	1.56
		0.010	1.07
		0.015	0.76
		0.030	0.68
		0.060	0.52

Table I (*Continued*)

Salt	Temp,[b] °C	Concn, *M*	$k_2 \times 10^{-5}$, M^{-1} min^{-1}
		0.12	0.41
		0.18	0.37
		0.24	0.34
19. Nickel chloride (Ni^{2+})	40	0	4.28
		0.001	3.37
		0.005	1.61
		0.010	1.02
		0.015	0.83
		0.030	0.61
		0.060	0.49
		0.12	0.38
		0.18	0.34
		0.24	0.29
20. Cobalt chloride (Co^{2+})	40	0	4.22
		0.001	3.67
		0.005	1.63
		0.010	1.00
		0.015	0.87
		0.030	0.65
		0.060	0.51
		0.120	0.41
		0.180	0.34
		0.240	0.33
21. Cadmium chloride (Cd^{2+})	40	0.0	4.09
		0.001	3.47
		0.005	1.71
		0.010	1.34
		0.015	1.22
		0.03	0.95
		0.06	0.79
		0.12	0.68
		0.18	0.62
		0.24	0.56

[a] All reaction mixtures contained an initial concentration of methyl orthobenzoate of *ca.* 5.0×10^{-5} *M*; 228 mμ. [b] Those reactions run at 25° contained a 0.02 *M* acetate buffer, 50% acid. Those reactions run at 40° contained a 0.01 *M* acetate buffer, 20% acid.

Table II. Effluent Volumes for Methyl Orthobenzoate for a Column of Sephadex G-15 as a Function of the Concentration of Sodium Dodecyl Sulfate and Certain Salts[a]

Sodium dodecyl sulfate, *M*	Salt,[b] *M*	Effluent vol, ml	$V_i/V_e - V_0$)[c]
...	...	181	0.618
0.006	...	150	0.832
0.010	...	132	1.042
0.010	NaCl, 0.24	127	
0.010	NH_4Cl, 0.24	127	
0.010	TMACl, 0.24	145	
0.010	TEABr, 0.12	145	

[a] For details for the dimensions of the column and the like, refer to the Experimental Section. [b] See Table I for abbreviations employed. [c] For definition of symbols employed, see Experimental Section.

in this table, an equilibrium constant for association of ortho ester with the micelles

$$K = \frac{(\text{ortho ester})_m}{(\text{ortho ester})_b(\text{sodium dodecyl sulfate})}$$

of 73 M^{-1} was obtained (see Experimental Section). The effluent volume of methyl orthobenzoate in the presence of 0.01 *M* sodium dodecyl sulfate is not appreciably affected by the addition of 0.24 *M* sodium chloride or ammonium chloride (Table II) indicating that these salts do not markedly influence the partitioning of the ortho ester between the micellar and bulk phases. In contrast, the addition of 0.24 *M* tetramethylammonium chloride or 0.12 *M* tetraethylammonium bromide increases this effluent volume (Table II) suggesting that these species reduce the affinity of the ortho ester for the micellar phase with respect to the bulk phase.

In Table III, second-order rate constants for hydrolysis of methyl orthobenzoate in aqueous solution are collected as a function of the concentration of sodium octyl, decyl, dodecyl, tetradecyl, and hexadecyl sulfates. The solubility properties of the latter two surfactants necessitated performing the kinetic studies at 30 and 45°, respectively. In the case of each surfactant, the rate constants for ortho ester hydrolysis increase with increasing surfactant concentration. Note that, qualitatively, the shape of the rate-concentration profile for each surfactant is the same as that noted above for sodium dodecyl sulfate. However, it is clear that all surfactants are not equally good catalysts; those containing the longer alkyl chains are both more effective catalysts at low concentrations and cause a larger net rate increase at the rate maximum. These points are made more clearly in Table IV in which the maximal rate increases, the concentrations at which the maximal rate increases occur, and the temperature dependence of the maximal rate increase are collected. Note that in each case in which the temperature dependence was studied, the maximal rate increase is decreased by increasing temperature and that this effect is rather more important with the short-chain salts than with those possessing longer chains.

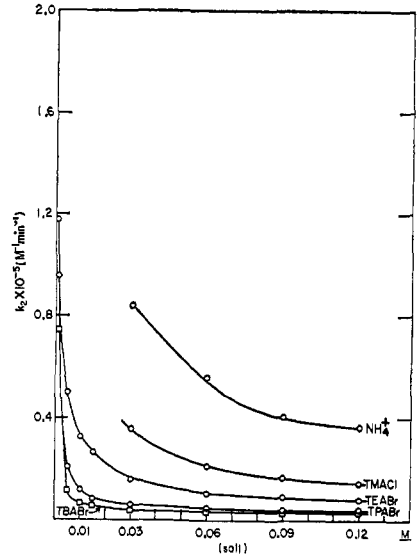


Figure 6. Second-order rate constants for methyl orthobenzoate hydrolysis in aqueous solutions contalning 0.01 *M* sodium dodecyl sulfate plotted against the concentration of a series of tetrasubstituted *n*-alkylammonium ions. See Table I for details and abbreviations.

Table III. The Effect of the Concentration of Several Sodium Alkyl Sulfates on the Second-Order Rate Constants for Hydrolysis of Methyl Orthobenzoate in Aqueous Solution[a,b]

Sodium alkyl sulfate	Temp, °C	Concn, M	$k_2 \times 10^{-6}$, M^{-1} min^{-1}
Octyl	25	0	0.0050
		0.05	0.0069
		0.075	0.0092
		0.100	0.012
		0.15	0.027
		0.20	0.035
		0.30	0.034
Decyl	25	0.015	0.0045
		0.030	0.031
		0.04	0.072
		0.05	0.10
		0.075	0.12
		0.10	0.11
		0.2	0.092
		0.3	0.062
		0.4	0.048
Dodecyl	25	0.0005	0.0043
		0.001	0.0045
		0.002	0.0047
		0.004	0.0050
		0.008	0.13
		0.012	0.25
		0.018	0.32
		0.024	0.351
		0.036	0.345
		0.048	0.357
		0.060	0.348
		0.072	0.314
		0.084	0.311
		0.096	0.274
Tetradecyl	30	0	0.0084
		0.0005	0.0092
		0.001	0.068
		0.002	0.26
		0.004	0.475
		0.008	0.685
		0.015	0.725
		0.020	0.793
		0.030	0.728
		0.040	0.674
Hexadecyl	45	0	0.0298
		0.0001	0.0338
		0.0004	0.293
		0.0008	0.522
		0.0012	0.844
		0.002	1.15
		0.003	1.50
		0.004	1.78
		0.006	2.56
		0.008	2.38

[a] Compounds 1–4 were studied in reaction mixtures containing 0.01 M acetate buffer, 20% acid, and an initial concentration of methyl orthobenzoate of *ca.* 5×10^{-5} M. [b] Hexadecyl sodium sulfate was studied in the presence of 0.01 M sodium phosphate, pH 6.4, and an initial concentration of methyl orthobenzoate of *ca.* 5×10^{-6} M.

Table IV. Temperature Dependence of the Maximal Rate Increases Elicited by a Series of Sodium Alkyl Sulfates for Methyl Orthobenzoate Hydrolysis in Aqueous Solution

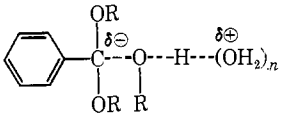
Sodium alkyl sulfate	Temp, °C	$k_2^0 \times 10^{-6}$,[a] M^{-1} min^{-1}	$k_2 \times 10^{-6}$,[b] M^{-1} min^{-1}	Max rate increase
Octyl	25.0	0.00502	0.0351 at 0.20 M	7.0
Decyl	40.0	0.0191	0.296 at 0.075 M	15.5
	32.5	0.0094	0.211 at 0.075 M	22.4
	25.0	0.00452	0.121 at 0.075 M	26.8
Dodecyl	40.0	0.0188	0.774 at 0.024 M	41.2
	32.5	0.0094	0.584 at 0.036 M	62.1
	25.0	0.00452	0.357 at 0.048 M	79.0
Tetradecyl	40.0	0.0168	1.37 at 0.030 M	81.5
	35.0	0.0122	1.06 at 0.015 M	86.9
	30.0	0.00864	0.793 at 0.020 M	91.8
Hexadecyl	45.0	0.0298	2.56 at 0.006 M	86

[a] Second-order rate constants in the absence of surfactant. [b] Second-order rate constants for the reaction in the presence of the indicated concentrations of surfactants at which values maximum catalysis occurs.

Discussion

One is not in a position at this time to account quantitatively for rates of organic reactions occurring in micellar phases. While the gross structural features of the micelles themselves seem reasonably clear in some cases,[35] structural details remain obscure. Related studies concerned with organic reactions at liquid interfaces have clearly revealed that the kinetics of these reactions are quite sensitive to the nature of the molecular organization at the surface.[36] There seems no reason to believe that this is not true of reactions involving micelles as well. Since the nature of the micellar surface is not fully understood and since the disposition of adsorbed organic molecules with respect to this surface is not generally known, a detailed analysis is precluded. Nevertheless, Duynstee and Grunwald, in their important work, have emphasized that differences in the rates of organic reactions occurring in aqueous or micellar phases must be principally attributed to medium and electrostatic effects.[9] The catalysis of methyl orthobenzoate hydrolysis by sodium dodecyl sulfate and effects of cations on this catalysis will be examined in these terms. As a preliminary to these considerations, we discuss the site of reaction and the influence of surfactant concentration on reaction rate.

The mechanism of hydrolysis of methyl orthobenzoate in aqueous solution has been the subject of substantial investigation.[37,38] The transition state for this reaction is perhaps best viewed as involving proton transfer from the hydrated proton to the substrate concerted with departure of the leaving alcohol.[38] Thus the transition state involves the incipient formation of a carbonium ion from the ortho ester. The Brønsted



α value for general acid catalyzed hydrolysis of these substrates is usually near unity,[39] suggesting that the substrate has made very substantial progress toward carbonium ion geometry in the transition state. This point of view is adopted in the discussion which follows.

The localization of the site within the micellar phase at which bond-changing reactions occur is of central importance for understanding the kinetics of these processes. Several lines of evidence would suggest that hydrolysis of methyl orthobenzoate, and perhaps many other reactions as well, occurs at the highly charged double layer which surrounds the micellar

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core and is within the shear surface of the micelle, the Stern layer. In the first place, the interesting proton magnetic resonance studies of Eriksson and Gillberg strongly suggest that molecules having appreciably polar character, such as benzene and nitrobenzene, are solubilized at the surface of a micelle derived from a cationic surfactant while molecules such as cyclohexane are solubilized in the interior.[40] Most organic substrates do possess rather polar functionalities. In the second place, it is a bit difficult to visualize reactions involving ionic species occurring readily within the hydrocarbon-like interior of the micelle. There does exist evidence which would suggest that a portion of the hydrocarbon chain of the individual surfactant molecules within the micelle is exposed to solvent water[41] (perhaps a consequence of the "rough-surfaced" character of the micelles themselves[42]) and some which may suggest appreciable amounts of water within the interior[43] but, as far as we are aware, none which would indicate inclusion of ions from the bulk phase within the interior of the micelles. In the third place, the rate of certain organic reactions is unaffected when one of the reactants is incorporated into the micellar phase and the other is excluded from it. Such a reaction is that between anisylthioethane and iodine cyanide.[11] It is difficult to rationalize this observation if the anisylthioethane were incorporated within the micellar interior and hence be isolated from the iodine cyanide. In the fourth place, inclusion of methyl orthobenzoate within the interior of the sodium dodecyl sulfate micelles would make difficult the interpretation of the salt effects described above and discussed below. Finally, provided that hydrophobic interactions between the substrate and micelle are at least partially responsible for adsorption of the organic substrate into the micellar phase (which is consistent with and supported by our observations that increasing hydrophobic character of the surfactant causes increased catalysis), geometric considerations alone would suggest that the reactive functionality of such a substrate could not project very far outside of the Stern layer and, hence, into the diffuse double layer surrounding the micelle but not included within its shear surface. On the whole, these considerations would strongly suggest that the actual bond-changing processes occur at the Stern layer and less strongly suggest that the principal habitat of most adsorbed reactive organic molecules is the same (clearly the principal site of occupancy and the site of reaction need not be the same). These conclusions are opposed to that of Menger and Portnoy that *p*-nitrophenyl acetate and related esters are incorporated into the interior of micelles derived from lauric acid.[18]

Principal features of the chemistry of the Stern layer include the following:[44] (i) the hydration of the charged groups within the Stern layer is similar to that of the charged groups alone;[45,46] (ii) the surface is rough;[42] (iii) the thickness is about equal to that of the hydrated ionic heads;[46] and (iv) a very substantial fraction of the ionic groups are neutralized through the inclusion of counterions. This matter is developed further below.

As indicated in Figure 1, second-order rate constants for methyl orthobenzoate hydrolysis are independent of the concentration of sodium dodecyl sulfate below the cmc, then rise rapidly, level off, and finally decrease with increasing concentrations of this surfactant.[4,5] This behavior, which is also observed with related catalysts (Table III), can be rationalized directly on the basis of (i) the necessity of the existence of micelles for catalysis, (ii) adsorption of a progressively greater fraction of the substrate into the micellar phase until that fraction approaches unity with increasing surfactant concentration, and (iii) inhibition of the micellar reaction by the sodium counterions of the surfactant. As developed above, cations, including sodium ion, are potent inhibitors of the micellar reaction. To ensure that the observed inhibition of the reaction at high surfactant concentrations was, in fact, due to the increase in sodium ion concentration, a related rate–concentration profile was obtained under conditions in which the total concentration of this ion was maintained constant through the addition of calculated amounts of sodium chloride. No inhibition was observed in this case. The equilibrium constant for association of methyl orthobenzoate with the sodium dodecyl sulfate micelles provides a satisfactory quantitative description of the dependence of rate constants for hydrolysis of this substrate on surfactant concentration below the point of initiation of inhibition. That is, the calculated extent of incorporation of the substrate into the micellar phase and the observed extent of catalysis are parallel functions of the surfactant concentration.

Our considerations thus far suggest that sodium dodecyl sulfate dependent catalysis of methyl orthobenzoate hydrolysis occurs principally, if not exclusively, in the micellar phase and, more precisely, at the Stern layer of this phase. We now wish to examine the properties of this phase with respect to those of the aqueous phase with reference to accounting approximately for the observed catalysis. We turn first to medium effects. Mukerjee and Ray have assigned an approximate value of 36 for the dielectric constant of the surface of micelles derived from N-alkylpyridinium ions on the basis of measurements of the position of charge transfer bands between the pyridinium moiety and certain anions.[47] Making the reasonable assumption that the situation is not too different at the surface of micelles derived from sodium dodecyl sulfate, it would appear that the medium polarity at the Stern layer is substantially lower than that in the bulk phase. Although extensive data concerning the effects of medium polarity on rates of ortho ester hydrolysis are not available, it has been established that addition of organic solvents to water tends to markedly inhibit this reaction and that the degree of inhibition is increased with decreasing dielectric constant of the organic component.[48] On the basis of these results, one might expect that the medium effect alone would decrease the rate of hydrolysis of methyl orthobenzoate by two- to fivefold. At any event, it is clear

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that the medium effect cannot account for the observed catalysis and, in fact, will tend to diminish the extent of catalysis in this system due to electrostatic factors.

Catalysis for methyl orthobenzoate hydrolysis by micelles derived from sodium dodecyl sulfate, as is the case for most but not all catalyses of organic reactions in micellar systems, can be qualitatively understood on the basis of electrostatic effects. The data collected in this work and in previous examinations of this reaction[4,5,23] indicate that the differences in free energies between ground and transition states are less in the micellar than in the bulk phase. Since the hydrophobic interactions which almost certainly account for incorporation of the ortho ester into the micellar phase ought to be about the same in the ground and transition states, the observed catalysis must be the consequence of electrostatic stabilization by the anionic micelle of the developing carbonium ion in the transition state. Perhaps additional insight into the source of the rate effects can be obtained by dividing the over-all reaction process into two stages: formation of the protonated ortho ester and decomposition of this species to the carbonium ion. In this case, the division into two stages is very likely artificial since, as noted above, the protonation and decomposition reactions may well be concerted. Nevertheless, no substantial conceptual errors are introduced into the considerations by making this division since those factors which would favor preequilibrium protonation of the substrate are the same as those which would favor more rapid protonation (*i.e.*, increased substrate basicity or increased concentration of the hydrated proton). Clearly, for a true A-1 process, the over-all rate constant is just the product of the equilibrium constant for synthesis of the protonated substrate and the rate constant for its decomposition. Viewed in these terms, it would seem likely that the major portion of the rate effect on the over-all reaction is a consequence of effects on substrate protonation rather than on decomposition of the protonated species. There exist two bases for suspecting that protonation of methyl orthobenzoate ought to be substantially favored in the Stern layer of the micellar phase relative to the aqueous phase. In the first place, the anionic micellar surface acts as a sink for cations and there is no reason to suspect that these cations will not include the hydrated proton as well. Thus, one expects to find that the concentration of hydrated protons is substantially higher in the Stern layer than in the aqueous phase.[49] Efforts to measure the concentration of hydrated protons at the micellar surface from the behavior of pH indicators do suggest that the above conclusion is true although it is difficult to dissociate the effects of the micellar surface on the basicity of the dye from those on the concentration of the hydrated proton.[50-52] In the second place, the basicity of the ortho ester, or other organic or inorganic molecules, will be greater in the Stern layer than in the aqueous phase as a result of the electric field of the former (the Wein effect).[53] It is doubtful that these two effects can be separated. Kurz has attributed the catalysis of acid-dependent alkyl sulfate hydrolysis which occurs upon micellization of these species[14,26,27] to the increased basicity of these species in the micellar phase.[14]

The salt effects on the sodium dodecyl sulfate dependent hydrolysis of methyl orthobenzoate (see Figures 2-6) are strikingly large; as far as we are aware, these include the largest salt effects ever observed for a nonenzymatic reaction in aqueous solution. Two general sources for the salt effects may be considered: first, the salts may tend to diminish the electrostatic stabilization of the developing carbonium ion in the transition state and, second, the salts may tend to exclude the substrate from the micellar phase. We begin the discussion with a consideration of the effects of the alkali metal ions, the species for which the most detailed relevant information is available.

All alkali metal cations studied are inhibitors of the micelle-dependent hydrolysis of methyl orthobenzoate. Studies of the incorporation of methyl orthobenzoate into the micellar phase employing molecular sieve chromatography suggest that high concentrations of sodium ion (at least) do not influence markedly the partitioning of this substrate between the micellar and aqueous phases (Table II). Thus, the source of the inhibition by these cations must be sought in terms of diminishing the electrostatic stabilization of the developing carbonium ion in the transition state. The addition of alkali metal cations to solutions of anionic surfactants is known to have the following consequences at least, all of which may influence the kinetics of the methyl orthobenzoate hydrolysis: (i) decrease the cmc,[54-57] (ii) increase the micellar size,[56,58-62] and (iii) decrease the effective charge per monomer in the micellar surface through decreased ionization of the sulfates.[60,62,63] The cation-induced decrease in the critical micelle concentration will serve only to increase slightly the fraction of surfactant molecules in the micellar phase as opposed to existing as free monomers and thus ought to have a modest rate-enhancing effect. The effect of increasing the micellar size, as a consequence of increasing the number of surfactant molecules per micelle, on the hydrolysis kinetics is uncertain. It is known that increasing micellar size through increase in the chain length of the alkyl sulfate (which does increase the number of surfactant molecules per micelle) has a rate-enhancing effect[64] (Table III); hence it seems unlikely that an increase in micellar size *per se* will cause marked inhibition. In contrast, the decrease in charge per monomer at the micellar surface is expected to have profound consequences for the catalyzed reaction. By decreasing the degree of ionization of sodium do-

(49) It ought to be clearly noted that the pH (a measure of the *activity* of the hydrated proton) need not be exactly the same in the micellar and bulk phases when the partitioning of the hydrated proton between the two is at equilibrium.

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decyl sulfate molecules within the micellar surface and hence the electric field at the surface, the ability of this surface to act as an electrostatic stabilizer of the developing carbonium ion may be markedly decreased. Viewed in terms of the protonation reaction alone, a decrease in the electric field at the surface of the micelle due to the binding of addition cations may cause (i) decreased basicity of the substrate and (ii) decreased concentration of the hydrated proton both as a consequence of the weaker field and as a consequence of competition of the added cations for available binding sites within the Stern layer.

That the observed inhibition by alkali metal cations is a consequence of their binding to the micellar surface is attested to by the parallel between their efficiency as inhibitors, $Cs^+ > Rb^+ > K^+ > Na^+ > Li^+$, and the following: (i) ability to lower the cmc for anionic surfactants;[54-56,61,65] (ii) ability to increase the polymerization number for anionic surfactants;[56,59,61] and (iii) ability to decrease the degree of ionization of micellated dodecyl sulfates.[61]

Much the same considerations apply to inhibition of sodium dodecyl sulfate dependent methyl orthobenzoate hydrolysis by ammonium ions. Quite in general, the more hydrophobic character possessed by the ion, the better inhibitor it becomes (Figures 4–6). The molecular sieve chromatography data (Table II) do indicate that tetramethyl- and tetraethylammonium ions tend to exclude the ortho ester from the micellar phase to some extent. However, the extent of exclusion by high concentrations of these ions seems decidedly too small to account entirely for the striking rate decreases which they elicit. That the ability of ammonium ions to inhibit the hydrolytic reaction in question is a consequence of binding of these cations by the micelles, whether the inhibition is secondarily caused by substrate displacement or by lessening of the electrostatic forces responsible for the catalysis, is strongly suggested by the fact that increasing the hydrophobic nature of the ammonium ion also increases their ability to lower the cmc of dodecyl sulfates and to increase the micellar size of these species.[56,66]

The various alkaline earth cations studied are all about equally effective as inhibitors of sodium dodecyl sulfate catalyzed methyl orthobenzoate hydrolysis (Figure 3). While adequate data to establish the cause of this inhibition are not available, these ions are known to have profound influences on the values for the cmc and micellar polymerization number for anionic surfactants.[67-70]

The results reported herein are in substantial accord with the few examples of salt effects on reactions in micellar systems previously reported. Kurz has established that sodium ion is an effective inhibitor for the acidic hydrolysis of micellated sodium dodecyl sulfate.[14] In this system, sodium ion and the hydrated proton proved to be about equally effective as inhibitors. Therefore, Kurz assigned the inhibition entirely to increasing double layer shielding with increasing salt concentration rather than to specific cation effects. In light of the results obtained in this study, a more extended investigation of micellar dodecyl sulfate hydrolysis would be of interest. Nogami and Awazu have observed that potassium, sodium, and lithium ions, in that order, are effective inhibitors for the sodium dodecyl sulfate catalyzed hydrolysis of the quaternary amine ester, methantheline bromide.[71] Finally, sodium ion has been shown to be an effective inhibitor for a reaction between a hydrophobic histidine derivative and an anionic long-chain *p*-nitrophenyl ester.[17] These results together with those presented herein clearly establish that considerable care must be exercised in the design of kinetic studies for reactions in micellar systems. It is clear that a case of catalysis might be entirely overlooked by an unfortunate choice of reaction conditions. Furthermore, rate constants for organic reactions in micellar systems must be related only to exactly those experimental conditions under which they were measured. Extrapolations of the type that may usually be made with safety for reactions in purely aqueous media are quite likely to be substantially in error for similar reactions in micellar systems.

Finally, one ought to recognize the parallels between the salt effects noted in this study and those observed in protein and enzyme chemistry. The specific binding of monovalent cations by proteins has been firmly established.[72] Several examples of cation inhibition or promotion of enzymatic reactions have been collected by Webb.[73] Two recent examples will suffice for the purpose of illustration. The RNA polymerase from *E. coli* is dramatically affected by monovalent ions both in terms of stimulation of the reaction and in terms of alteration in primer specificity.[74] In these regards, cesium and potassium ions are rather more effective than sodium or ammonium ions. Similarly, propionyl-CoA carboxylases from two mammalian sources are activated by cesium, rubidium, and potassium ions while sodium and lithium ions show little effect.[75,76] It seems entirely possible that a more sophisticated understanding of the nature of salt effects on reactions in micellar systems may help to explain those observed in enzymatic reactions.

Two final points deserve brief attention. First, there is the observation (Table IV) that increasing the chain length of the alkyl sodium sulfate not only increases its catalytic efficiency for ortho ester hydrolysis at low catalyst concentrations but also results in an increased maximal catalytic efficiency independent of catalyst concentration. The first aspect of this behavior may be accounted for on the basis of increasing affinity of the substrate for the micellar phase as the hydrophobic character of the surfactant is increased. The second aspect of the behavior must be the consequence

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of subtler considerations since at high enough surfactant concentrations presumably all of the substrate will be associated with the micellar phase regardless of chain length. Thus increasing chain length must either cause a more favorable geometrical disposition of the substrate with respect to the Stern layer, or result from increased surface charge on the micelle itself,[14] or both. At any event, these observations are consistent with the arguments developed above. In agreement with our findings, Kurz has observed that the acid-catalyzed hydrolysis of micellar sodium alkyl sulfates becomes more rapid with increasing size of the alkyl chain.[14] Finally, we have observed that the maximal rate accelerations obtained for the sodium alkyl sulfate catalyzed hydrolysis of methyl orthobenzoate decrease with increasing temperature. Put another way, the enthalpy of activation for the surfactant-catalyzed reaction is less than that for the uncatalyzed reaction. Similarly, Kurz has observed that the catalysis of hydrolysis of sodium alkyl sulfates which accompanies micellation of these substrates is due to changes in the enthalpy of activation and not in the entropy of activation.[14] Preliminary considerations indicate that the situation in our case is more complicated: a large favorable enthalpy decrease (which may approach 10 kcal/mol in some cases) is substantially offset by a large decrease in the entropy of activation. The result is the observed modest rate increases. Why the activation parameters should change in this fashion for these reactions is not clear at this time.

Secondary Valence Force Catalysis. VII. Catalysis of Hydrolysis of *p*-Nitrophenyl Hexanoate by Micelle-Forming Cationic Detergents[1]

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Abstract: The hydroxide ion dependent hydrolysis of *p*-nitrophenyl hexanoate and *p*-nitrophenyl laurate is subject to marked catalysis by alkyltrimethylammonium detergent salts. In contrast, the rate of the corresponding reaction of *p*-nitrophenyl acetate is rather insensitive to the concentration of these species. Evaluation of the pertinent equilibrium constants for association of the acetate and hexanoate with micelles formed from tetradecyltrimethylammonium chloride through molecular sieve chromatography on Sephadex G-10 reveals that the distinct behavior exhibited by these esters is principally a reflection of the greater tendency of the latter to associate with the catalyst in solution. Catalysis of the basic hydrolysis of *p*-nitrophenyl hexanoate by alkyltrimethylammonium salts is accentuated as the length of the alkyl chain is increased from 8 to 18. Monovalent anions are potent inhibitors of the tetradecyltrimethylammonium chloride catalysis for the basic hydrolysis of *p*-nitrophenyl hexanoate; an increase in bromide ion concentration from zero to 0.20 *M* inhibits the detergent-dependent reaction by more than an order of magnitude. The increasing order of effectiveness of anions as inhibitors of this reaction is: $F^- < Cl^- < Br^- < NO_3^-$. These facts suggest that the inhibition is largely a consequence of displacement of hydroxide from the surface of the micelle as a consequence of binding of other anions.

Particular points of interest for the development of an understanding of the mechanism of catalysis of organic reactions occurring on the surface of micelles have been discussed in the accompanying report.[3] In this paper, we describe, in some detail, catalysis by alkyltrimethylammonium ions for the hydrolysis of *p*-nitrophenyl esters. This work is an extension and elaboration of our previous efforts with these systems.[4] A preliminary account of some of this work has been published.[5]

Experimental Section

Materials. *p*-Nitrophenyl acetate was synthesized from *p*-nitrophenol and acetic anhydride according to the general method of Bender and Nakamura.[6] *p*-Nitrophenyl laurate[7] was prepared by a slight modification of this procedure: 0.125 mol of *p*-nitrophenol, 0.10 mol of lauroyl chloride, and 0.10 mol of pyridine were dissolved in 100 ml of dry toluene and refluxed for 1 hr. The solution was neutralized with saturated $NaHCO_3$ and washed with water, 5% NaOH, 0.1 *N* HCl, and finally with water. The toluene solution was dried over anhydrous $MgSO_4$ and evaporated to dryness. The ester obtained was a light yellow waxy solid, mp 40–41° (lit.[7] 46°), carbonyl stretching frequency (liquid film) at 1755 cm^{-1}, and was not purified further. *p*-Nitrophenyl hexanoate was prepared through the dropwise addition of 12.8 g of hexanoic acid in 100 ml of benzene to a refluxing solution prepared by mixing 13.9 g of *p*-nitrophenol in 150 ml of tetrahydrofuran and 25 g of dicyclohexyl-

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