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Chemistry of Succinimido Esters. XVI.*¹Kinetic Studies on the *N*-Arylacetylation of Amino Acidsby *N*-Succinimidyl Arylacetates in Aqueous Solution

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The *N*-arylacetylation of amino acid (2) by *N*-succinimidyl arylacetates (1a) to give the corresponding *N*-arylacetyl amino acid was studied kinetically in an aqueous solution [pH = p*K*_a of the amino group in (2)] at 20°C. The reaction was competitive with the decomposition of (1a) and the rate was expressed as $V = (k_d + k_2 [2]) [1a]$, where k_d and k_2 are the rate constants for the decomposition and *N*-arylacetylation, respectively.

The second order rate constant, k_2 , was correlated with the nucleophilicity (p*K*_a) of (2), giving slopes of 0.7 ~ 0.8 for log vs. p*K*_a plots. The rate of ortho-substituted (1a) was less than those of meta- and para-substituted (1a), owing to the steric hindrance of the ortho-substituted (1a). Hammett plots for meta- and para-substituted (1a) showed a linear relationship with $\rho = 0.53 \sim 0.77$. The rate of *N*-arylacetylation predominated due to the inductive and steric effects of (1a) and (2). The rate ratios, $10^{-3} k_2/k_d$, exceeded unity except in some cases for (2). The reactivity of (1a) was also compared with those of *N*-succinimidyl benzoates (1b) and *N*-acylsuccinimides (1c).

A possible mechanism involving nucleophilic attack is proposed and discussed based on the above results.

1 Introduction

The ester carbonyl group of *N*-succinimidyl carboxylate (1) is activated by the electron-withdrawing nature of the *N*-succinimidyl group and easily attacked nucleophilically by the amino compounds¹⁾. This *N*-carbonylation (amido formation)*² takes place both in aqueous²⁾ and organic³⁾ solutions. The former reaction has been used for *N*-carbonylation of water-soluble amines²⁾ and chemical modification of amino groups (ϵ -amino groups of Lys residues and α -amino group of *N*-terminal) in proteins⁴⁾, and the latter for the preparation of ceramides (*N*-acyl derivatives of sphingolipid bases) with the use of *N*-acyloxysuccinimides (1c)⁵⁾ and the labelling (*N*-arylcabonylation) of aliphatic amines with use of *N*-succinimidyl benzoates (1b)⁶⁾.

In the previous paper on the reactions of *N*-succinimidyl arylacetates (1a) and aliphatic

amines⁷⁾, we reported that (1a) was used for the *N*-arylacetylation reagents of amino compounds in aqueous solution. In the present paper, we selected amino acids (2) as substrates and studied kinetically the *N*-arylacetylation to obtain a possibility of (1a) as modification reagents of the amino groups in proteins and also compared the reactivities of *N*-succinimidyl carboxylates [(1a), (1b), and (1c)] in response to p*K*_a of the amino group in (2) to discover more precisely the mechanism involving a nucleophilic attack.

X = H, *m*-CH₃O, *p*-Cl
m-F, *m*-Br, *o*-CH₃O,
o-F, *o*-Cl, *o*-Br.

X = *m*-CH₃, H, *m*-CH₃O,
m-F, *m*-Cl, *m*-Br,
o-F, *o*-Cl, *o*-Br.

R = CH₃ (CN = 2),
n-C₅H₁₁ (CN = 6).

*1 Chemistry of Succinimido Esters. XV. Ref. 6b).

*2 In this paper, the *N*-carbonylation means *N*-arylacetylation, *N*-arylcabonylation, and *N*-acylation of amino groups of (2) with respect to (1a), (1b), and (1c), respectively.

2 Experiments

2.1 Materials

Phenylacetic, benzoic, and fatty acids (GR or above 98 % of purity) were purchased from Aldrich Chemical Co., Ltd., Tokyo Kasei Kogyo Co., Ltd. or Nakarai Chemical Co., Ltd. DSC*³ (SP for peptide synthesis) and amino acids (made by Kyowa Hakko Co., Ltd) were purchased from Wako Pure Chemical Inds., Ltd.

N-Succinimidyl carboxylates [(1 a), (1 b), and (1 c)] were prepared by the coupling reaction of DSC*³ with the corresponding acids in the presence of pyridine in acetonitrile according to the previously reported methods^(2),7),8). Yields were above 70 % (purity > 99 %) after recrystallization from an appropriate solvent and the physical properties were accordance with those in the literatures^(2),7),8).

Acetonitrile, *n*-hexane, and ethanol (SP for HPLC analyses) were purchased from Katayama Chemical Ind., Ltd., and the other solvents were purified by the ordinary methods⁽⁹⁾. Buffer reagents (GR) were purchased from Nakarai Chemical Co., Ltd. Buffers: pH 8.17~9.41 0.05 M Na₂B₄O₇-NaH₂PO₄ and pH 9.60~10.75 0.05 M Na₂B₄O₇-NaOH.

2.2 Rate measurement

UV analyses were performed by the JASCO UV-430 Spectrophotometer equipped with the EHC-363 Cell Holder (JASCO). The rate was measured spectrophotometrically by following the absorbance at 258 nm of *N*-hydroxysuccinimide (4) formed during the reaction.

The reaction was carried out in a cuvette (light path length: 1 cm) at 20°C. Since (1) was

insoluble and decomposed easily in the buffer solution, (1) was dissolved in dioxane and an aliquot (10~50 μL) was added to the stirred reaction solution (3 mL).

The apparent first order rate constant, *k_a*, was calculated from the slope of ln (*A_∞* - *A_t*) vs. (reaction time) by the least-square method, where *A_∞* and *A_t* are the absorbances at time of infinity and *t*, respectively. The correlation factors were more than 0.999 for all cases.

2.3 Analytical methods

HPLC, GLC, TLC and GC-MS analyses of (1) were done by the previously reported methods^(2),8).

3 Results

3.1 Rate equation

The reaction of (1 a) with (2) to give the corresponding *N*-arylacetyl amino acid (3 a) was studied kinetically in aqueous solution (pH = p*K_a*) at 20°C.

The apparent first order rate constant, *k_a*, was invariable and independent of the concentration of sodium chloride (0~0.05 M), *i.e.*, no ion strength effect was observed. Thus, the rate was measured in a 0.05 M buffer in this paper. We employed the reaction condition of [Buffer]₀ > [2]₀ > [1]₀ for simplifying the kinetics.

a : Y = CH₂Ar, b : Y = Ar, c : Y = R

The effect of the initial concentration of (2) on the rate for the reaction of (1 a) with (2) was investigated. As shown in Fig. -1, the apparent first order rate constant, *k_a*, increased linearly with the concentration of (2) with an intercept of *k_a* = *k_d*. This suggests that the *N*-arylacetylation [Eq. (1)] is competitive with the decomposition of (1 a) [Eq. (2)] in aqueous solution, and the rate is expressed as follows:

The similar competition was observed for the

$$V = (k_a + k_2 [2]) [1 a] \quad (3)$$

k_a: the first order rate constant for the decomposition of (1 a),

k₂: the second order rate constant for the *N*-arylacetylation of (2) by (1 a).

N-arylacarbonylation of (2) by (1 b) and *N*-

* 3 Abbreviations

DSC : *N,N'*-Disuccinimidyl carbonate, log (*K/K₀*) : The relative acid strength of substituted benzoic acids, where *K* and *K₀* are the ionization constants of substituted and non-substituted benzoic acids in water, respectively. p*K_a* : Dissociation constant of the protonated amino acid (-NH₃⁺), *N*-α-Ac Lys : *N*-α-Acetyl-L-lysine, *N*-ε-Ac Lys : *N*-Acetyl-L-lysine, ε-NH₂ Cap : ε-Aminocaproic acid, γ-NH₂ Bu : γ-Aminobutyric acid, 10⁻³ *k₂*/*k_a* : The rate ratio at the concentration of [2]₀ = 10⁻³ M : the concentration of free amino group in (2) is 50 % of added (2) according to the definition of the dissociation constant.

Fig. -1 Dependence of the apparent first order rate constant, k_a , on the initial concentration of (2) for the *N*-arylacetylation of (2) by (1 c) in aqueous solution (pH = pK_a) at 20°C. Plots of k_a vs. $[2]_0$.

acylation of (2) by (1 c) in aqueous solution (pH = pK_a).

3.2 Reactivity of amino acid (2)

In the previous paper^{2b)}, it was reported that the rate for the *N*-acylation of (2) by (1 c) at a certain (constant) pH did not give good correlation to pK_a (i.e., the plot of $\log k_2$ vs. pK_a gave curvature), because the dissociation of (2) involved in the reaction. To avoid this complication, the rate for *N*-arylacetylation was measured at pH = pK_a ³. Furthermore, we observed that the mercapto group in Cys (freshly prepared sample showed higher reactivity than the stocked one, because the mercapto group is presumably easily auto-oxidized by oxygen in air) reacted with (1). Therefore, we excluded it in this study.

The second rate constant for the *N*-arylacetylation of (2) by (1 a) with different pK_a was measured to clarify the effect of nucleophilicity of amino group in (2). The results are summarized in Table-1. The rate constant roughly correlated with pK_a , a linear free energy relationship was observed as shown in Fig. -2. The slopes of $\log k_2$ vs pK_a plots were 0.65~0.85. Fig. -2 also demonstrates that the rates of α -amino acids which have a substituent in addition to α -amino group at C₂ carbon in (2) are smaller than those of the other

Fig. -2 Correlation between the second order rate constant, k_2 in $M^{-1} \cdot s^{-1}$, and the nucleophilicity (pK_a) of the amino group in (2) for the *N*-carbonylation of (2) by (1) in aqueous solution (pH = pK_a) at 20°C. The representative plots of $\log k_2$ vs. pK_a . From the data in Table-1 and the related experiments.

amino acids (e.g., γ - and ϵ -amino acids), because of the steric hindrance of the substituent. The slopes of the $\log k_2$ vs. pK_a plots for the former amino acids were smaller than those of the latters. The similar tendency was observed for the *N*-arylacetylation of (2) by (1 b) and *N*-acylation of (2) by (1 c) as shown in Fig. -2.

3.3 Substituent effect of (1 a)

The effect of substituent in (1 a) for the *N*-arylacetylation of (2) was investigated. The rates for para- and meta-substituted (1 a) correlated with $\log (K/K_0)$ value³ of the corresponding benzoic acid¹⁰⁾, i.e., the $\log k_2$ vs. $\log (K/K_0)$ plots gave good linear (free energy) relationship, as shown in Fig. -3. Both ortho-substituted (1 a) and (1 b) reacted with (2) slower than the corresponding meta- and para-substituted (1 a) and (1 b) because of the steric hindrance of the substituents (Table-1) and the rate for ortho-substituted (1 a) except *o*-F-(1 a) also correlated with $\log (K/K_0)$, giving a positive slope which is smaller than that for meta- and

Table-1 The representative second order rate constants, k_2 , for the *N*-carbonylation of (2) by (1) in aqueous solution (pH=p*K*_a) at 20°C.

Amino acid		k_2 (M ⁻¹ + s ⁻¹) at 2°C		
(2)	p <i>K</i> _a ^{a)}	(1 a) (X=H) ^{b)}	(1 b) (X=H) ^{c)}	(1 c) (CN=2) ^{d)}
ε-NH ₂ Cap	10.75	413	81.2	213
Pro	10.60	77	35.1	170
γ-NH ₂ Bu	10.59	355	65.7	211
<i>N</i> -α-Ac Lys	10.53	372	69.7	197
Ala	9.69	32.0	6.57	30.3
Ile	9.68	31.4	6.86	36.3
Glu	9.67	15.7	4.16	20.3
Val	9.62	23.6	5.23	30.0
Thr	9.62	10.0	2.74	16.3
Asp	9.60	8.3	2.58	10.4
Leu	9.60	23.5	6.07	28.0
Gly	9.60	144	22.3	115
Cit	9.41	21.7	4.53	23.3
Met	9.21	15.7	3.56	18.4
His	9.17	15.6	3.00	14.5
Ser	9.15	10.7	2.35	14.1
Gln	9.13	12.5	2.60	14.5
PhA	9.13	9.5	1.97	12.9
Arg	9.04	17.5	3.45	17.7
<i>N</i> -ε-Ac Lys	8.95	10.7	2.24	10.7
Asn	8.80	5.0	1.15	5.4
Gly-Gly	8.17	10.2	1.54	11.7

a) The amino group in (2).

b) *N*-Phenylacetylation of (2).c) *N*-Arylcarbonylation of (2). d) *N*-Acylation of (2).

para-substituted (1 a). The reactivity of ortho-halo (1 a) was in the order of *o*-F > *o*-Cl > *o*-Br (dot lines in **Fig. -3**; A > B means that compound A reacts faster than compound B in this paper), because of its steric hindrance. The similar tendency was observed for the *N*-arylcarbonylation of (2) by (1 b) (**Fig. -3**), and the rate for (1 c) (CN=6) was smaller than that of (1 c) (CN=2) for *N*-acylation, because of the inductive effect of alkyl group in (1 c) (**Fig. -2** and **Table-2**).

The rate for the *N*-arylacetylation was also correlated with Hammett σ value¹¹⁾, *i.e.*, the Hammett plot [plot of log (k_x/k_H) vs. σ , where k_x and k_H are the second order rate constants for the substituted and non-substituted (1 a) and (1 b), respectively] showed good linearity, as shown in **Fig. -4**. The ρ values of *N*-carbonylation of (2) by (1) and the decomposi-

tion of (1) are also summarized in **Table-2**. The ρ values for the *N*-arylacetylation of α -amino acids with a substituent in addition to α -amino group at C₂ position in (2) trend to be higher than those of the other amino acids. However, the opposite tendency was observed for the *N*-arylcarbonylation of (2) by (1 b) (**Table-2**). Furthermore, the ρ value of the *N*-arylacetylation was smaller than that of the corresponding *N*-arylcarbonylation as shown in **Table-2**.

Table-2 also presents that the ρ values for the decomposition of (1 a) and (1 b) are almost constant and independent of pH, and that the value of the former reaction is smaller than that of the latter.

The rate ratio for the *N*-acylation (R_N) of ϵ - and γ -amino acids by (1 c) (CN=2) against (1 c) (CN=6) is smaller than that for α -amino acid, however, the ratio (R_D) is almost invariable with

Fig. -3 Correlation between the second order rate constant and the relative acid strength of substituted benzoic acids for the *N*-arylacetylation of (2) by (1a) and the *N*-arylcabonylation of (2) by (1b) in aqueous solution (pH = p*K*_a) at 20°C. The representative plots of log *k*₂ vs. log (*K*/*K*₀) of ArCO₂OH.

the basicity of solvent (pH) (Table-2).

3.4 Reactivity of *N*-succinimidyl carboxylate (1)

The reaction of (2) with (1) was studied under the same conditions (at pH = p*K*_a in a 0.05 M of buffer and 20°C) and the rates were compared to discover precisely the proposed mechanism involving a nucleophilic attack of free amino group in (2) on the carbonyl carbon atom of (1)^(2),7).

Table-1 demonstrates that the rate for the *N*-carbonylation of ϵ - and γ -amino acids is in order of (1a) > (1c) > (1b) and (1a) $\geq$ (1c) > (1b) for *N*-amino acid. The similar tendency was already reported for the *N*-carbonylation of aliphatic primary amines by (1) in aqueous solution⁷⁾.

3.5 Rate ratios, 10⁻³*k*₂/*k*_a

The rate ratios, 10⁻³*k*₂/*k*_a³, for the *N*-arylacetylation of (2) by (1a) against the decomposition of (1a) in aqueous solution were calculated and the efficiency of (1a) as an *N*-arylacetylation reagent for the reaction of (2)

Fig. -4 The representative Hammett plots [log (*k*_x/*k*_H) vs. σ] for the *N*-arylacetylation and *N*-arylcabonylation of (2) by (1a) and (1b) in aqueous solution (pH = p*K*_a) at 20°C.

in aqueous solution was evaluated. The results were summarized in Table-3. The rate ratios for the *N*-arylacetylation were above unity except some α -amino acids. The similar tendency was observed for the *N*-arylcabonylation and *N*-acetylation as shown in Table-3. The ratios for the *N*-carbonylation of ϵ - and γ -amino acids by (1) were in the order of (1a) (X = H) $\geq$ (1c) (CN = 2) > (1b) (X = H), however, (1c) (CN = 2) $\geq$ (1b) (X = H) > (1b) (X = H) for α -amino acids. The ratios for the *N*-arylcabonylation and *N*-acylation increased with increasing the electron withdrawing nature of the substituent of the aromatic ring in (1b) and the inductive effect of the alkyl group in (1c), although they decreased for the substituent in (1a) (Table-3).

Discussion

4.1 Mechanism

The first-order dependence of the rate on the concentration of (2) for the *N*-arylacetylation of (2) by (1a) suggests a rate-determining step involving an attack of free base (2) (Fig. -1). The positive correlation of the rate with the Hammett σ (Fig. -4) and the nucleophilicity (p*K*_a) of the amino group in (2) (Fig. -3) also suggest a nucleophilic attack.

From these observations, we concluded a mechanism involving a nucleophilic attack of free amino group in (2) on the carbonyl carbon atom in (1c), which is supported by the facts that the

Table-2 Hammett ρ values for the *N*-arylacetylation, *N*-arylcarbonylation and decomposition [(1 a) and (1 b)], and the rate ratios for the *N*-acylation and decomposition of (1 c) in aqueous solution (pH=pK_a) 20°C.

Amino acid (2)	(1 a)		(1 b)		(1 c)	
	$\rho^a)$	$\rho^b)$	$\rho^c)$	$\rho^d)$	R _N ^{e)}	R _D ^{f)}
ϵ -NH ₂ Cap	0.53	0.76	1.34	0.88	1.94	1.64
Pro	0.54	0.74	1.07	0.90	4.07	1.68
γ -NH ₂ Bu	0.55	0.74	1.25	0.90	1.90	1.68
<i>N</i> - α -Ac Lys	0.64	0.73	1.28	0.88	1.79	1.65
Ala	0.72	0.75	1.09	0.89	2.48	1.69
Ile	0.75	0.75	0.85	0.89	2.72	1.69
Glu	0.76	0.75	0.91	0.89	2.90	1.69
Val	0.67	0.78	0.79	0.90	2.78	1.67
Thr	0.72	0.78	0.70	0.90	2.86	1.67
Asp	0.67	0.78	1.05	0.90	3.20	1.67
Leu	0.77	0.78	0.90	0.90	2.70	1.67
Gly	0.58	0.78	1.06	0.90	2.26	1.67
Cit	0.71	0.80	0.92	0.86	2.70	1.65
Met	0.70	0.79	0.85	0.90	2.81	1.68
His	0.72	0.77	1.07	0.97	2.46	1.71
Ser	0.73	0.77	0.84	0.97	2.80	1.71
Gln	0.68	0.77	0.94	0.97	2.80	1.71
PhA	0.77	0.77	0.91	0.97	2.72	1.71
Arg	0.63	0.78	0.89	0.92	2.67	1.74
<i>N</i> - ϵ -Ac Lys	0.69	0.80	0.90	0.94	2.62	1.75
Asn	0.63	0.83	0.90	0.95	2.50	1.78
Gly-Gly	0.51	0.83	0.92	0.90	2.52	1.75

a) *N*-Arylacetylation of (2).

b) Decomposition of (1 a).

c) *N*-Arylcabonylation of (2).

d) Decomposition of (1 b).

e) $R_N = k_2[(1c)(CN=2)]/k_2[(1c)(CN=6)]$ for the *N*-acylation of (2).

f) $R_D = [k_d(1c)(CN=2)]/k_d[(1c)(CN=6)]$ for the decomposition of (1 c).

rate correlated with Hammett σ value for the *N*-arylcarbonylation of (2) by (1 b) (Fig. -4) and that (1 c) (CN=2) reacted faster than (1 c) (CN=6) because of the inductive effect of alkyl group in (1 c) (Fig. -2 and Table-2). The similar

mechanism was also proposed for the *N*-aryl-acetylation of aliphatic primary amines by (1 a) in aqueous solution⁷⁾.

4.2 Reactivity of (2)

As shown in Fig. -2, the rates for the *N*-arylacetylation of α -amino acids with a substituent in addition to α -amino group at C₂ position in (2) were smaller than those of the other amino acids (e.g., ϵ - and γ -amino acids). The similar reactivity was observed for the *N*-arylcarbonylation and *N*-acylation (Fig. -3). In the previous paper, we have already reported that the straight chain and isobutyl amines reacted faster than those of primary amines with a branched alkyl group at C₂ position^{2a), 2d)}. The rate also correlated positively with the log (K/K_d) value. The

Scheme-1 Possible mechanism for the *N*-arylacetylation of (2) by (1 a). A nucleophilic attack of the free amino group in (2) on the carbonyl carbon atom in (1 c) is involved in the rate-determining step.

Table-3 The rate ratios $10^{-3}k_2/k_a$, for the *N*-carbonylation of (2) by (1) in aqueous solution ($\text{pH}=\text{p}K_a$) at 20°C.

Amino acid (2)	(1 a) ^{a)}		(1 b) ^{b)}		(1 c) ^{c)}	
	X=H	X= <i>m</i> -Br	X=H	X= <i>m</i> -Br	CN=2	CN=6
ϵ -NH ₂ Cap	4.0	3.3	1.8	2.8	3.7	3.2
Pro	1.0	0.8	1.1	1.3	3.8	1.6
γ -NH ₂ Bu	4.6	3.8	2.1	2.8	4.7	4.1
<i>N</i> - α -Ac Lys	5.5	5.1	2.5	3.6	5.1	4.7
Ala	2.3	2.2	1.2	1.4	3.7	2.5
Ile	2.1	2.2	1.3	1.2	4.4	2.8
Glu	1.1	1.1	0.8	0.8	2.5	1.4
Val	2.0	1.8	1.1	1.0	4.3	2.6
Thr	0.8	0.8	0.6	0.5	2.3	1.3
Asp	0.7	0.6	0.5	0.6	1.5	0.8
Leu	2.0	2.0	1.3	1.3	4.0	2.5
Gly	12.0	10.0	4.5	5.5	16.2	11.9
Cit	2.5	2.3	1.3	1.4	4.6	2.8
Met	2.6	2.4	1.5	1.5	5.3	3.2
His	2.9	2.7	1.5	1.6	4.3	3.3
Ser	2.0	1.9	1.1	1.0	4.6	2.8
Gln	2.3	2.1	1.3	1.2	4.8	2.9
PhA	1.8	1.8	1.0	0.9	4.3	2.7
Arg	3.9	3.4	2.0	1.9	6.8	4.4
<i>N</i> - ϵ -Ac Lys	2.9	2.7	1.6	1.5	5.1	3.4
Asn	1.8	1.5	1.0	1.0	3.3	2.4
Gly-Gly	11.5	8.6	4.3	4.4	22.5	16.5

a) *N*-Arylacetylation of (2) by (1 a).b) *N*-Arylcarbonylation of (2) by (1 b).c) *N*-Acylation of (2) by (1 c).

similar results were obtained for the *N*-arylcarbonylation (**Fig. -3**).

These facts suggest that both the inductive and the steric (hindrance) effects of (2) predominate the reactivity of (2).

4.3 Substituent effect of (1)

The rates for the *N*-arylacetylation correlated with the σ value and the nucleophilicity ($\text{p}K_a$) of (2) for the *N*-arylacetylation and *N*-arylcarbonylation (**Figs. -2 and 4**). Furthermore, (1 c) (CN=2) reacted faster than (1 c) (CN=6) as shown in **Fig. -2**. The rates for meta- and para-substituted (1 a) were larger than that of ortho-substituted (1 c) (**Fig. -3**). The similar reactivity was observed for the *N*-arylcarbonylation as shown in **Fig. -3**.

The Hammett ρ values for the *N*-arylacetylation were smaller than those of the *N*-arylcarbonylation

(**Table-2**). It was reported that the ρ value of the dissociation constant of substituted phenylacetic acid was smaller than that of substituted benzoic acid because the inductive effect of the substituent was weakened by intercepting of the bond between *N*-succinimidyl and aryl groups with the methylene group in (1 a)¹²⁾. This is the case.

The above facts suggest that the rate is predominated by both the electron-deficiency of carbonyl carbon in (1) and the steric effect of the aromatic ring in (1) for the *N*-carbonylation of (2) by (1).

4.4 Reactivity of (1)

As shown in **Table-1**, the reactivity of (1) for the *N*-carbonylation of ϵ - and γ -amino acids is in order of (1 a) (X=H) $\geq$ (1 c) (CN=2) $>$ (1 b) (X=H). The similar tendency has been already

reported for the *N*-carbonylation of aliphatic primary amines by (1)⁷⁾. However, the order was (1c) (CN=2) $\geq$ (1a) (X=H) > (1b) (X=H) for α -amino acids. The reactivity of (1a) (X=H) $\geq$ (1c) (CN=2) could be explained by the inductive effect of the aromatic ring in (1a). But it seems strange that (1c) reacted faster than (1b), based on the electronic effect of the aromatic and alkyl group of these compounds. In the previous paper⁷⁾, we proposed the following sterical models for the *N*-carbonylation of aliphatic primary amines by (1) as shown below and reported that the reactivity of (1c) > (1b) could be explained by them. This is the case.

Scheme-2 Proposed structures of the transition states for the *N*-carbonylation of (2) by (1)⁷⁾.

4.5 Rate ratio

As shown in **Table-3**, the rate ratios, $10^{-3} k_2/k_d$, for the *N*-arylacetylation exceeded unity except some amino acids. These observations suggest that (1a) could be used for the modification reagents of amino groups (ϵ -amino groups of Lys residues and α -amino group of *N*-terminal) in proteins. The similar results are observed for the *N*-arylcabonylation and *N*-acylation (**Table-3**).

The ratios for the *N*-carbonylation of ϵ - and γ -amino acids by (1) were in the order of (1a) (X=H) $\geq$ (1c) (CN=2) > (1b) (X=H), however, (1c) (CN=2) $\geq$ (1a) (X=H) > (1b) (X=H) for α -amino acids. The ratios for the *N*-arylcarbonylation and *N*-acylation increased with increasing the electron withdrawing ability of Z in (1), although they decreased with the strength of electron withdrawing power of the substituent in (1) (**Table-3**). These facts suggest that the ratios are predominated by both inductive and steric effects of the substituents in (1) and (2).

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スクシンイミドエステルの化学(第16報) 水溶液中における *N*-スクシンイミジルアリー ルアセテートによるアミノ酸の *N*-アリー ルアセチル化反応の速度論的研究

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N-スクシンイミジルアリールアセテート(1a)とアミノ酸(2)から相当する *N*-アリールアセチルアミノ酸を生成する *N*-アリールアセチル化反応を水溶液中[pH=(2)のアミノ基の pK_a], 20°C で速度論的に検討した。反応は(1a)の分解反応と競争的であり, 速度は $V=(k_d+k_2[2])[1a]$ で表すことができた。ここで, k_d 及び k_2 は分解反応及び *N*-アリールアセチル

化反応の速度定数を示す。

N-アリールアセチル化の二次速度定数, k_2 , は(2)のアミノ基の求核性(pK_a)と良好な正の相関性を示し, $\log k_2$ vs. pK_a のプロットの傾きは0.7~0.8であった。オルト置換(1a)による反応の速度は, 立体障害のためメタ及びパラ置換(1a)の場合よりも遅かった。メタ及びパラ置換(1a)の二次速度定数は Hammett の σ 値と良好な正の相関性を示し, その ρ 値は0.53~0.77であった。種々の検討から, *N*-アリールカルボニル化の速度は(1a)及び(2)の誘起効果及び立体障害に支配されることが分かった。速度比, $10^{-3}k_2/k_d$, は若干のアミノ酸を除いて1.0よりも大きかった。また, より詳しい反応の遷移状態を知るため, (1a)と *N*-スクシンイミジルベンゾエート(1b)及び *N*-アシロキスクシンイミド(1c)との反応性の比較を行った。

以上の結果から, 反応は求核的に起こることが分かり, その詳細について考察を行った。

国際油脂情報

[Cocomunity 15 July, 1989 吉富和彦]

★APCC 専務理事席から

“Cocomunity”は Community よりも2年若いだけだ。1971年に初めて発行されて以来18年間, 月に2度滞りなく刊行されてきた。初刊においてその目的を次のように概説した。

Cocomunity はアジアのココナッツ産業を構成する団体間の密接な協調の役目を果たすことを意図する。Asian Coconut Community を設立するための政府の調印や批准は十分でない。ココナッツの栽培業者, 処理(製油)業者, 商人や研究開発関係者等がともに組織に参加し, 協調のきづなを強固にする必要がある。

この目的を果たすために Cocomunity はその範囲, 形式と内容を拡大してきた。今日, そのサービス範囲はアジアに限らない。アジア太平洋地域のココナッツ産業に中心を置きながら, その情報網を本地域外の国々まで広げている。このことは, ココナッツ産業に関心を持つ人たちの協調精神を全世界にもたらすのに役立ってきた。

本誌は生産者と消費者を含めほぼ40ヵ国に配布されている。上記のほか国際的な機関, ココナッツ製品を取り扱っている多国籍企業, 政策, 企画部門担当者からも求められている。顧客は増えている。彼等は産業の断面を構成しその関心は変化している。

Cocomunity は独占的にココナッツに関連する唯一の国際的な刊行誌である。従って大きい責任を持っており, またそれを認識している。われわれは中国の諺の“天の彼方に天あり, そしてその天の彼方にはもうひとつの天がある”を信じる。われわれは始めの天にすらまだ到達していない。

このことは読者が何を欲するかを知りたい理由である。読者は何を望まず, どんな分野をさらに望んでいるか, それをわれわれは知りたい。

★アメリカのブッシュ大統領, 反熱帯産油キャンペーン不支持

地方新聞によれば, アメリカのブッシュ大統領はアメリカ大豆協会の反熱帯産油キャンペーンを支持せず, また科学的根拠のないいかなる表示も支持しないという。アメリカ大豆協会はアメリカ国内で販売される熱帯産油について表示を必要とする立法をキャンペーンしてきた。

★ココナッツ情報に関するワークショップ

ココナッツ集積情報システムに関する APCC/IDRC ワークショップがインドネシアのジャカルタにおいて1989年8月14~16日に開催される。会場はカルチカ・プラザ・ホテルである。本ワークショップは事務局とメンバー国を包括する協力計画によって, ココナッツ産業に関する情報の流れを強化することにその狙いがある。メンバー国は農民, 処理業者や商人等に情報を伝えて彼等の計画が進展することを期待している。