CHEMISTRY LETTERS, pp. 109-112, 1976. Published by the Chemical Society of Japan

NUCLEOPHILIC ION PAIRS. FACILE CLEAVAGE OF AN AMIDE SUBSTRATE BY HYDROXAMATE ANIONS

Seiji SHINKAI and Toyoki KUNITAKE
Department of Organic Synthesis, Faculty of Engineering,
Kyushu University, Fukuoka 812

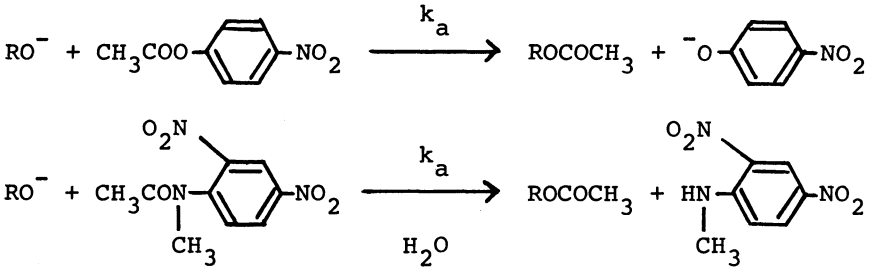
An amide substrate(N-methyl-2,4-dinitroacetanilide) is readily cleaved by tetraethylammonium hydroxamate ion pairs in dry, aprotic solvents at room temperature, and the reaction is efficiently suppressed by minute amounts of water. This is the first example of efficient nucleophilic catalysis of amide cleavage at ambient conditions.

We wish to report herein the first example of efficient amide cleavage by a nucleophile at ambient conditions. In spite of the extensive efforts in this area, the nucleophilic acyl transfer has been possible only for highly activated amides at very slow rates.[1,2)]

Some anionic nucleophiles such as thiolates, alkoxides, and hydroxamates have been found to be remarkably reactive in cationic micelles[3-8)]: e.g., 10^2-10^3 rate enhancements for acyl transfer from p-nitrophenyl acetate(PNPA). We suggested recently that these rate enhancements arise from formation of desolvated, hydrophobic ion pairs between anionic nucleophiles and cationic surfactant molecules.[9)] As an extention of this work, we prepared tetraethylammonium N-mehtylmyristohydroxamate(MMHA·NEt_4), mp 43-45°, and tetraethylammonium N-benzylbenzohydroxamate(BBHA·NEt_4), mp 125-130°, and investigated their reactions with PNPA and N-methyl-2,4-dinitroacetanilide(MDNA).

MMHA: $CH_3(CH_2)_{12}CONO^-$ (with CH_3)

BBHA: $C_6H_5CONO^-$ (with $CH_2C_6H_5$)



The reactions were followed by monitoring the absorptions of p-nitrophenolate(401 nm) and 2,4-dinitroaniline(410 nm). The formation of the latter product were separately ascertained spectroscopically and by tlc. The reaction rates

were mostly determined from the pseudo-first-order plot(correlation coefficient> 0.99), and were confirmed to be first-order with respect to hydroxamate ion pairs(MMHA·NEt_4 and BBHA·NEt_4) and substrates(PNPA and MDNA).

Table 1 summarizes the second-order rate constants(k_a) for the acyl transfer reactions. The nucleophilicity of MMHA·NEt_4 could be conveniently evaluated by the reaction with PNPA, since the nucleophilic attack is shown to be the rate-determining step for esters with good leaving groups such as p-nitrophenolate. It is noted that the reactivity of MMHA·NEt_4 toward PNPA in dry, aprotic solvents (DMF, acetonitrile, benzene) is almost comparable to that in cationic micelles. In contrast, the reaction is very slow in protic solvents(water, ethanol, formamide), and addition of extremely small amounts of water to aprotic solvents

TABLE 1. Nucleophilic reactions of MMHA·NEt_4 with PNPA and MDNA at 30°

Solvent	$[H_2O]$ mM	k_a $M^{-1}s^{-1}$ PNPA	MDNA
DMF	2.2-3.0	1130	4.08
Acetonitrile	3.3-5.3	845	4.50
	70		1.33
	570	12.6	
	960-990	8.46	0.0304
Benzene	0.2		3000
	4.5-6.1	350	136
	18		25.7
	27		13.3
Ethanol	27	0.63	3×10^{-4}
Formamide		$< 10^{-4}$	1×10^{-4}
Water[a]		32.6	$< 10^{-5}$
Cationic Micelle		2060[b]	3×10^{-5}
Cationic Polysoap[c]		$(1\text{-}3) \times 10^4$	
α-Chymotrypsin[d]		4000	
Acetonitrile[e]	5.0		0.582

[a] N-Methylisobutyrohydroxamic acid was used instead; T. Kunitake, Y. Okahata, and R. Ando, Bull. Chem. Soc. Japan, 47, 1509 (1974).

[b] 22°C, pH 9.99 (ref. 6).

[c] from ref. 8.

[d] M. L. Bender, G. E. Clement, F. J. Kézdy and H. d'A. Heck, J. Amer. Chem. Soc., 86, 3860 (1964).

[e] BBHA·NEt_4 was used.

brings large rate decreases. A very large rate difference(up to 10^7) has been reported for the reaction of methyl iodide and chloride ion between aprotic and protic solvents.[10] However, protic molecules added in concentrations slightly greater than chloride ion did not sharply lower the rates of the reaction in aprotic solvents. It is interesting that water molecules in concentrations comparable to that of the nucleophile yielded very efficient rate suppression in the present system.

Surprisingly, an amide substrate MDNA was also readily cleaved by the hydroxamate ion pairs in dry, aprotic solvents. As for example, the half life of the reaction was about five seconds with 2.29 mM MMHA·NEt_4 at 30° in benzene containing ca. 5 mM H_2O. This is an enormous rate enhancement compared with the previously known example of acyl transfer reaction from amide substrates.[1,2]

The reaction rates were again sensitive to the water concentration. It is worth emphasizing that the increase of the water concentration from 0.2 to 18 mM caused the rate decrease from 3000 to 27.5 $M^{-1}s^{-1}$. Long-chain hydroxamate MMHA in the aqueous CTAB micelle was totally unreactive toward MDNA. Thus, k_a = 3000 $M^{-1}s^{-1}$ observed in dry benzene(0.2 mM H_2O) was more than 10^8 times greater than that in the aqueous CTAB micelle. However, the reaction of the MMHA anion with PNPA in the aqueous CTAB micelle was about 10 times as fast as that in benzene. The 10^9 reversal in reactivity is truly remarkable.

These results suggest that the cleavage of the amide substrate is not solely related to the nucleophilicity of the hydroxamate anions. It is said that the cleavage of esters with good leaving groups is a simple acyl transfer, whereas the amide cleavage requires proton sources to avoid the energetically-unfavorable formation of the amine anion.[11] This was found to be the case, and direct evidence for the (conceivably partial) involvement of water molecule at the rate-determining step was provided by the kinetic isotope effect of $k_a^{H_2O}/k_a^{D_2O}$ = 1.30 ± 0.05 at [H_2O] = 4 to 25 mM(benzene, 30°). As expected, no isotope effect was detected for the reaction of MMHA with PNPA: $k_a^{H_2O}/k_a^{D_2O}$ = 1.03 ± 0.07 in benzene.

The k_a values for the amide cleavage were larger in benzene than in DMF or acetonitrile. Therefore, water in dipolar aprotic solvents is concluded to be inferior as proton source to that in benzene, probably because the water molecule in the former solvents is stabilized by hydrogen bonding and/or dipolar interaction.[10,12,13] The lack of the reactivity of MMHA in the CTAB micelle toward MDNA can be similarly attributed to inefficient proton transfer. Therefore, the slowness of the amide cleavage in aqueous and protic systems can be ascribed to an unfavorable partitioning of a tetrahedral intermediate to products. Subsequent studies in this laboratory showed that less activated amide substrates can be also cleaved by the hydroxamate ion pairs.

Based on these results we propose that the nucleophilicity of the hydroxamate anion(or probably oxyanions in general) is remarkably enhanced as desolvated (dehydrated), loose ion pairs, and that proton transfer is most efficient from a poorly solvated water molecules. The active site of hydrolytic enzymes is

usually situated in the hydrophobic region, and oxyanionic nucleophiles and proton transfer from water and hydroxyl groups play important roles. Therefore, the present study may offer an important clue for elucidation of microenvironmental effects which lead to high efficiencies in the enzymatic catalysis.

We thank Miss R. Ando and Mr. N. Nakashima for their capable experimental assistance.

REFERENCES

1) C. E. Stauffer, J. Amer. Chem. Soc., 96, 2489 (1974).
2) R. M. Pollack and T. C. Dumsha, ibid., 97, 377 (1975).
3) C. A. Bunton and L. G. Ionescu, ibid., 95, 2912 (1973).
4) W. Tagaki, T. Amada, Y.Yamashita, and Y. Yano, Chem. Commun. 1972, 1131.
5) K. Martinek, A. V. Levashov, and I. V. Berezin, Tetrahedron Lett., 1975, 1275.
6) I. Tabushi, Y. Kuroda, and S. Kita, ibid., 1974, 643.
7) T. Kunitake, Y. Okahata, and T. Sakamoto, Chem. Lett., 1975, 459.
8) T. Kunitake, S. Shinkai, and S. Hirotsu, J. Polymer Sci., Polymer Lett. Ed., 13, 377, (1975).
9) T. Kunitake, S. Shinkai, and Y. Okahata, Bull. Chem. Soc. Japan, in press.
10) A. J. Parker, Quart. Rev., 16, 163 (1962).
11) W. P. Jencks, "Catalysis in Chemistry and Enzymology", McGraw-Hill, New York, N. Y., 1969, Chapter 10.
12) D. J. Cram, B. Rickborn, C. A. Kingsbuty, and P. Haverfield, J. Amer. Chem. Soc., 83, 3768 (1961).
13) A. J. Parker, Austral. J. Chem., 16, 585 (1963).
14) J. H. Fendler, E. J. Fendler, R. T. Medary, and V. A. Wood, J. Amer. Chem. Soc., 94, 7288 (1972).
15) J. H. Fendler, E. J. Fendler, and S. A. Chang, ibid., 95, 3273 (1973).
16) J. H. Fendler and L-J. Liu, ibid., 97, 999 (1975).
17) The cmc is estimated to be 3-7 mM for MMHA·NEt_4 in benzene.[14-16)]

(Received December 12, 1975)