equivalent forms, i.e., eq 2–4. The parameters ΔH^0 and D(RH), in terms of which are represented activation energies for exothermic free radical reactions, are shown to be linearly dependent on each other. The same parameters also exhibit linear dependence on the ionization potentials of alkyl free radicals, on Taft's alkyl inductive substituent constants, and on heterolytic bond-dissociation energies for the process $R^+ + H^- \rightarrow RH$. Since all the above-mentioned parameters are linearly interrelated, it appears that the Evans–Polanyi-type relations could be trivial, alternative cases of the E_a vs. σ_I(R) correlations.[9] The conventional forms of the Evans–Polanyi correlations are not very informative because they fail to suggest any interaction mechanism by which the observed variation in the kinetic data arises and because the parameters ΔH^0 and D(RH) exhibit relatively small ranges of structural effect. The latter disadvantage results in less accurate predictions of reactivity when Evans–Polanyi relations are used for such a purpose.

A considerable number of molecular and/or substituent parameters have been shown in this paper and in previous ones[8-10] to be interrelated, i.e., IP(R), σ_I(R), υ_R, υ_{OR}, υ_{SR}, $\upsilon_{NR_1R_2}$, E_s^c(R), E_s(R), IP(RX), D(RH), $D(R^+H^-)$, and ΔH^0. This points to the conclusion that a given set of kinetic or physical data can be represented by several alternative self-consistent but, nevertheless, arbitrary ways. Equation 16 provides rather convincing evidence that representation of physical (or kinetic) data in terms of substituent parameters may be arbitrary. It becomes, therefore, evident that instead of proliferating "new" substituent constants, we should examine which of the existing parameters serve the purpose of linear free-energy relationships best. It is the feeling of this author that the parameter of choice for representing kinetic or physical data and for predicting reactivity should be the ionization potentials of free radicals. The reason for this is that IP(R) values have a very large range of structural effects, i.e., are very sensitive to structural variation in R, and they are accessible by direct experimental methods.

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Enantioselective Ester Hydrolysis by Hydroxamic Acids of *N*-Benzyloxycarbonyl-L-amino Acids or Optically Active Amines in Cetyltrimethylammonium Bromide Micelles

Hirotaka Ihara, Shuji Ono, Hideto Shosenji, and Kimiho Yamada*

Department of Synthetic Chemistry, Faculty of Engineering, Kumamoto University, Kumamoto 860, Japan

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Hydrolysis of *p*-nitrophenyl esters of amino acids by hydroxamic acids of *N*-benzyloxycarbonyl-L-amino acids or optically active amines of L-amino acids in the presence of CTABr micelles showed effective enantioselectivities (D/L = 2.51 and 2.65, respectively) as well as enhanced rate constants (k_{obsd} = 0.8 s^{-1} for hydroxamic acid), demonstrating the propriety of synthetic design for enzyme models that we previously reported. In the case of the aminolysis reaction, no enantioselectivity was observed with an optically active amine which has an amino group far from the asymmetric carbon atom. On the other hand, optically active amines with amino groups at positions α to the asymmetric carbon atoms showed effective enantioselectivities. Furthermore, the reaction products of optically active amines and D substrates gave highly optically active substances.

In our previous reports cetyltrimethylammonium bromide (CTABr) micelles have proved to provide effective incorporation sites for enantioselectively catalyzed hydrolysis by *N*-lauroyl-L-histidine.[1,2] In addition, the enantioselectivity depended on the steric factors of the compounds.[3,4]

This work deals with the catalyzed hydrolysis of optically active esters by hydroxamic acids of L-amino acids and optically active amines that demonstrates potent enantioselectivity in a micellar system. A great many hydroxamic acid derivatives showing distinguished catalytic actions on the hydrolysis of esters in the mixed micellar system[5,6] have been synthesized. However, few papers have been published on their applications to enantioselective catalysis. There have been no reports on enantioselective aminolysis in the micellar system either.

The optically active hydroxamic acids were prepared from *N*-benzyloxycarbonyl-L-phenylalanine[7] and N^{α},N^{ϵ}-bis(benzyloxycarbonyl)-L-lysine[8] by converting them into mixed anhydrides with ethyl chloroformate at −15 °C followed by treatment with hydroxylamine or methylhydroxylamine. *N*-Benzyloxycarbonyl-L-phenylalanine hydroxamic acid (**1a**), mp 99.0–99.5 °C, *N*-benzyloxycarbonyl-L-phenylalanine *N'*-methylhydroxamic acid (**1b**), oil, N^{α},N^{ϵ}-bis(benzyloxycarbonyl)-L-lysine hydroxamic acid

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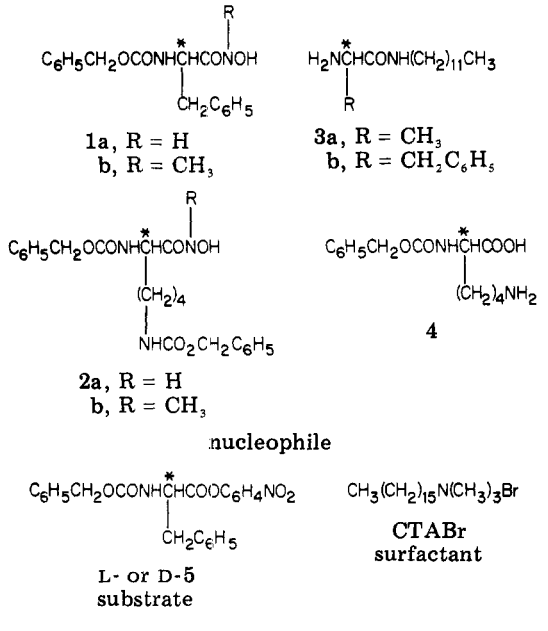
Table I. Hydrolysis of L- or D-5 Catalyzed by Optically Active Hydroxamic Acids and Amines in CTABr Micelles[b]

nucleophile	buffer[a]	[nuc] × 10^4, M	pH	k_{obsd} × 10^3, s^{-1} L-5	k_{obsd} × 10^3, s^{-1} D-5	D/L
1a	A	1.6	7.40	2.32	2.49	1.07
1a	B	1.6	7.93	23.30	24.98	1.07
1b	A	1.6	7.40	38.32	61.92	1.60
1b	B	1.6	7.93	78.50	113.28	1.44
2a	A	1.6	7.40	60.88	65.77	1.08
2a	B	1.6	7.93	177.15	189.15	1.07
2b	A	1.6	7.40	21.42	47.29	2.21
2b	A	1.6	7.93	110.13	235.55	2.14
3a	A	4.0	7.93	0.75	1.51	2.01
3a	C	4.0	7.93	1.73	2.54	1.47
3a	C	10	7.93	1.22	3.23	2.65
3b	A	4.0	7.93		0.01	0.01
3b[c]	A	10	7.93	0.07	0.12	1.71
3b	C	4.0	7.93		0.01	0.01
4[c]	A	4.0	7.90	1.58	1.53	0.97

[a] Buffer: (A) 0.04 M Tris, 0.20 M KCl; (B) 0.01 M Tris, 0.08 M KCl; (C) 0.01 M Tris, 0.01 M KCl. [b] 25.0 °C, [CTABr] = 4 × 10^{-3} M, [Sub] = 0.7–2.3 × 10^{-5} M. [c] = 4 × 10^{-3} M, CH_3OH-CH_3CN-H_2O (10.0:6.67:83.33, v/v/v).

(**2a**), mp 141.5–142.5 °C, and N^{α},N^{ϵ}-dibenzyloxycarbonyl-L-lysine N'-methylhydroxamic acid (**2b**), mp 84.0–84.5 °C, were prepared.

The optically active amines L-alanyllaurylamide (**3a**) (mp 129–131 °C) and L-phenylalanyllaurylamide (**3b**) (mp 111.5–114.5 °C) were prepared by reaction of the corresponding *N*-benzyloxycarbonyl-L-amino acids with laurylamine in the presence of dicyclohexylcarbodiimide[8,9] followed by catalytic removal of the benzyloxycarbonyl function over Pd/C.[10] *N*-Benzyloxycarbonyl-L-lysine (**4**) [mp 239.0–241.0 °C (lit.[11] 235–237 °C)] was prepared by the benzyloxycarbonylation of L-lysine.



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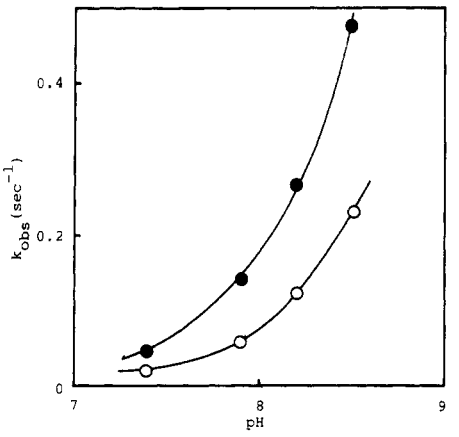

Figure 1. pH–rate profile for **2b**-catalyzed hydrolysis of L- or D-5: 25.0 °C, 0.04 M Tris buffer, 0.20 M KCl, [CTABr] = 1 × 10^{-3} M, [**2b**] = 1.6–1.9 × 10^{-4} M, [Sub] = 0.4–2.7 × 10^{-5} M. (○) L-5; (●) D-5.

The optically active esters were prepared from *N*-benzyloxycarbonyl-L- or -D-phenylalanine by the standard method:[12] *p*-nitrophenyl ester of *N*-benzyloxycarbonyl-L-phenylalanine (L-5), mp 124.5–126.0 °C (lit.[12] 126–126.5 °C); *p*-nitrophenyl ester of *N*-benzyloxycarbonyl-D-phenylalanine (D-5), mp 125.5–126.0 °C.

The purities of these compounds were determined by means of elemental analyses and IR and NMR spectra. Hydrolysis was followed spectrophotometrically at 25 °C, pH 7–9, in Tris buffer in the presence of CTABr.

The results of the measurements are summarized in Table I. **1b** and **2b** exhibited pronounced enantioselectivities. No significant enantioselectivities have so far been observed with hydroxamic acids. It should be noted that the hydroxamic acids of L-amino acids reacted more preferentially with the D substrate than with the L substrate, in contrast to the reversed preferences of L-amino acids which have been examined as enantioselective enzyme models.[4,13,14]

Table I also lists the results of aminolysis using optically active amines as catalysts. **4**, which has an amino group ϵ to the asymmetric carbon atom, showed no enantioselectivity, whereas **3a** and **3b**, with amino groups α to the asymmetric carbon atoms, gave rise to effective enantioselectivities, and both of them reacted more preferentially with the D substrate than with the L substrate. The rate of reaction of **3b** was inferior to that of **3a**, possibly because of the steric hindrance by the benzyl group.

As shown in Table I, increasing ion strength remarkably reduced the reaction rate of the hydroxamic acids as well as of the optically active amines, whereas the enantioselectivities increased slightly. This is considered to arise from reduced participation of hydroxide ions in the reaction around the micelles, which was enhanced by the increased ion strength as evidenced by a decrease in critical micelle concentration (cmc).[15]

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(15) At pH 7.93, the cmc values were 2.95 × 10^{-5}, 5.95 × 10^{-5}, and 7.20 × 10^{-5} M, respectively, for solutions containing 0.20, 0.08, and 0.01 M KCl under the experimental conditions. The solution containing 0.20 M KCl gave cmc's of 3.31 × 10^{-5} and 3.18 × 10^{-5} M at pH 7.93 and 8.61, respectively.

Further investigation with various concentrations proved that the enantioselectivity of **3a** was independent of the concentration of the amine, analogous to the micellar system catalysts in our previous paper.[2] The rate constant increased with increasing concentration of **3a**. It reached a saturation at concentrations above 0.5×10^{-4} M.

Figure 1 shows the pH dependency of the rate constant for catalyzed hydrolysis by **2b**. The hydroxamate anion appears to behave as the nucleophile inducing the acyl transfer, because the rate increased exponentially around the pH, which is predictable from the spectrophotometrically determined pK_a value of 8.46 for the hydroxamic acid. On the other hand, the enantioselectivity remained constant with a D/L value of 2.1–2.3 throughout the measured pH range. Presumably pH did not affect the structural fit between the reagents which, as we have mentioned previously,[4] is the most essential factor for enantioselectivity.

2a gave the greatest rate constant. Reduction of the concentration of CTABr from 4×10^{-3} M to 1×10^{-3} M, accompanied by the reduction of that of KCl from 0.2 M to 0.01 M at pH 7.4, enhanced the rate by a factor of 15, giving a rate constant k_{obsd} of 0.3 s^{-1} and of greater than 0.5 s^{-1} for L- and D-**5**, respectively. Presumably decreased micelle concentration and ion strength accelerated reaction by hydroxide ion. At high pH the hydrolysis was so fast that the present measurement could not follow it. By lowering the temperature to 10 °C, the D/L value was increased to 2.51 for the reaction with **2b** at pH 7.78. A similar increase of enantioselectivity at lower temperatures has been observed for *N*-lauroyl-L-histidine.

We previously emphasized the importance of three requirements for the enantioselective enzyme model:[1,2] (1) the asymmetric center and active site must exist close together in the reaction system; (2) strong interactions must exist among reagents; (3) the catalyzed reaction must occur in a hydrophobic field in order to avoid the reaction with nonselective hydroxide ion. The present system, which was designed to substantiate these requirements, successfully provided the effective enantioselective reaction.

Furthermore, the reaction products of optically active amines and D substrates in a CTABr micellar system gave highly optically active substances, indicating promising application of these micellar catalysts to polypeptide syntheses.

1a: mp 99.0–99.5 °C; $[\alpha]^{20}_D$ −20.5° (*c* 1, DMF). Anal. Calcd for $C_{17}H_{18}N_2O_4$ (mol wt, 314.34): C, 65.0; H, 5.8; N, 8.9. Found: C, 65.9; H, 5.7; N, 8.8.

1b: oil; $[\alpha]^{20}_D$ −0.4° (*c* 1, DMF). Anal. Calcd for $C_{18}H_{20}N_2O_4 \cdot 4H_2O$ (mol wt, 400): C, 54.0; H, 7.0; N, 7.4. Found: C, 53.0; H, 6.3; N, 7.8.

2a: mp 141.5–142.5 °C; $[\alpha]^{20}_D$ −2.2° (*c* 2, DMF). Anal. Calcd for $C_{22}H_{27}N_3O6$ (mol wt, 429.47): C, 61.5; H, 6.3; N, 9.8. Found: C, 61.9; H, 6.4; N, 9.8.

2b: mp 84.0–84.5 °C; $[\alpha]^{20}_D$ +6.9° (*c* 1, DMF). Anal. Calcd for $C_{23}H_{29}N_3O_6 \cdot 1.5H_2O$ (mol wt, 471): C, 58.7; H, 6.9; N, 9.0. Found: C, 58.4; H, 6.9; N, 9.6.

3a: hydrochloride; mp 129–131 °C; $[\alpha]^{20}_D$ + 2.6° (*c* 1, CH_3OH). Anal. Calcd for $C_{15}H_{33}N_2OCl$ (mol wt, 282.89): C, 61.5; H, 11.4; N, 9.6. Found: C, 60.7; H, 11.5; N, 9.4.

3b: hydrochloride; mp 111.5–114.5 °C; $[\alpha]^{20}_D$ +37.4° (*c* 1.7, CH_3OH). Anal. Calcd for $C_{21}H_{37}N_2OCl$ (mol wt, 368.99): C, 68.4; H, 10.1; N, 7.6. Found: C, 68.0; H, 10.2; N, 7.3.

4: mp 238.5–241.0 °C (lit.[11] 235–237 °C). Anal. Calcd for $C_{14}H_{20}N_2O_4$ (mol wt, 280.32): C, 59.9; H, 7.2; N, 10.0. Found: C, 59.6; H, 7.2; N, 10.0.

L-**5**: mp 124.5–126.0 °C (lit.[12] 126–126.5 °C); $[\alpha]^{20}_D$ −24.8° (*c* 2, DMF) (lit.[12] −24.7 (*c* 2, DMF)). Anal. Calcd for $C_{23}H_{20}N_2O_6$ (mol wt, 420.42): C, 65.7; H, 4.8; N, 6.7. Found: C, 65.7; H, 4.8; N, 6.8.

D-**5**: mp 125.5–126.5 °C; $[\alpha]^{20}_D$ +26.3° (*c* 1, DMF). Found: C, 65.6; H, 4.7; N, 6.5.

Registry No. **1a**, 73048-81-4; **1b**, 73048-82-5; **2a**, 73048-83-6; **2b**, 73048-84-7; **3a**·HCl, 73088-59-2; **3b**·HCl, 73048-85-8; **4**, 2212-75-1; L-**5**, 2578-84-9; D-**5**, 2578-85-0; *N*-(benzyloxycarbonyl)-L-phenylalanine, 1161-13-3; N^{α},N^{ϵ}-bis(benzyloxycarbonyl)-L-lysine, 405-39-0; hydroxylamine, 7803-49-8; methylhydroxylamine, 593-77-1; *N*-(benzyloxycarbonyl)-L-alanine, 1142-20-7; laurylamine, 124-22-1; L-lysine, 6899-06-5; *N*-(benzyloxycarbonyl)-D-phenylalanine, 2448-45-5.