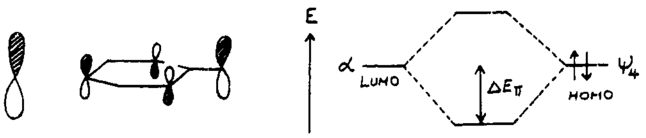

Figure 2. NBMO interaction between vacant carbon p orbital and benzyl anion.

uents measured include p-OCH$_3$, whose σ^+ value (−0.78) differs widely from its σ value (−0.27).

Figure 1 shows the resultant ESP plot of the log $k_{\mathrm{OCH_3}}/k_{\mathrm{H}}$ values vs. ρ.[11] The correlation of the experimental values with the line defined by the coordinates (0,0) and the slope −0.78 is excellent. The graph also shows data for systems **11–19** obtained by extrapolation from benzoate hydrolysis, which also closely fit the correlation. This result clearly indicates that effect 3 is not a significant contributor to deviations from the ESP for para-substituted resonance donors. Any such deviations must be sought in the operation of effects 1 or 2, experimental errors or mechanistic complexities, of which effect 2 forms an example. **6**, **7**, and **16** have been found previously to have a degree of steric acceleration associated with them;[13] however, this steric effect does not prevent the aryl group from exerting its maximum effect on stabilizing the carbonium ion. Thus, deviations from the line in Figure 1 are indicative *specifically* of resonance loss due to twisting (effect 1). For example, various data[12,13,15,16,17] for solvolysis of aryldi-*tert*-butylcarbinyl p-nitrobenzoate reveal severe restriction of resonance due to aryl twisting (effect 1); the relevant point[15] on Figure 1 is well off the line.

Why should the methoxy substituent, and apparently other resonance donors, yield an invariant σ^+ value rather than the spectrum of values predicted? The qualitative answer may be that the energy levels defining the through conjugation responsible for adherence to σ^+ are either present or absent; the quantum theory does not permit infinite gradation. The interaction of such substituents with the carbonium ion type transition state can be pictured as a LUMO(carbonium ion)–HOMO(substituent) interaction. This leads to an interaction energy $\Delta E\pi$ of the form

$$\Delta E\pi = (C_{\mathrm{H}}C_{\mathrm{L}}\beta)^2/(E_{\mathrm{L}} - E_{\mathrm{H}}) \qquad (3)$$

where $\Delta E\pi$ is the stabilization energy resulting from interaction of the substituent with the positive center, C_{H} and C_{L} are the coefficients of the HOMO and LUMO, respectively, at the point of union, and E_{H} and E_{L} are their energies. This treatment has, however, been used to argue both for variable[18] *and* constant[19] σ^+ values. In its simplest (but possibly still relevant) form the interaction may be likened to the union of a vacant carbon p orbital and the HOMO of the benzyl anion, both NBMOs (Figure 2). In this case

$$\Delta E\pi = 2\alpha\beta \qquad (4)$$

where α and β are the NBMO coefficient and resonance integral, respectively.[20] α will thus measure the influence of the substituent; variations in degree of interaction between HOMO and LUMO, i.e., extent of charge development in the transition state, will be given by the β term, which has been shown to reflect variations in ρ.[20–22] It is likely that this partitioning effect may be retained in more sophisticated theoretical treatments.

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Registry No.—**1**, 61971-63-9; **2**, 64822-39-5; **3**, 41327-33-7; **4**, 23852-76-8; **5**, 64822-35-1; **6**, 54265-32-6; **7**, 37776-01-5; **8**, 20547-61-9; **9**, 55408-73-6; **10**, 60921-49-5; **11**, 60174-87-0; **12**, 37776-03-7; **13**, 20550-37-2; **14**, 62861-28-3; **15**, 57955-44-9; **16**, 64822-42-0; **17**, 64822-46-4; **18**, 57955-42-7; **19**, 54265-31-5; **20**, 41327-36-0; **21**, 61971-59-3; **22**, 65275-59-4.

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Hydrophobic Forces in Selective Hydrolyses of Nonionic *p*-Nitrophenyl Ester and Anionic 3-Nitro-4-acyloxybenzoic Acid Substrates by Hydroxamic Acids

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The elucidation of binding-step mechanism in enzyme reactions is one of the goals in biochemical researches.[1] Recently, hydrophobic (apolar) forces have received considerable attention in the biochemical studies on the hydrolysis of ester substrates by such synthetic enzyme models as poly[4-vinylimidazole],[2] a copolymer of N-methylacrylohydroxamic acid

Table I. $k_{a,obsd}$ ($M^{-1}s^{-1}$) Values for the Hydrolyses of S_n and S_n^- by C_m

S_n or S_n^-	Registry no.	C_4[b]	C_4 + CTAB	r[a]	C_6[c]	C_6 + CTAB	r	C_8[d]	C_8 + CTAB	r	C_{10}[e]	C_{10} + CTAB	r
S_2	830-03-5	26.1	44.4	1.7	27.9	121.4	4.4	28.5	535.2	18.6	40.1	1032.6	25.8
S_4	2635-84-9	12.0	25.6	2.1	12.1	110.9	9.2	13.2	496.4	37.6	20.2	1296.3	64.2
S_6	956-75-2	10.8	33.7	3.1	12.4	150.6	12.2	13.2	628.8	47.6	20.0	1554.4	77.7
S_{10}	1956-09-8	0.56	33.0	58.9	0.63	152.8	242.5	1.4	759.3	542.4	5.8	2292.3	395.2
S_{12}	1956-11-2	0.15	30.6	204.0	0.35	141.3	403.7	0.77	469.5	609.7	4.7	1382.7	294.2
S_{16}	1492-30-4	0.074	4.9	66.2	0.14	19.7	140.7	0.54	168.4	311.9	4.4	450.8	102.5
S_2^-	1210-97-5	26.8	31.7	1.18	25.3	96.7	3.82	27.2	325.0	11.9	31.3	413.1	13.2
S_4^-	56003-42-0	8.3	8.7	1.05	8.6	45.9	5.34	8.8	184.9	21.0	12.2	480.0	39.3
S_6^-	65293-27-8	8.3	7.5	0.90	8.6	33.8	3.93	9.9	190.3	19.2	13.8	497.4	36.0
S_{10}^-	65293-28-9	7.3	6.2	0.85	8.7	30.9	3.55	8.7	143.6	16.5	20.3	298.4	14.7
S_{12}^-	23967-09-1	7.0	5.3	0.76	7.7	28.5	3.70	8.5	145.7	17.1	14.9	346.1	23.2
S_{16}^-	65354-57-6	0.2	5.0	25.0	0.4	25.7	64.3	1.6	156.8	98.0	9.7	312.9	32.3

[a] r = ratio of $k_{a,obsd}$ value in the presence of CTAB to that in its absence. [b] Registry no. 4312-91-8. [c] Registry no. 4312-93-0. [d] Registry no. 7377-03-9. [e] Registry no. 2259-85-0.

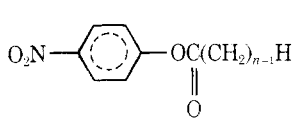
and 4-vinylimidazole,[3] polyelectrolytes,[4,5] N-alkylamines,[6] and surfactants[7-9] including L-histidine[10,11] and imidazole[12] derivatives.

However, the magnitude of the hydrophobic interaction between substrates and catalysts is directly dependent on their apolar alkyl chain lengths and on the micellar effects of surfactants. In this regard, the previous studies on the catalytic hydrolysis of ester substrates[5,6,13] have demonstrated the importance of the hydrophobic interaction between long alkyl chains in substrates and catalysts (and/or surfactants) for the acceleration of the reaction, but there are few documents dealing systematically with the contributions of apolar chains in substrates, catalysts, and/or surfactants to the hydrophobic forces.

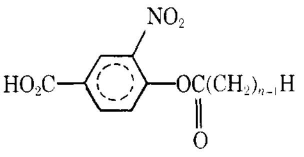
$H(CH_2)_{m-1}CONHOH$

C_m

(m = 4, 6, 8, and 10)


$O_2N{-}C_6H_4{-}OC(=O)(CH_2)_{n-1}H$

S_n


$HO_2C{-}C_6H_3(NO_2){-}OC(=O)(CH_2)_{n-1}H$

S_n^-

(n = 2, 4, 6, 10, 12, and 16)

The present authors report, here, the selective hydrolysis of ester substrates by nucleophilic agents through the hydrophobic forces in the hydrolysis of nonionic substrates of p-nitrophenyl esters (S_n) or anionic substrates of 3-nitro-4-acyloxybenzoic acids (S_n^-) by the nucleophilic agents of hydroxamic acids (C_m) in the absence or presence of cetyltrimethylammonium bromide (CTAB). The present hydrolysis of 5×10^{-5} M S_n and S_n^- substrates by 5×10^{-4} M C_m agents at 31.0 °C, pH 9.06 in 0.083 M Tris–KCl buffer in 10% (v/v) CH_3CN-H_2O, obeys a pseudo-first-order rate law, and the second-order rate constant $k_{a,obsd}$, which is independent of the initial concentrations of the substrates and the nucleophilic agents, was evaluated as:

$$k_{a,obsd} = (k_{total} - k_{spont})/[C_m]_0$$

where k_{total} or k_{spont} denotes respectively the first-order rate constant for the hydrolysis of S_n and S_n^- with or without C_m, and the subscript zero means the initial state of the reaction. Through the present reaction, not only the nucleophilic hydrolysis of the substrates by the C_m agent (hydroxamates at pH 9.06[14]) but also spontaneous hydrolysis of the substrates by the buffer components were recognized. However, the k_{spont} values were always less than 10% of the k_{total} ones in the absence of CTAB or less than 1% of the k_{total} ones in the presence of CTAB. Then, the effect of the apolar chain length in the S_n (or S_n^-) substrates and the nucleophilic C_m agents on the hydrolysis rate will be discussed on the basis of the $k_{a,obsd}$ values. The $k_{a,obsd}$ values obtained in a series of experiments are shown in Table I.

In the absence of CTAB, any substantial contribution of the hydrophobic forces to the hydrolysis acceleration was not recognized in the reactions between the nonionic S_n (n = 2–16) or anionic S_n^- (n = 2–16) substrates and the C_m (m = 4 and 6) agents. The C_m (m = 4 and 6) species possessing no critical micelle concentrations (cmc)[15] decrease the $k_{a,obsd}$ value monotonically with increasing the acyl chain length in the S_n and S_n^- substrates, probably due to the steric hindrance of the long acyl chains in the substrates against the interaction between the substrates and the nucleophilic C_m (m = 4 and 6) species.[5,7,12] However, the C_m (m = 8 and 10) species showing respective cmc around 1×10^{-4} and 5×10^{-5} M appreciably accelerate the hydrolyses of all the S_n and S_n^- substrates in comparison with the C_m (m = 4 and 6) ones, and, interestingly, they exhibit a selective enhancement of the hydrolysis rate of the anionic S_6^- and S_{10}^- substrates, respectively. This selective hydrolysis acceleration might be expected through the selective incorporation of the anionic S_n^- (n = 6 and 10) by the micellar C_m (m = 8 and 10) having the alkyl chain length similar to that in the said substrates through the appropriate hydrophobic interaction between them. In the case of the hydrolysis of the nonionic S_n substrates, such a selective acceleration of the reaction was not recognized. The micellar C_m (m = 8 and 10), as well as the C_m (m = 4 and 6) species, remarkably decreased the hydrolysis rates of the S_n (n = 10–16) substrates possessing long acyl chains, as compared with those of the S_n (n = 2–6) by the micellar C_m (m = 8 and 10). The sharp drop of the hydrolysis rates by the change in the acyl chain length (from n = 6 to 10) in the nonionic S_n substrates, which was also observed in their spontaneous reactions, might be due to a direct shielding of the susceptible carbonyl group in the substrates by the coiling-up of the long acyl chains.[13] Presumably, the coiling-up of the acyl chain is retarded in the anionic S_n^- substrates by the nitro and carbonyl groups on the benzene ring in S_n^-, and, consequently, the relatively high reaction rates were observed in the hydrolysis of the anionic S_n^- (n = 10–16) rather than in the hydrolysis of the nonionic S_n (n = 10–16) ones. It is noteworthy, here, that the hydrolysis of the anionic S_{16}^- substrate having cmc around 1×10^{-5} M was more markedly accelerated (as the C_m varied from m = 4 to 10) than that of the other anionic S_n^- (n = 2–12) ones which have no cmc.

Probably this is not only due to the increase in the hydrophobic interaction between S_{16}^- and C_m with increasing alkyl chain length in the latter but also due to the comicellar effect of the S_{16}^- and C_m (m = 8 or 10) micelles on the hydrolysis acceleration.

In the presence of 5×10^{-3} M CTAB surfactant (cmc = ca. 1×10^{-3} M), the micellar effect of the surfactant was substantially recognized in the present hydrolysis reactions. Such a micellar effect of surfactants on the rate enhancement of the ester hydrolyses has also been observed in the previous works.[16,17] However, the magnitude of the micellar influence of CTAB on the hydrolysis acceleration, which can be measured by the ratio of the $k_{a,obsd}$ value in the presence of CTAB to that in its absence, is fairly different between the hydrolyses of the nonionic and anionic substrates. The C_m (m = 4–10) and CTAB system increases the hydrolysis rates of both kinds of substrates, as the C_m species varies from m = 4 to 10. But, the acceleration of the hydrolysis of the nonionic S_n (n = 10–16) substrates by the C_m (m = 4–10) and CTAB system (especially by the micellar C_m (m = 8–10) and CTAB one) is remarkable in comparison with that of the hydrolysis of S_n^- (n = 10–16) by the same system, even though the hydrolyses of S_n (n = 10–16) by the C_m (m = 4–10) species are very slow in the absence of the CTAB surfactant. This is probably owing to the retardation of the coiling-up of the long acyl chain in the S_n (n = 10–16) substrates by the effective hydrophobic interaction between the S_n (n = 10–16) substrates and the CTAB micelles or between the S_n (n = 10–16) substrates and the C_m (m = 8 or 10)–CTAB comicelles; The comicelle formation of C_m (m = 8 or 10) and CTAB is attained not only through the hydrophobic interaction between them but also through the electrostatic charge attraction between the anionic C_m and the cationic CTAB.

In regard to the selective hydrolysis of the substrates in the presence of the CTAB surfactant, the comicellar system of C_8–CTAB selectively incorporated the nonionic S_{10} and the anionic S_6^-, and that of C_{10}–CTAB selected S_{10} and S_6^- (and/or S_{12}^-). The difference in the selective incorporation of the nonionic and anionic substrates by the C_m (m = 8 or 10)–CTAB comicelles is probably due to the difference in the frameworks of the above substrates. Namely, the anionic substrate (S_6^-) involves more bulky substituents in its benzene ring than the nonionic one (S_{10}). At any rate, the comicellar influence of the C_m (m = 8 or 10)–CTAB system on the S_n and S_n^- substrates was characterized by the selective incorporation of both kinds of substrates (S_{10}, S_6^- and/or S_{12}^-) through the hydrophobic approximation effect[18] of the micelles.

Experimental Section

Materials. The nucleophilic C_m (m = 4–10) agents were prepared by the reaction of $H(CH_2)_{m-1}CO_2C_2H_5$ (m = 4–10) and hydroxylamine, and satisfactory elementary analyses were obtained as below. C_4: Anal. Calcd for $C_4H_9NO_2$: C, 46.59; H, 8.80; N, 12.58. Found: C, 46.72; H, 8.34; N, 12.69. C_6: mp 45–47 °C. Anal. Calcd for $C_6H_{13}NO_2$: C, 54.94; H, 9.99; N, 10.68. Found: C, 55.53; H, 9.78; N, 10.40. C_8: mp 75.6–77.2 °C. Anal. Calcd for $C_8H_{17}NO_2$: C, 60.34; H, 10.76; N, 8.80. Found: C, 60.55; H, 10.52; N, 8.58. C_{10}: mp 85.9–86.7 °C. Anal. Calcd for $C_{10}H_{21}NO_2$: C, 64.13; H, 11.30; N, 7.48. Found: C, 64.96; H, 11.10; N, 7.41.

3-Nitro-4-acyloxybenzoic acids (S_2^-–S_{16}^-) were prepared according to Overberger et al.[2] Satisfactory elementary analyses were also given for S_n^- (n = 2–16), and those for new compounds are shown below. S_4^-: mp 113–114 °C. Anal. Calcd for $C_{11}H_{11}NO_6$: C, 52.17; H, 4.35; N, 5.53. Found: C, 52.47; H, 4.25; N, 5.64. S_6^-: mp 75.0–76.0 °C. Anal. Calcd for $C_{13}H_{15}NO_6$: C, 55.51; H, 5.38; N, 4.98. Found: C, 54.86; H, 5.29; N, 4.94. S_{10}^-: mp 70.1–72.0 °C. Anal. Calcd for $C_{17}H_{23}NO_6$: C, 60.52; H, 6.87; N, 4.15. Found: C, 60.29; H, 6.79; N, 4.10. S_{16}^-: mp 87.1–89.0 °C. Anal. Calcd for $C_{23}H_{35}NO_6$: C, 65.53; H, 8.37; N, 3.32. Found: C, 65.24; H, 8.21; N, 3.66.

Commercially available p-nitrophenyl esters (S_2–S_{16}) were used as nonionic substrates without further purification, because elementary analyses of S_n (n = 2–16) gave satisfactory results.

Hydrolysis. The hydrolyses of S_n and S_n^- (5×10^{-5} M) by C_m (5×10^{-4} M) were carried out at 31.0 °C, pH 9.06 in 0.083 M tris(hydroxymethyl)aminomethane buffer involving 0.083 M KCl (μ = 0.083) in H_2O including 10 vol % CH_3CN, and the reactions were followed spectrophotometically by taking notice of phenolate anion formation.

Registry No.—$H(CH_2)_3CO_2C_2H_5$, 105-54-4; $H(CH_2)_5CO_2C_2H_5$, 123-66-0; $H(CH_2)_7CO_2C_2H_5$, 106-32-1; $H(CH_2)_9CO_2C_2H_5$, 110-38-3; hydroxylamine, 7803-49-8.

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A Method for β-C-Acylation and β-Alkylation of α,β-Unsaturated Ketones

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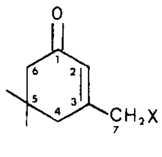
In connection with our interest in the chemistry of 3-substituted 2-cyclohexen-1-ones,[1-3] we required facile synthesis of the β-C-acyl and β-alkyl cyclenones 1.



1a X = COC_2H_5
1b X = COC_6H_5
1c X = $CO(CH_2)_2CH(CH_3)_2$
1d X = CN
1e X = $CO_2C_2H_5$

Until now, there has been no easy method described to obtain this type of cyclenones with consistent yields.[4-6] So, taking into account the hydrolyzability of an enol ether function we synthesized **1d** and **1e.** Using this advantage and the possibility of transforming a cyano group into a carbonyl