out several further tests here using a 14b-Å cutoff. The differences in lattice energy between the different crystal forms are essentially independent of cutoff at these cutoff distances.
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(24) Prompted by the results of this study, we have carried out several preliminary attempts to obtain polymorphs of adipamide (presumably containing the usual cyclic dimer as in *o*-chlorobenzamide) by varying the solvent. So far these attempts have been unsuccessful, but we are continuing to use varying conditions of solvent and temperature.

Nucleophilic Ion Pairs. 5. Facile Cleavage of Amide Substrates by a Hydroxamate Anion in Aprotic Solvents. Efficient Inhibition by Minute Amounts of Water[1]

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Abstract: A quaternary ammonium salt of the hydroxamate anion was found to cleave several *N*-methylanilide substrates very readily at room temperature in dry, aprotic media. In contrast, the reaction was very slow in protic media and, for example, a rate difference of $>10^5$ was observed between dimethylformamide and formamide media for the reaction of *N*-methyl-*p*-nitroacetanilide and tetraethylammonium *N*-methylmyristohydroxamate. The reaction was efficiently suppressed by minute amounts of water and a kinetic isitope effect (k_{H_2O}/k_{D_2O}) of 1.3–1.5 was observed for some substrates. These results indicate that both the nucleophilic attack and the proton transfer to the tetrahedral intermediate were facilitated in dry, aprotic media. The reaction of the hydroxamate and *p*-nitrophenyl acetate was facilitated in dry, aprotic media and in aqueous cationic micelles. Thus, the complete suppression of the amide cleavage in the cationic micelle was attributed to the inefficient proton transfer to the tetrahedral intermediate.

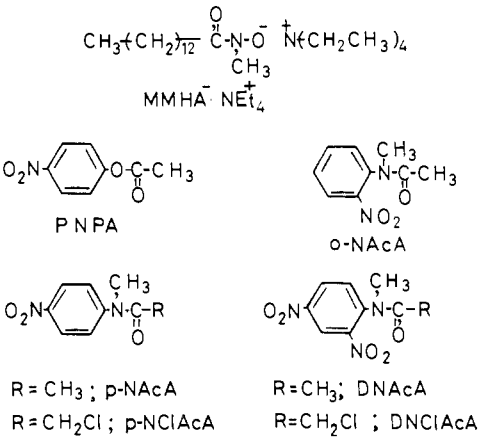
In model studies of the hydrolytic enzyme, most of the research has been carried out with activated substrates such as phenyl esters. Similar studies with amides and aliphatic esters have been relatively fruitless, because of the much smaller reactivities of these substrates. For instance, a highly activated amide like trifluoroacetanilide is hydrolyzed by imidazole catalysts at very slow rates.[2,3]

Recently, a variety of anionic nucleophiles including hydroxamates was found to be remarkably activated in the presence of cationic micelles and cationic polymer micelles. We believe that the large rate enhancement is mainly derived from formation of the hydrophobic ion pair between the anionic nucleophile and the quaternary ammonium group in the hydrophobic region of the micelles.[4] If this concept is valid, such ion pairs should also be highly reactive in organic media. Thus, we prepared tetraethylammonium *N*-methylmyristohydroxamate ($MMHA^-NEt_4^+$) and studied its reaction with several amide and ester substrates. This study shows for the first time that amide substrates are cleaved quite readily at ambient conditions, and that a small water concentration can considerably affect the reactivity of the hydroxamate anion in contradiction to the commonly accepted notion that the last trace of water hardly changes the anion reactivity in dipolar aprotic solvents.[5-7]

The enhanced reactivity of these ion pairs in the proton abstraction reaction has been published.[8]

Experimental Section

Materials. The preparation of $MMHA^-NEt_4^+$ was reported previously.[8] *o*-Nitro-*N*-methylacetanilide (*o*-NAcA) was prepared by methylation of *o*-nitroacetanilide (mp 88–90 °C, lit.[10] 93 °C). *o*-Nitroacetanilide (3.1 g, 0.017 mol) was dissolved in 30 mL of anhydrous tetrahydrofuran (THF) and 1 g (0.04 mol) of NaH as a suspension in 30 mL of THF was added dropwise with stirring over 30 min. After hydrogen evolution ceased, 2 mL (0.032 mol) of CH_3I was added and the reaction mixture was stirred for 3 h at room temperature. Then it was neutralized with acetic acid, solvent was evaporated, and the residue was recrystallized from benzene and cyclohexane to give slightly yellow needles, mp 68–70 °C (lit.[10] 71.2–71.4 °C).



p-Nitro-*N*-methylacetanilide (*p*-NAcA) was similarly prepared by methylation of *p*-nitroacetanilide and recrystallized from benzene and hexane, to give slightly yellow needles, mp 150–152 °C (lit.[11] 153–154 °C). *p*-Nitro-*N*-methylchloroacetanilide (*p*-NClAcA) was obtained from *p*-nitro-*N*-methylaniline (mp 150–153 °C, lit.[12] 150–157 °C) by reaction with 0.5 equiv of chloroacetyl chloride in refluxing benzene. The aniline hydrochloride was filtered and the solution was evaporated to dryness. Recrystallization of the residue from benzene and ligroin gave slightly yellow plates, mp 109–111 °C (lit.[13] 109–110 °C).

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2,4-Dinitro-*N*-methylacetanilide (DNAcA) was obtained by nitration of *N*-methylacetanilide in refluxing dilute nitric acid (d = 1.03), followed by acetylation with acetic anhydride and one drop of H_2SO_4; recrystallization from ethanol gave yellow needles, mp 71.5–73.5 °C (lit.[14] 78 °C).

2,4-Dinitro-*N*-methylchloroacetanilide (DNClAcA) was prepared from 2,4-dinitro-*N*-methylaniline (mp 175–178 °C, lit.[15] 175 °C) and chloroacetic anhydride according to the procedure of de Monchy[14] yielding a yellow powder after recrystallization from ethanol, mp 71–73 °C. Anal. ($C_9H_8N_3O_2Cl$) C, H, N.

NMR and IR spectra of the amide substrates were consistent with the respective structures.

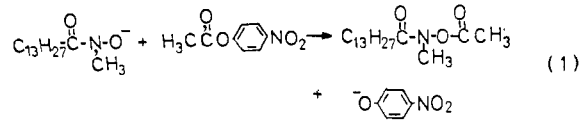
Solvent Purification and the Water Determination. Acetonitrile was distilled from P_2O_5 and stored on molecular sieve 5A. Dimethylformamide (DMF) was distilled from NaH powder and stored on molecular sieve 5A. Ethanol was distilled from Mg metal. Other solvents were purified by careful distillation. The water content of the solvents was determined by a Coulometric Karl-Fischer apparatus (Hiranuma Aquacounter AQ-1). Its sensitivity is better than 10 μg of water for 1-mL solutions; i.e., ca. 0.5 mM water. Two to three determinations were averaged and the relative error was smaller than 5% for benzene and smaller than 10% for DMF and acetonitrile. The water concentration of the reaction mixture was determined after the reaction was over.

Kinetics. All kinetic measurements were carried out at 30 ± 0.1 °C in modified Thunberg cuvettes or in cuvettes fitted with serum caps. The stock solution of $MMHA^-NEt_4^+$ was prepared on the day of use. A typical example of the reaction procedure is as follows. In a drybox, 0.1 mL of the $MMHA^-NEt_4^+$ solution was placed in the side arm of a Thunberg cuvette and a substrate solution was placed in the cell compartment. After temperature equilibration (5–10 min) in the thermostated cell housing of a Hitachi 124 UV-visible spectrophotometer, the reaction was initiated by mixing the contents of the cuvette. When capped cuvettes were used, they were dried by evacuation and N_2 purging and the reagents were charged by using syringes. The progress of the reaction was monitored at the following wavelengths: 401 (PNPA), 390 (*o*-NAcA, *p*-NAcA, and *p*-NClAcA) and 400 nm (DNAcA and DNClAcA). The last two wavelengths are those where the largest absorbance changes are observed between acetanilides and anilines. In all cases, one of the reactants was present in large excess over the other, so that pseudo-first-order kinetic behavior was observed. The pseudo-first-order rate constant for acyl transfer ($k_{a,obsd}$) was calculated by the least-squares method using the data of up to 4 half-lives (correlation coefficients better than 0.998).

The isotope effect was studied in benzene, because the rate was most sensitive to the water concentration in this medium. D_2O-containing benzene was prepared by mixing highly dehydrated benzene (ca. 0.3 mM H_2O) and D_2O-saturated benzene (ca. 25 mM). Since the rate measurements were carried out at $[D_2O]$ = 3.7–25 mM, the concentration of D_2O should amount to 92–99% of the total water concentration.

Results of Ester Cleavage

In the reaction of $MMHA^-NEt_4^+$ and PNPA, the amount of the *p*-nitrophenolate anion released was always equal to that of $MMHA^-NEt_4^+$ within ±3% (in the presence of excess $MMHA^-NEt_4^+$). Furthermore, when solvent acetonitrile was evaporated from the reaction mixture, the residue possessed a new IR absorption at 1790 cm^{-1}, which is attributed to the ester carbonyl of the acetyl hydroxamate. Therefore, simple



(1)

acetyl transfer occurs from PNPA to the hydroxamate anion.

The pseudo-first-order rate constant ($k_{a,obsd}$) determined under the condition of $[MMHA^-NEt_4^+] \ll [PNPA]$ was proportional to the PNPA concentration (1.0–8.8 mM). Therefore, the reaction rate in acetonitrile is first order both in $MMHA^-NEt_4^+$ and in PNPA.

$$v_{obsd} = k_a[MMHA^-NEt_4^+][PNPA] \quad (2)$$

Table I. Solvent Effect on the Reaction of $MMHA^-NEt_4^+$ and PNPA

solvent	$[H_2O]$, mM	k_a, $M^{-1}\,s^{-1}$
dimethylformamide	2.2	1130
acetonitrile	3.3	845
	96	309
	190	27.4
benzene	6.1	350
ethanol	27	0.63
formamide		$<10^{-4}$
water[a]		32.6
aqueous cationic micelle[b]		2060
aqueous cationic polysoap[c]		(1–3) × 10^4

[a] k_a for *N*-methylisobutyrohydroxamic acid. Cited from ref 4. [b] 22 °C, pH 9.99, [hexadecyltrimethylammonium bromide] = 1.0×10^{-3} M. Cited from I. Tabushi et al., *Tetrahedron Lett.*, 643 (1974). [c] Cited from T. Kunitake, S. Shinkai, and S. Hirotsu, *Biopolymers*, **15**, 1143–1153 (1976).

Solvent Effect. The k_a value determined in various media are summarized in Table I. The rate constant is surprisingly solvent dependent. Several features deserve particular emphasis. In the first place, aprotic solvents (DMF, acetonitrile, and benzene) provide very favorable reaction environments. If k_a in water can be approximated by that of the *N*-methylisobutyrohydroxamate anion (MMHA is not soluble in water), the k_a values in aprotic solvents are larger than that in water by 10–30 times. The rate constants in the aprotic solvents are smaller than that of MMHA in a cationic micelle (2000 $M^{-1}\,s^{-1}$ at 22 °C).[4] Secondly, the acyl transfer reaction is very slow in protic organic solvents like ethanol and formamide. The rate difference between DMF and formamide exceeds 10^7.

Influence of Water Concentration. The k_a value is extremely dependent on the water concentration. As shown in Table I, the increase in the water concentration from 3.3 to 190 mM in acetonitrile resulted in a rate decrease by a factor of 31 and similar results were obtained in DMF and in benzene. Thus, in this system, the rate constant would be meaningless without accurate determination of the water concentration. Since the reaction rate variation is particularly pronounced at low water concentrations, it is difficult to evaluate the *true* nucelophilicity of $MMHA^-NEt_4^+$ in *pure* solvents.

Influence of Other Additives. The reaction in benzene was carried out in the presence of 5.8 mM D_2O (the H_2O content was less than 1 mM), and in the presence of 5.8 mM H_2O, but a rate difference was not detected: $k_a^{H_2O}/k_a^{D_2O} = 1.03 \pm 0.07$. Addition of methanol suppressed the reaction, although its effect was not as large as that of water. Addition of NaI quenched the reaction very efficiently. The k_a value in acetonitrile in the presence of 333 mM NaI was 2.46 $M^{-1}\,s^{-1}$. This value is smaller than that in water. These results are summarized in Table II.

Results of Amide Cleavage

Course of Reaction. The hydroxamate ion pair can readily cleave some amide substrates in dry, aprotic solvents. The reaction with excess $MMHA^-NEt_4^+$ was monitored by repeated UV scans. For example, in the reaction of $MMHA^-NEt_4^+$ and *N*-methyl-2,4-dinitroacetanilide (DNAcA), an absorption (shoulder) at 300 nm due to the substrate decreased with time and a new absorption maximum appeared at 356 nm (in DMF) or at 348 nm (in acetonitrile). The latter absorption is attributed to *N*-methyl-2,4-dinitroaniline, the expected cleavage product. Isosbestic points were found at 265 and 317 nm (in DMF). No spectral change was observed in the absence of the hydroxamate anion. The quantitative conversion of DNAcA to *N*-methyl-2,4-dinitroaniline was confirmed by thin layer

Table II. Effect of NaI, D_2O, and Methanol on the Reaction of $MMHA^-NEt_4^+$ and PNPA

solvent	$[H_2O]$, mM	[NaI], mM	$[CH_3OH]$, M	k_a, $M^{-1}\,s^{-1}$
acetonitrile	3.3			845
	3.3	11.1		15.2
	3.4	55.5		9.14
	6.0	111		4.00
	5.8	333		2.46
benzene	5.8			350
	5.8[a]			341
			0.83	43.3
	29 ± 3		3.33	17.0
			5.00	16.8
			8.33	13.9

[a] D_2O.

chromatography (silica gel and 2-propanol). Thus, clean acyl transfer occurs from the amide substrate to the hydroxamate anion without accumulation of absorbing intermediates and intervention of side reactions.[16]

An IR spectrum of the solid product recovered by evaporation of solvent acetonitrile possessed a relativly weak ester absorption at 1790 cm^{-1} and a strong OH stretching absorption at 3340 cm^{-1}. Therefore, the acetyl hydroxamate formed appears to be mostly decomposed by tetraethylammonium hydroxide to the hydroxamic acid and the acetate anion (Scheme I).

The second stage does not occur in the reaction of $MMHA^-NEt_4^+$ and PNPA, because the *p*-nitrophenolate anion formed by acyl transfer does not react with the acetyl hydroxamate.

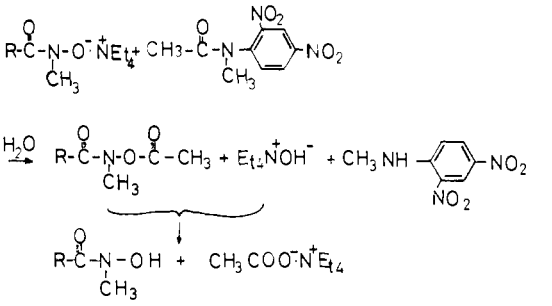
Solvent Effect. The reaction was carried out at 30 °C under the pseudo-first-order condition: $[MMHA^-NEt_4^+] \gg$ [amide substrate]. The pseudo-first-order rate constant, k_{obsd}, was determined at a constant water concentration and plotted against the hydroxamate concentration (1-10 mM). Excellent linear relations (correlation coefficient >0.99) were obtained except for the reaction of $MMHA^-NEt_4^+$ and DNAcA in benzene. The correlation for this reaction was less satisfactory ($r = 0.96$), probably because the rate was very sensitive to the water concentration.

Thus, the reaction rate is expressed by

$$v_{obsd} = k_a[MMHA^-NEt_4^+][\text{amide substrate}] \quad (3)$$

The kinetic constants obtained in various solvents for $MMHA^-NEt_4^+$ are summarized in Table III. Enormous rate enhancements are achieved in *dry*, aprotic solvents. DNAcA is cleaved by $MMHA^-NEt_4^+$ (2.29 mM) in benzene containing 4.5 mM H_2O with a second-order rate constant of 136 $M^{-1}\,s^{-1}$. This value corresponds to a half-life of 2.2 s. In contrast, the same reaction virtually did not occur in protic media (ethanol, formamide, water). *o*-NAcA was not cleaved by the hydroxamate ion pairs even in aprotic media, whereas the para isomer (*p*-NAcA) reacted readily. Replacement of the acetyl group with the chloroacetyl group greatly accelerated the reaction.

Scheme I



Influence of Water Concentration. The reaction rate of $MMHA^-NEt_4^+$ with the amide substrate was again very sensitive to the water concentration of the medium. A particularly large effect was observed in benzene. In the reaction of $MMHA^-NEt_4^+$ and DNAcA in benzene, the increase in the water concentration from 0.2 to 18 mM changed the rate constant from 3000 to 25.7 $M^{-1}\,s^{-1}$. When the nucleophile and water have comparable concentrations, the water exerts a very significant influence. Figure 1 shows the dependence of k_a on the water (H_2O and D_2O) concentration in benzene. Similar but less sensitive tendencies were found in DMF and in acetonitrile. The rate depression by minute amounts of water was commonly observed for the other amide substrates, *p*-NAcA and *p*-NClAcA, but the cleavage of *p*-NClAcA was less sensitive to the water concentration (Figure 2).

As illustrated in Figure 1, the kinetic isotope effect was clearly detected for the reaction of $MMHA^-NEt_4^+$ and DNAcA. A similar effect was found for *p*-NClAcA but not for *p*-NAcA. The isotope effect is summarized in Table IV.

Influence of Other Additives. The addition of 11 mM NaI caused a 100-fold rate reduction in the reaction of $MMHA^-NEt_4^+$ and DNAcA in acetonitrile (water concentration, 5 mM). On the other hand, addition of $Et_4N^+I^-$ of up to 11 mM produced only 20% rate reduction under the same condition. It is clear that Na^+ ion is responsible for the rate reduction.

Influence of Water Concentration on Absorbance of $MMHA^-NEt_4^+$. The absorbance of the hydroxamate anion at 250-260 nm decreased with increasing water concentration.

Table III. Solvent Effect on the Reaction of $MMHA^-NEt_4^+$ and Amide Substrates

solvent	k_a, $M^{-1}\,s^{-1}$ [b] *o*-NAcA	*p*-NAcA	*p*-NClAcA	DNAcA	DNClAcA
dimethylformamide	$<1 \times 10^{-5}$ (1-10 mM)	2.72 (4.6 mM)	225 (1.6 mM)	4.08 (3.0 mM)	
acetonitrile		0.104 (11 mM)	5.6 (2.0 mM)	4.50 (5.3 mM)	
benzene	$<1 \times 10^{-5}$ (1-10 mM)	0.352 (4.6 mM)	31.7 (5.4 mM)	136 (4.5 mM)	76500 (5 mM)
ethanol		5×10^{-5} (5-10 mM)	0.075 (5-10 mM)	3×10^{-4} (2.7 mM)	0.483 (5-6 mM)
formamide		$<1 \times 10^{-5}$ (5-10 mM)	$<1 \times 10^{-5}$ (10-15 mM)	1×10^{-4} (5-10 mM)	5×10^{-3}
aqueous cationic micelle[a]		2×10^{-4}	$<1 \times 10^{-4}$	3×10^{-5}	

[a] [hexadecyltrimethylammonium bromide] = 1.0×10^{-3} M, pH 9.3, $\mu = 0.01$. [b] The number in parentheses indicates the water concentration of the reaction medium.

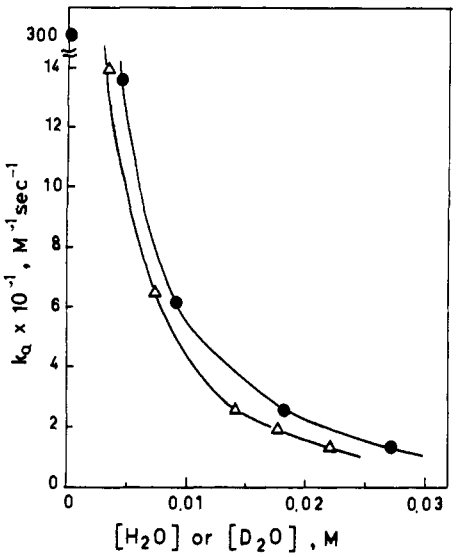


Figure 1. Second-order rate constants for the reaction of $MMHA^-NEt_4^+$ and DNAcA as a function of the concentration of H_2O (●) and D_2O (△). $[MMHA^-NEt_4^+] = 2.29 \times 10^{-3}$ M, $[DNAcA] = 1.25 \times 10^{-4}$ M. 30 °C, benzene solvent.

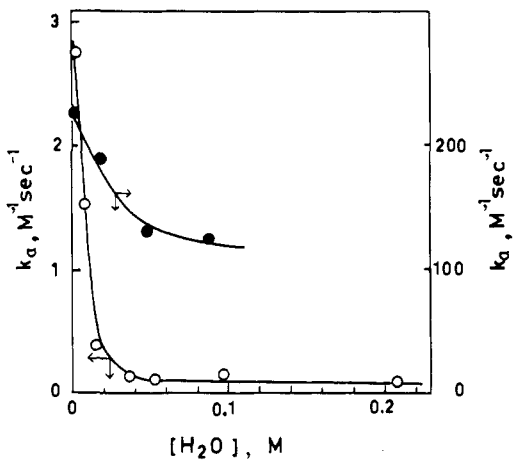
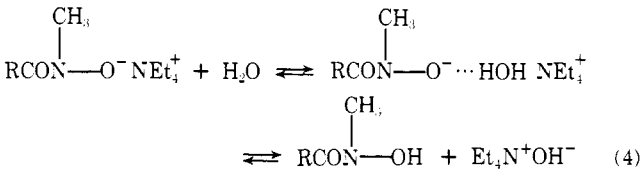


Figure 2. Second-order rate constants for the reaction of $MMHA^-NEt_4^+$ with *p*-NAcA (○) and with *p*-NClAcA (●) as a function of the concentration of H_2O. $[MMHA^-NEt_4^+] = 1.90 \times 10^{-3}$ M, $[p\text{-NAcA}] = 5.39 \times 10^{-5}$ M, $[p\text{-NClAcA}] = 3.92 \times 10^{-5}$ M. 30 °C, DMF solvent.

The relative absorbance for $MMHA^-NEt_4^+$ (at 255 nm) in acetonitrile as a function of the water concentration is plotted in Figure 3. The increase in the water concentration from 4 to 185 mM resulted in the 44% decrease in the absorbance. The decrease may be attributed to the formation of the hydrogen-bonded species and/or to the partial disappearance of the anionic species by the equilibrium of eq 4. A similar increase in



(4)

the water concentration produced a 90% decrease in the reactivity of $MMHA^-NEt_4^+$ toward PNPA and DNAcA. Thus, the rate depression by water is presumably caused by the decreased reactivity of the hydroxamate anion and by the decrease in the amount of the anion. The former factor must be dominant at low water concentrations. The nucleophilicity of $Et_4N^+OH^-$ toward PNPA and DNAcA (solvents, acetonitrile) was estimated to be ca. 20% of that of $MMHA^-NEt_4^+$.[17]

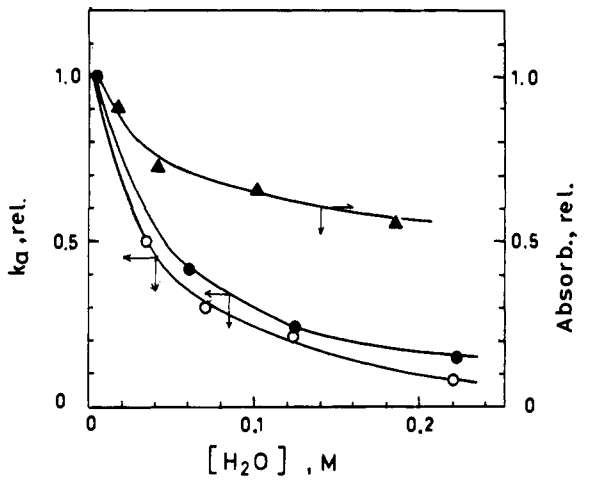


Figure 3. Influence of added water on the relative rates (●, $MMHA^-NEt_4^+$-PNPA; ○, $MMHA^-NEt_4^+$-DNAcA) and on the relative absorbance of $MMHA^-NEt_4^+$ at 255 nm (▲). $[MMHA^-NEt_4^+] = (1\text{-}30) \times 10^{-4}$ M, 30 °C, acetonitrile solvent. $k_{a,rel} = k_a$ at a given water concentration divided by k_a at $[H_2O] = 4.5$ mM. $Absorbance_{rel}$ = OD at a given water concentration divided by OD at $[H_2O] = 4.0$ mM.

Table IV. Kinetic Isotope effect[a]

substrate	$k_a^{H_2O}/k_a^{D_2O}$	range of concentration of water (H_2O or D_2O), mM
ester PNPA	1.03 ± 0.07	5.8
amide *p*-NAcA	1.00 ± 0.03	2-10
amide *p*-NClAcA	1.45 ± 0.05	4-25
amide DNAcA	1.30 ± 0.05	4-25

[a] Solvent, benzene.

Discussion

The present study established that the quaternary ammonium salt of a hydroxamate anion is extremely nucelophilic in dry, aprotic solvents. The observed rates are by far the largest in the nucleophilic cleavage of amide substrates in a nonenzymatic system. The rate difference in the reaction of $MMHA^-NEt_4^+$ and PNPA is over 10^8 for DMF and formamide (Table I); the difference for the reaction of $MMHA^-NEt_4^+$ and the amide substrates used are over 10^5-10^7 (Table III). Thus, the hydrogen bonding with protic solvent molecules drastically deactivates the hydroxamate nucelophile. In the same vein replacement of the countercation by Na^+ results in much lower reactivity because of the increased tightness of the ion pair.

The reactivity lowering of anionic reagents in protic solvents is well documented.[18,19] Cram et al.[20] described a variation of the rate constant of over 10^8-fold for a methoxide-catalyzed racemization in mixed solvents of dimethyl sulfoxide and methanol. Chloride ion reacts with methyl iodide more than 10^6 times faster in DMF than in methanol.[21] However, these reactions do not appear to be particularly sensitive to the small water concentration. LeRoux and Sugden[22] reported that the rate of bromide exchange between bromide ion and *n*-butyl bromide was nine times greater in anhydrous acetone than that in acetone containing 5 vol % water. Similar rate differences were found by other workers.[5,7] Thus, Parker concluded that protic molecules added in concentrations slightly greater than the anionic reactant do not sharply lower rates of reaction in acetone, DMF, dimethyl sulfoxide, or acetonitrile.[19]

The reactivity of the hydroxamate ion pair is much more sensitive to the water concentration. The variation of the water concentration below 1 M produced rate differences of 50–100 times. These results may be compared more appropriately to the fluoride ion catalysis. Tetraethylammonium fluoride acts as a very strong base in dry, aprotic solvents, but not in protic solvents.[23,24] The hydration energies for fluoride and oxy anions are much larger than those for chloride and bromide anions.[25] Therefore, the efficient rate suppression due to concomitant water must be closely related to the hydration energy.

These effects can explain the depression of the reactivity of hydroxamate anion in protic solvents and by concomitant water. However, they cannot provide satisfactory explanations for the following observations: (1) $MMHA^-$ anion in the CTAB micelle is most reactive toward PNPA (ester substrate) but totally unreactive toward DNAcA (amide substrate). (2) The cleavage of DNAcA is faster in benzene than in DMF or acetonitrile, whereas the reverse is true for the ester cleavage.

These results may be interpreted by considering the elementary process of the acyl transfer reaction. In the cleavage of esters with good leaving groups (such as *p*-nitrophenolate), the nucleophilic attack (k_1) is rate limiting and the leaving group is eliminated very efficiently in the anionic form: $k_2 \gg k_1$.

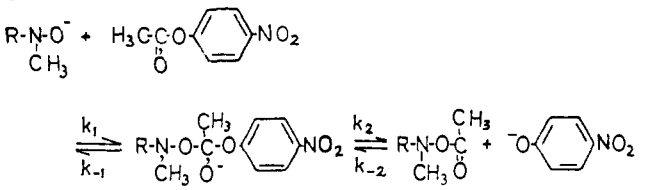
For such reactions, the hydroxamate anion acts as a very good nucleophile in aprotic solvents and in cationic micelles. The remarkable nucleophilicity of the $MMHA^-$ anion in the cationic micelle is satisfactorily explained by the concept of the "hydrophobic ion pair" we proposed previously.[4] The absence of the kinetic isotope effect is consistent with the rate-limiting nucleophilic attack. Furthermore, the reactivity of $MMHA^-NEt_4^+$ is greater in dipolar solvents (DMF and acetonitrile) than in benzene.

The observed relative reactivity of the $MMHA^-$ nucleophile in the ester cleavage should be equally applicable to the amide cleavage as far as the nucleophilic attack (k_1) is concerned. Then the discrepancies of the solvent effect observed between the ester and amide cleavages would be attributed to the difference in the decomposition stage of the tetrahedral intermediate. In the amide cleavage (Scheme III),[26] proton transfer to the tetrahedral intermediate and its cleavage are favored over the simple elimination in order to avoid formation of the energetically unfavorable aniline anion: $k_p, k_2' \gg k_2$.

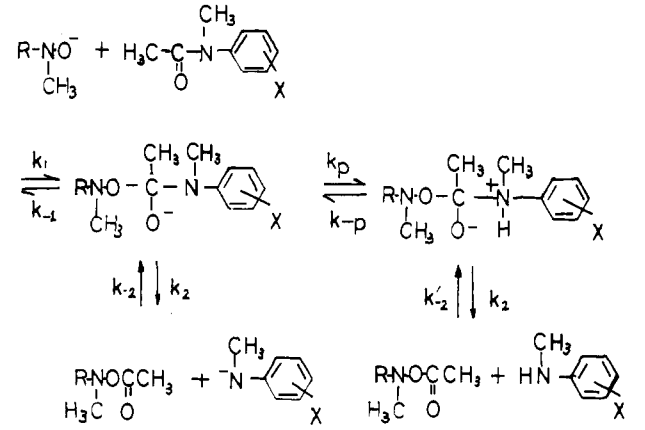
As shown in Table IV, the kinetic isotope effect (1.30–1.45) was found for the cleavage of *p*-NClAcA and DNAcA. Therefore, proton transfer must be a part of the rate-limiting process: k_1 is not much greater than k_p. A kinetic isotope effect of 2–3 ($k_a^{H_2O}/k_a^{D_2O}$) was reported for general-acid-catalyzed processes in the aqueous system.[27] The corresponding data in organic media are scarce. Breslow and McClure gave $k_a^{H_2O}/k_a^{D_2O} = 1.47$–$2.27$ for the general-acid-catalyzed cleavage of maleamic acid in acetonitrile containing 1 M H_2O.[28] The isotope effect was not observed for the cleavage of *p*-NAcA. This substrate is less activated than *p*-NClAcA and DNAcA, and the formation of the tetrahedral intermediate (k_1) may become totally rate limiting.

The presence (and absence) of the isotope effect seems to be related to the relative k_a value in different media. The k_a(benzene)/k_a(DMF) value is 30 for DNAcA, 0.5 for *p*-NClAcA, and 0.1 for *p*-NAcA. The nucleophilicity per se of the hydroxamate anion is greater in dipolar, aprotic solvents than in benzene, as demonstrated in the ester cleavage. However, k_a for DNAcA in benzene is much greater than that in DMF. The proton transfer is partially rate limiting for this substrate, and water molecules in dipolar, aprotic solvents seem to be less effective as the proton source than those in benzene. In the cleavage of *p*-NAcA proton transfer is not involved in the rate-limiting step, and the greater nucleophilicity of $MMHA^-NEt_4^+$ in DMF relative to that in benzene is directly reflected in k_a; k_a(benzene)/k_a(DMF) = 0.1.

Scheme II



Scheme III



Water molecules in dipolar, aprotic media are stabilized by the strong interaction with solvent molecules. In contrast, water molecules dissolved in hydrocarbons are essentially monomeric.[29] The proton transfer must be much more facile from monomeric water molecules in benzene than from strongly associated water molecules in dipolar solvents. It is also possible that the water molecule is strongly associated with the tetrahedral intermediate in benzene but is not in dipolar media.

The k_a value of 3000 M^{-1} s^{-1} observed for the cleavage of DNAcA in dry benzene (0.2 mM H_2O) was more than 10^8 times greater than that observed in the CTAB micelle. However, k_a for the cleavage of PNPA in the CTAB micelle was about 10 times as large as that in benzene (Table I). The 10^9 reversal in reactivity between the ester and amide cleavages is truly dramatic. The nucleophilic process (k_1) must be equally efficient in ester and amide cleavages, but the proton transfer must be especially inefficient from well-solvated water molecules in the CTAB micelle.

Finally, the role of reversed micelles may be dismissed in the present system on the following grounds: (1) $k_{a,obsd}$ for the amide cleavage was proportional to $[MMHA^-NEt_4^+]$ even in the concentration range where similar surfactants are known to aggregate extensively;[30] (2) the "reversed micelle" may not be formed in dipolar aprotic media;[31] (3) tetraethylammonium *N*-benzylbenzohydroxamate, which cannot form micelles, also cleaves amide substrates efficiently.[1]

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Hydration of Thioesters. Evaluation of the Free-Energy Changes for the Addition of Water to Some Thioesters, Rate–Equilibrium Correlations over Very Wide Ranges in Equilibrium Constants, and a New Mechanistic Criterion

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Abstract: Free energies of hydration of *S*-ethyl thioformate and trifluorothioacetate have been determined. The starting point for *S*-ethyl thioformate is the calorimetric heat of hydrolysis of triethyl monothioorthoformate, which leads to $\Delta H_f^\circ(1) = -116.6 \pm 0.4$ kcal mol^{-1}. From this may be calculated the free-energy change for addition of water to *S*-ethyl thioformate, as 4.7 ± 2.7 kcal mol^{-1}. For *S*-ethyl trifluorothioacetate, the starting points are the upper limit for the free energy of addition of hydroxide derived from Schmir's kinetic analysis and the lower limit imposed by the lack of any detectable accumulation of an intermediate. The limits permit calculation of the free-energy change for addition of water as $+3.8 \pm 1.6$ kcal/mol. The free energies for addition of water to these thiol esters, combined with estimated pK_a values for the tetrahedral intermediates, permit construction of more complete reaction coordinate diagrams than has previously been possible and the calculation of all of the rate constants required to describe the kinetics. With rate and equilibrium constants for addition reactions of amides, esters, thioesters, ketones, and aldehydes now available it is possible to construct rate-equilibrium comparisons over wide ranges of reactivity (as much as 20 orders of magnitude in equilibrium constant). It has been found that the data for these reactions may be described in terms of simple nonlinear curves, described by a one-parameter equation based on Marcus theory, provided that the rate and equilibrium constants are calculated for the microscopic process which is rate determining. It seems highly probable that this will be a powerful new technique for mechanistic analysis, whenever data over a wide enough range of reactivity are available. In the case of uncatalyzed hydration this approach leads to a clear conclusion that the rate-determining step is formation of a zwitterionic adduct, which rapidly undergoes proton transfer to give the neutral adduct. Although very few data are available for thiol additions to carbonyl compounds, a similar analysis leads to the conclusion that the rate-determining step for uncatalyzed thiol addition involves hydronium ion acting as general acid catalyst for the addition of thiolate ion leading to the neutral adduct. This mechanistic analysis immediately leads to a simple explanation for the previously puzzling phenomenon that acyl activated thiol esters show acid inhibition, whereas thiol esters without electron-withdrawing acyl substituents show acid catalysis.

Introduction

Although tetrahedral intermediates are generally considered to be involved in the majority of acyl transfer reactions,[2] the number of instances where there is direct and compelling experimental evidence for their involvement is still relatively limited.[3] One of the first clear examples was the demonstration of a tetrahedral intermediate in the hydrolysis of ethyl trifluorothiolacetate.[3] Since then, studies of other thiol ester hydrolyses have shown complicated pH rate profiles, indicative of changes in rate-determining step and, hence, of an intermediate[4] (presumably tetrahedral). A method has been developed for calculating the free energies of formation of tetrahedral intermediates by a simple extrathermodynamic approach which has been applied to addition reactions of esters[5,6] and amides.[7] This paper reports an extension of this procedure to thiol esters. In addition, it was found that for the case of trifluorothiolacetates (where the thermochemical approach would be very difficult) a combination of kinetic, thermodynamic, and spectroscopic information permits the specification of the free-energy level of the intermediate within rather narrow limits.

Thiol esters with electron-withdrawing acyl groups are unusual in that acid inhibition,[3a,4b] rather than acid catalysis, is observed. This behavior has been rationalized in terms of rate-determining attack of water to give the neutral tetrahedral intermediate, followed by rapid proton loss and expulsion of thiolate, provided the pH is not too low. As the pH is lowered

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