Reactivity of Aromatic *o*-Hydroxy Oximes. I. Synthesis and Aminolysis of Acylglycine Esters of Aromatic *o*-Hydroxy Oximes

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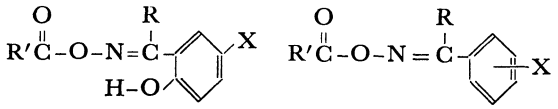
Active esters (**1**) of glycine with *o*-hydroxybenzaldehyde oxime, *o*-hydroxyacetophenone oxime, *o*-hydroxybenzophenone oxime, and their 5-Cl and 5-NO_2 derivatives were prepared by several methods. For aminolysis with benzylamine, esters **1** show higher reactivity than similar esters containing no hydroxyl group in the ortho position. It is suggested that esters **1** forms an intramolecular hydrogen bond between the hydrogen of the hydroxyl group at the ortho position and the hydroxyimino nitrogen so as to have its carbonyl group activated for the aminolysis; this mechanism of activation seems to be a sort of "intramolecular acid-catalysis." Among the series of esters **1**, esters of *o*-hydroxybenzaldehyde oxime and its 5-Cl and 5-NO_2 derivatives are most reactive in the aminolysis. The reactivity of esters **1** is also discussed in relation to pK_a values of aromatic *o*-hydroxy oximes.

In the coupling reaction of acylamino acid with amino acid alkyl esters, various oximes are used as their alcoholic components.[1-7] As compared with esters of *p*-nitrophenol, pentachlorophenol, and *N*-hydroxysuccinimide, even the most active esters of these oximes show rather a low reactivity for the condensation with amino component.

Losse *et al.*[2] reported that esters of *m*-nitroacetophenone oxime react faster with amino acid alkyl esters than those of acetophenone oxime. But the reactivity of the former is still lower than that of *p*-nitrophenol ester for the aminolysis. Itoh[4] showed that oximes of type $HO-N=C\langle^{CN}_{COR}$ (R=OEt, NH_2) are effective in peptide synthesis.

A general consideration drawn from all the above cases is that an ester is activated by introduction of an electron-withdrawing substituent to its alcoholic component. According to this general consideration, it should be expected that introduction of electron-withdrawing substituent X such as NO_2 or CN to an alcoholic component (oximes **3**) is to increase the reactivity, whereas X=OH or OR is to have a deactivating effect.



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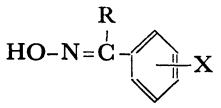

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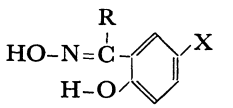

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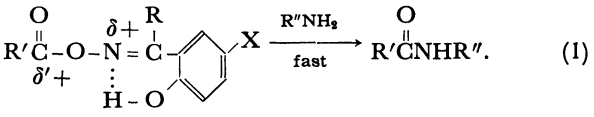
When oximes containing hydroxyl group at the ortho position in a benzene nucleus were used as active esters, we found that reactions with benzylamine were accelerated greatly. This unexpected result let us to conclude that the activation of **1** was a consequence of hydrogen bond formation between the phenolic hydrogen atom and the spacially adjacent unshared electron pair of the nitrogen atom in the hydroxyimino group. Such interaction induces the electron density at the nitrogen atom to decrease so that esters **1** may show a high reactivity:



(1)

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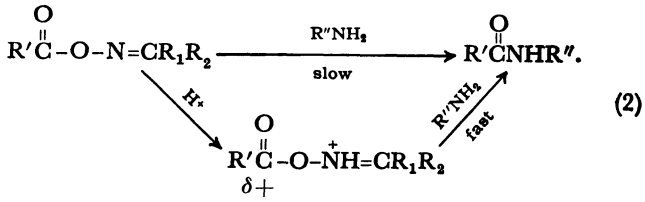
It is known that addition[5-8] of a weak acid (acetic or formic acid) as catalyst to oxime esters will cause rapid and smooth condensation:



(2)

The mechanism of activation for our system corresponds to the presence of weak acids.

From the consideration descrived above, we prepared esters **1** from *N*-(benzyloxycarbonyl)glycine (Z-Gly) and various oximes of *o*-hydroxybenzaldehyde, *o*-hydroxyacetophenone, *o*-hydroxybenzophenone, and their 5-Cl and 5-NO_2 derivatives, and measured rates of aminolysis with benzylamine in order to compare reactivities of esters **1** and **2**.

We also discuss the reactivity of aminolysis of **1** in connection with pK_a values of aromatic *o*-hydroxy oximes **4**.

Results and Discussion

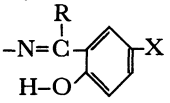
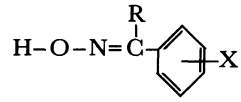
All aromatic *o*-hydroxy oximes **4** were of (*E*) configuration and are summarized in Table 1 together with oximes **3**.

Acylated Position of Aromatic o-*Hydroxy Oximes* **4**.
There are many papers on the aminolysis of oxime esters of acylamino acid. But there is no study on the reaction of esters of oxime **4** except for a report of Przybylski and Miecznikowska[19] on a coupling method using dicyclohexylcarbodiimide (DCC) and *o*-hydroxybenzladehyde oxime as an "Eintopf" procedure. It is of interest which position is esterified by acylamino acid, phenolic hydroxyl, or hydroxyimino group in the case of **4** with a bifunctional nature. There have been many reports[9,10,13,20-24] on the acetylation of these oximes.

Table 1. Yields and properties of oximes[a)]

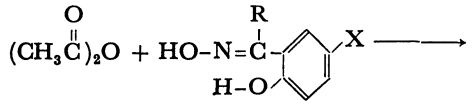
Oxime of	Abbreviation (HOX)[b)]	Yield %	TLC R_f	Mp θ_m/°C Observd	Mp θ_m/°C Lit
o-Hydroxybenzaldehyde	HOHBA	84.8	0.60[c)]	55—56	57[16)]
o-Hydroxyacetophenone	HOHAP	95.0	0.68[c)]	112—114	112—112.5[16)]
o-Hydroxybenzophenone	HOHBP	62.0	0.77[d)]	139—140	142—143[15)]
5-Chloro-2-hydroxybenzaldehyde	HOHBA-5Cl	76.1	0.79[e)]	123—124	123—124[16)]
2-Hydroxy-5-nitrobenzaldehyde	HOHBA-5NO_2	83.4	0.58[e)]	212—214	220[16)]
5-Chloro-2-hydroxyacetophenone	HOHAP-5Cl	72.4	0.88[f)]	174—178	180[17)]
2-Hydroxy-5-nitroacetophenone	HOHAP-5NO_2	62.4	0.73[f)]	225—226	231[30)]
5-Chloro-2-hydroxybenzophenone	HOHBP-5Cl	77.6	0.79[d)]	139—141	144—144.5[22)]
2-Hydroxy-5-nitrobenzophenone	HOHBP-5NO_2	64.4	0.78[d)]	193—196	
p-Chlorobenzaldehyde	HOBA-pCl	73.2	0.64[c)]	100—102	106—107[16)]
m-Nitrobenzaldehyde	HOBA-mNO_2	61.9	0.58[c)]	118—120	121—123[16)]
p-Chloroacetophenone	HOAP-pCl	74.4	0.67[c)]	95—96	97[16)]
m-Nitroacetophenone	HOAP-mNO_2	57.3	0.58[g)]	130—131	133—134[16)]
Benzaldehyde	HOBA	88.7	0.84[d)]	119—120[h)]	118—119[h,16)]
Acetophenone	HOAP	87.7	0.75[d)]	56—59	59[16)]
Benzophenone	HOBP	98.1	0.78[d)]	139—140	143[16)]

a) All oximes prepared are of (*E*) configuration and were characterized by elemental analysis.

b) HOX:  or 

c) R_{f9}. d) R_{f8}. e) R_{f4}. f) R_{f5}. g) R_{f2}. h) Bp, °C (mmHg, 1 mmHg=133.322 Pa).

In the reaction of aromatic o-hydroxy oximes **4** with acetic anhydride under mild conditions, compounds **5** are usually obtained:



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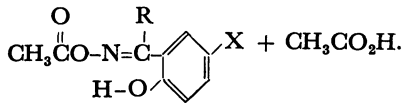

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We tried to condense oximes **4** with acetic acid by a direct condensation using DCC and obtained the same products as in the reaction with acetic anhydride.

Esters **1** and **2** of Z–Gly with oximes **4** and **3** have been prepared (A) by direct condensation using DCC, (B) with carbonic carboxylic anhydride, or (C) with acid chloride. Representatives of them are summarized in Table 2.

Rate of Aminolysis. Effect on o-*Hydroxyl Group*: To compare reactivities of esters **1** and **2**, we measured their rates of aminolysis with benzylamine in THF at 30 °C. The results are shown in Fig. 1.

All aromatic o-hydroxy oxime esters **1** have a higher reactivity than oxime esters **2** containing no o-hydroxyl group. It is demonstrated that the existence of o-hydroxyl group greatly accelerates the rate of aminolysis.

We concluded that the activation of **1** is caused by hydrogen bond formation[9–13,25)] between the phenolic hydrogen atom and the spacially adjacent lone-pair electrons of the nitrogen atom in hydroxyimino group, and that the electron-withdrawing nature of aromatic

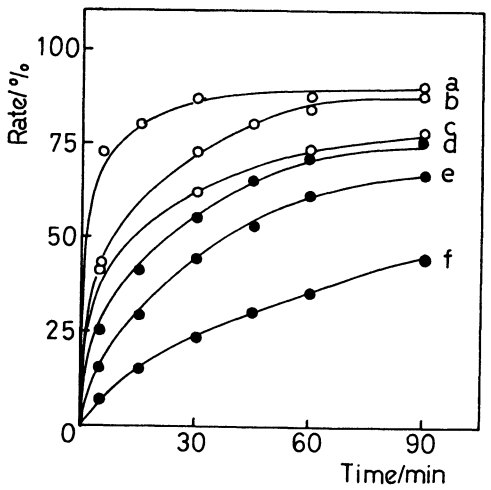
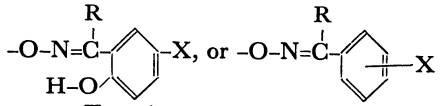


Fig. 1. Aminolysis rates of Z-Gly-OY[a)] with benzylamine. Effect on o-hydroxyl group in an alcoholic component.
a: Z-Gly-OHBA, b: Z-Gly-OHBP, c: Z-Gly-OHAP, d: Z-Gly-OBA, e: Z-Gly-OBP, f: Z-Gly-OAP.
a) -OY denotes an oxime residue such as



Type 1 Type 2

—○—: type 1, —●—: type 2. These abbreviations are used in Figs. 2 and 3.

o-hydroxy oximes is increased as a result of decrease in the electron density at the hydroxyimino nitrogen atom (see Eq. 1). A nonbonding interaction between the phenolic hydrogen atom and the lone-pair electrons on the hydroxyimino nitrogen would be favored by their

TABLE 2. OXIME ESTERS OF *N*-(BENZYLOXYCARBONYL) GLYCINE

Ester	Method	Yiled %	Mp θ_m/°C	Found (Calcd) (%) C	H	N
Z-Gly-OHBA	(A)	72.1	108—111	62.05 (62.19)	5.02 (4.91)	8.53 (8.53)
Z-Gly-OHBA	(B)	45.7	108—110	61.76 (62.19)	4.90 (4.91)	8.34 (8.53)
Z-Gly-OHAP	(A)	78.9	113—115	63.25 (63.15)	5.22 (5.33)	8.29 (8.18)
Z-Gly-OHAP	(B)	55.0	109—110	63.33 (63.15)	5.30 (5.33)	8.34 (8.18)
Z-Gly-OHBP	(A)	66.5	117—119	68.33 (68.31)	4.99 (4.98)	6.97 (6.93)
Z-Gly-OHBA-5Cl	(A)	78.5	129—133	56.04 (56.29)	4.15 (4.17)	7.54 (7.72)
Z-Gly-OHBA-5NO_2	(A)	30.2	133—137	54.76 (54.69)	4.04 (4.05)	11.05 (11.26)
Z-Gly-OHAP-5Cl	(A)	54.2	123—125	57.52 (57.38)	4.58 (4.55)	7.37 (7.43)
Z-Gly-OHAP-5NO_2	(A)	87.0	125—128	56.16 (55.82)	4.56 (4.42)	10.87 (10.85)
Z-Gly-OHBP-5Cl	(A)	49.2	121—123	62.95 (62.95)	4.36 (4.36)	6.39 (6.38)
Z-Gly-OHBP-5NO_2	(A)	66.3	157—159	61.64 (61.47)	4.52 (4.26)	9.39 (9.35)
Z-Gly-OBA	(C)	36.0	100—102	65.04 (65.38)	5.19 (5.16)	9.09 (8.97)
Z-Gly-OAP	(A)	75.4	71[a]	66.50 (66.25)	5.90 (5.56)	8.86 (8.58)
Z-Gly-OBP	(C)	82.9	65[b]	71.25 (71.21)	5.15 (5.19)	7.31 (7.21)
Z-Gly-OBA-*p*Cl	(B)	30.3	123—124	58.94 (58.88)	4.30 (4.36)	8.12 (8.08)
Z-Gly-OBA-*m*NO_2	(A)	52.8	132—133[c]	57.18 (57.14)	4.22 (4.23)	11.76 (11.76)
Z-Gly-OAP-*p*Cl	(B)	41.9	104—105	59.87 (59.92)	4.69 (4.75)	7.74 (7.76)
Z-Gly-OAP-*m*NO_2	(A)	56.4	76—78[d]	58.22 (58.22)	4.64 (4.61)	11.23 (11.32)

a) Lit:[1] mp 95.5—97 °C. b) Lit:[1] mp 78—79 °C. c) Lit:[1] mp 126.5—128 °C. d) Lit:[1] mp 79—80 °C.

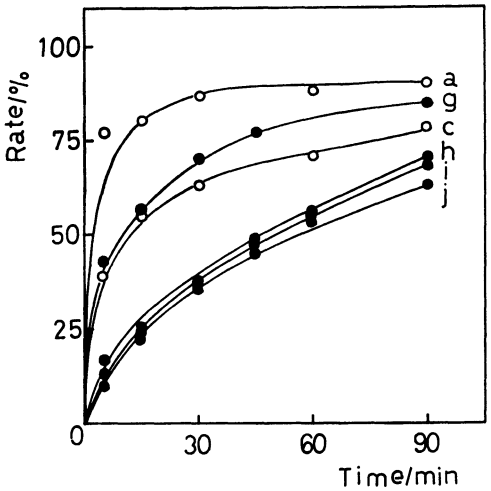


Fig. 2. Aminolysis rates of Z–Gly–OY with benzylamine. Comparison between effect on *o*-hydroxyl group and that due to an electron-withdrawing substituent X of oximes **3**.
a and c: See, Fig. 1, g: Z–Gly–OBA–*m*NO_2, h: Z–Gly–OBA–*p*Cl, i: Z–Gly–OAP–*m*NO_2, j: Z–Gly–OAP–*p*Cl.

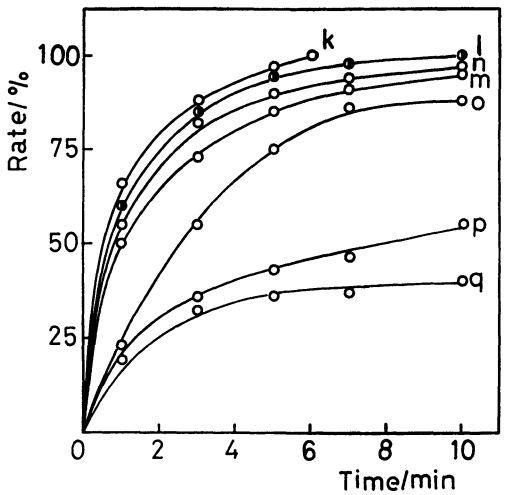


Fig. 3. Aminolysis rates of Z–Gly–OY with benzylamine. Effect on substituent X in aromatic *o*-hydroxy oximes **4**.
k: Z–Gly–OHBA–5NO_2, l: Z–Gly–ONp[a], m: Z–Gly–OHBP–5NO_2, n: Z–Gly–OHBA–5Cl, o: Z–Gly–OHAP–5NO_2, p: Z–Gly–OHBP–5Cl, q: Z–Gly–OHAP–5Cl.
a) –ONp=*p*-nitrophenol residue. —◑—: **1**.

proximity, in which **1** assumes an (*E*) configuration. Therefore, the aminolysis of **1** proceeds faster than those of **2**.

Although a considerable number of acylamino acid active esters have been prepared since the first application of *p*-nitrophenyl ester to peptide synthesis, the new method of activation adopted in this study has not so far been presented. Typical active esters comprise electron-withdrawing groups. The reason for the high reactivity of esters **1** in spite of the existence of the electron-donating hydroxyl group, is that the particular configuration of oximes **4** favors hydrogen bond formation so as to activate **1** *via* the mechanism of "intramolecular acid-catalysis."

As shown in Fig. 1, the reactivity of oxime esters having different substituents R decreases in the order;

$$H > C_6H_5 > CH_3. \quad (3)$$

The effect of phenyl group on the reactivity is less than that of hydrogen. Both the phenyl groups in this molecule can not be coplanar owing to the bulkiness of substituent $R=C_6H_5$. This noncoplanarity[10,12] of aromatic rings for HOHBP and its 5-Cl and 5-NO_2 derivatives (all abbreviations shown in Table 1) results in two "mutually independent" conjugate systems, with reduction in the electron-withdrawing effect of the phenyl substituent.

Comparison between the Effects of o*-Hydroxyl Group and of Electron-withdrawing Substituents X for Oximes 3*: Amino-

lysis rates for various substituents (X=Cl and NO_2) are shown in Fig. 2.

Z-Gly-OHBA and Z-Gly-OHAP have higher reactivity than the series of oxime esters **2**:

$$\text{Z-Gly-OHBA} > \text{Z-Gly-OBA-}m\text{NO}_2 > \text{Z-Gly-OBA-}p\text{Cl}, \quad (4)$$

$$\text{Z-Gly-OHAP} > \text{Z-Gly-OAP-}m\text{NO}_2 > \text{Z-Gly-OAP-}p\text{Cl}. \quad (5)$$

It is found that the introduction of hydroxyl group to the ortho position of aromatic oximes is superior in activating effect to the substitution of NO_2, and much more to that of Cl. It is worthwhile to point out that the activation of nonbonding interaction owing to hydrogen bonding (and thus "intramolecular acid-catalysis") is more effective than the activation through a conjugate system provided by the electron-withdrawing group such as NO_2.

Effect of Substituent X in Aromatic o-Hydroxy Oximes **4**: The effect of substituent X on the aminolysis rate is illustrated in Fig. 3, including Z-Gly-ONp for comparison. The reactivities of the active esters from HOHBA-5NO_2, HOHBA-5Cl, or HOHBP-5NO_2 are nearly equal to that of *p*-nitrophenol.

The order of reactivity is

$$NO_2 > Cl > H. \quad (6)$$

Typical examples may be provided with esters of HOHBA and its 5-NO_2 and 5-Cl derivatives. Although no series of HOHAP and HOHBP are shown in Fig. 3, the same tendency can be found to exist from a comparison with Fig. 1. This result may be understood in terms of the inductive effect that the substitution of NO_2 or Cl at the 5-position to the hydroxyimino group in an aromatic nucleus will reduce strongly the electron density on the phenolic oxygen in combination with the hydrogen bond favorable to the *o*-hydroxyl group. Therefore, the ease of the protonation of the hydroxyl group to the nitrogen atom of the hydroxyimino group increases extremely.

Relation between pK_a *values of Oximes* **3** *and* **4** *and the Reactivity for the Aminolysis of Their Active Esters.* The pK_a values of the oximes prepared are listed in Table 3.

Aromatic *o*-hydroxy oximes **4** exhibit stronger acidity than the corresponding oximes **3** containing no *o*-hydroxyl groups. Regardless of the character of R, the order of pK_a values with respect to X in **4** is

$$NO_2 < Cl < H. \quad (7)$$

The order of pK_a values with respect to R is

$$H < C_6H_5 < CH_3. \quad (8)$$

It is demonstrated that the reactivity order for the aminolysis of esters **1** is parallel to the order of pK_a values of corresponding oximes **4**.

It is well known that only the phenolic proton in **4** dissociates.[9,11,12] Therefore, the proton transfer to the hydroxyimino nitrogen has enhanced the acidity as a result of an intramolecular hydrogen bond formation between the phenolic proton and the hydroxyimino nitrogen.

When pK_a values are subject to a detailed check, no good relations are always found for **4** having X=Cl or H between the order of rate of aminolysis and that of pK_a values given by relation 8.

Patel and Patel[11] reported that the electronegative substituent Cl will reduce the electron density of HOHBP-5Cl and thus facilitate the dissociation of phenolic proton. But they[11] also postulated that the Cl would act also as a p-π donor. The irregularity found in pK_a values may be explained on their conclusion and postulate.

Experimental

All melting points were uncorrected. IR spectra were recorded on a JASCO A-102 spectrophotometer. The homogeneity of substances and the purity of isomers were checked by TLC using silica gel (Kiesel Gel 60 F254, Merck) and various developing solvent systems: R_{f2}, $CHCl_3$–MeOH–AcOH (95 : 5 : 3); R_{f4}, $CHCl_3$–MeOH–benzene (95 : 5 : 3); R_{f5}, $CHCl_3$–MeOH–ethyl acetate (95 : 5 : 3); R_{f6}, $CHCl_3$–MeOH–petroleum ether (95 : 5 : 3); R_{f8}, $CHCl_3$–MeOH–petroleum ether (95 : 3 : 3); R_{f9}, $CHCl_3$–MeOH–AcOH (95 : 2 : 3); R_{f13}, $CHCl_3$–MeOH (100 : 1). R_f spots were made visible with iodine vapor or UV light for all oximes and demonstrated by the combination of hydrobromic acid and 0.2% ninhydrin in acetone for Z-Gly derivatives.

Starting Materials. HOBA,[16] HOAP,[16] HOBP,[16] HOAP-*p*Cl,[16] HOBA-*p*Cl,[16] HOBA-*m*NO_2,[16] and HOHBA[16] were prepared in aqueous EtOH by the reaction of corresponding aldehydes or ketones with hydroxylamine hydrochloride and sodium carbonate (or sodium acetate) according to the usual method.[14] Aromatic *o*-hydroxy ketones, *o*-hydroxyacetophenone,[26] 5-chloro-2-hydroxyacetophenone,[26] *o*-hydroxybenzophenone,[27] and 5-chloro-2-hydroxybenzophenone[28] were prepared by Fries rearrangement of the corresponding phenyl esters in the presence of anhydrous aluminium chloride

Table 3. pK_a values of oximes **3** and **4**

Oxime (R=H)	pK_a	Oxime (R=C_6H_5)	pK_a	Oxime (R=CH_3)	pK_a
HOHBA	9.3	HOHBP	9.3	HOHAP	9.2
HOHBA-5Cl	8.8	HOHBP-5Cl	9.0	HOHAP-5Cl	8.8
HOHBA-5NO_2	6.7	HOHBP-5NO_2	7.3	HOHAP-5NO_2	7.4
HOBA	10.9	HOBP	11.8	HOAP	12.0
HOBA-*p*Cl	10.1			HOAP-*p*Cl	10.3
HOBA-*m*NO_2	10.1			HOAP-*m*NO_2	10.1
HONp[a]					

a) HONp : *p*-Nitrophenol.

and then their oximes were prepared according to the usual method,[14] except for HOHBP and its derivatives which were prepared as described below. 2-Hydroxy-5-nitrobenzaldehyde[29] and 2-hydroxy-5-nitroacetophenone[30] were prepared by nitration from corresponding parent compounds and their oximes were obtained according to the usual method.[14]

HOHBP: Both isomers were prepared by the method of Kohler and Bruce.[15] We obtained products of mp 139—140 °C for (*E*) and 132—133 °C for (*Z*) isomer. The mp values of the (*E*) and (*Z*) isomers of HOHBP prepared here did not agree with those given by Kohler and Bruce,[15] who reported 142—143 °C for the (*E*) and 141—142 °C for the (*Z*) isomer. We separated a mixture of (*E*) and (*Z*) isomers prepared by the usual method.[14] TLC values were as follows: $R_{f13}=0.54$ for the (*E*), 0.22 for the (*Z*), and 0.54+0.22 for the mixture. These values are identical with those obtained by the method of Kohler and Bruce. The magnitude of R_f values for the (*E*) isomer was greater than that of the (*Z*) isomer. The same tendency was also observed by Ashbrook.[32] We used the (*E*) isomer in this study.

HOHBP-5Cl: This compound was also prepared essentially as described above: mp 139—141 °C (Lit,[18] 144—144.5 °C).

HOHBP-5NO$_2$: To a suspension of 2-chloro-5-nitrobenzoic acid (50.0 g, 0.248 mol) in benzene (250 ml), phosphorus pentachloride (51.6 g, 0.248 mol) was added at room temperature with stirring. The mixture was then refluxed for 3 h. After the evolution of HCl had ceased, the excess of solvent was evaporated, leaving a viscous oil. 2-Chloro-5-nitrobenzoyl chloride was obtained from the oil: 154—155 °C (7.5 mmHg) 50.8 g (93.1%).

The acid chloride (52.9 g, 0.24 mol) was dissolved in dry benzene (300 ml) and then anhydrous aluminium chloride (48.1 g, 0.36 mol) was added. After refluxing for 1 h the mixture was cooled and poured into a mixture of cracked ice (500 ml) and concd HCl (180 ml), then the benzene layer was separated and the aqueous layer was extracted twice with benzene (200 ml). The benzene solution was washed twice with 2 mol dm^{-3} NaOH and water, and dried over magnesium sulfate. The solvent was removed by distillation, and a recrystallization of the resulting solid from EtOH gave 2-chloro-5-nitrobenzophenone: 53.7 g (85.4%), mp 83—85 °C.

Found: C, 59.70; H, 3.07; N, 5.38%. Calcd for $C_{13}H_8NO_3Cl$: C, 59.67; H, 3.08; N, 5.35%.

A mixture of 2-chloro-5-nitrobenzophenone (30.0 g, 0.115 mol), water (300 ml), and KOH (9.70 g, 0.128 mol) was charged in an autoclave. After heating at 150—160 °C with stirring for 5 h, the clear solution was cooled and then strongly acidified by adding concd HCl. The resulting solid was filtered off and washed with water. A recrystallization of the solid from EtOH gave 2-hydroxy-5-nitrobenzophenone: 15.7 g (56.1%), mp 122—123 °C (lit,[31] 124—124.5 °C).

HOHBP-5NO$_2$ was prepared essentially as described by Kohler and Bruce[15] (and, in part, Blatt and Russell[9]) for HOHBP. 2-Hydroxy-5-nitrozophenone (25.0 g, 0.103 mol) was added to 40% KOH (150 ml). To this mixture was added hydroxylamine hydrochloride (50.0 g, 0.72 mol) at room temperature with stirring. After 5 h the solution was acidified with concd HCl and the precipitated pale yellow solid was collected and washed successively with water and with a small amount of 50% MeOH. Recrystallization of the solid from benzene and a small amount of petroleum ether gave the product: 17.1 g (64.4%), mp 193—196 °C, $R_{f8}=0.78$.

Found: C, 60.38; H, 3.85; N, 10.76%. Calcd for $C_{13}H_{10}N_2O_4$: C, 60.47; H, 3.90; N, 10.85%.

Preparation of Active Esters 1 and 2. Typical example are as follows.

Method (A) Z-Gly-OHAP-5NO$_2$: Z-Gly (9.40 g, 44.9 mmol) and HOHAP-5NO$_2$ (8.80 g, 44.9 mmol) were dissolved in DMF (100 ml) and DCC (9.70 g, 47.1 mmol) was added to the solution below 0 °C with stirring. After a night the *N,N'*-dicyclohexylurea was filtered off and ethyl acetate and water were added to the filtrate. The organic layer was separated, washed with water, and dried. Evaporation of the dried solution gave a solid. This material was recrystallized from ethyl acetate–petroleum ether to give 15.1 g (87.0%), mp 125—128 °C, $R_{f6}=0.87$.

Found: C, 56.15; H, 4.56: N, 10.87%. Calcd for $C_{15}H_{17}N_3O_7$: C, 55.82; H, 4.42: N, 10.85%.

Method (B) Z-Gly-OHAP: To a solution of Z-Gly (4.18 g, 20 mmol) and triethylamine (2.8 ml, 20 mmol) in dioxane (50 ml) below −10 °C was added dropwise (over a period of 1 min) isobutyl chloroformate (2.73 g, 20 mmol) with stirring. After 5 min, HOHAP (3.02 g, 20 mmol) in dioxane (20 ml) was added. After 1 h the mixture was brought to room temperature and stirred overnight. Ethyl acetate (200 ml) and water (200 ml) was added to the mixture. The organic layer was separated, and the solution was washed with 1 mol dm^{-3} NaHCO$_3$ and water, and dried. The solvent was evaporated and the crude solid was recrystallized from ethyl acetate–petroleum ether: 3.75 g (55.0%); mp 109—110 °C; $R_{f9}=0.70$.

Found: C, 62.05; H, 5.02; N, 8.53%. Calcd for $C_{17}H_{16}N_2O_5$: C, 62.19; H, 4.91; N, 8.53%. The same material was also prepared from (Z-Gly)$_2$O and HOHAP.

Method (C) Z-Gly-OBA: To a solution of Z-Gly-Cl[33] (11.38 g, 50 mmol) in THF (120 ml) below −10 °C was added dropwise over a period of 10 min a solution of HOBA (6.06g, 50 mmol) in THF (50 ml) and triethylamine (7.0 ml, 50 mmol) with stirring. After being kept for 10 min below −10 °C, the mixture was allowed to stand overnight and then was worked up as in Method (B): 15.6 g (36.0%); mp 100—102 °C; $R_{f5}=0.76$.

Found: C, 65.04; H, 5.19: N, 9.09%. Calcd for $C_{17}H_{16}N_2O_4$: C, 65.38; H, 5.16; N, 8.97%.

Determination of the Rate of Aminolysis. In to a 50 ml volumetric flask was put a solution containing 2.0 mmol of an appropriate derivative in distilled THF. To the solution having been heated and thermostated (20±0.1 °C) was added a thermostated solution of 4.0 mmol of benzylamine in distilled THF (50 ml). At predetermined time intervals, a 10 ml aliquot of the solution was withdrawn and diluted with 40 ml of distilled water. The excess of benzylamine was back-titrated with 0.1 mol dm^{-3} HCl with Bromocresol Green solution as the indicator.[1] Blank tests showed that any presence of free oxime did not influence the accuracy of titration. Each point in Figs. 1—3 represents a mean of three to six values.

The Acetyl Derivative of HOHBA. This compound was obtained by treating the oxime with (a) an excess of acetic anhydride (Ac$_2$O) or (b) DCC. *(a)*: Ac$_2$O (75 ml) was added to the oxime. The mixture was warmed for 30 min. The solid acetyl derivative formed by stirring with an excess of cold water was collected and washed with water. Pale pink crystals (10.25 g, 57.2%) were obtained by crystallization from benzene–petroleum ether: mp 69—71 °C (lit,[20] 69 °C).

Found: C, 60.33; H, 5.11; N, 7.94%. Calcd for $C_9H_9NO_3$: C, 60.33; H, 5.06; N, 7.82%.

(b): AcOH (6.01 g, 100 mmol) and HOHBA (6.86 g, 50 mmol) were dissolved in THF (80 ml) and DCC (11.3 g, 55 mmol) was added to the solution below 0 °C with stirring. The mixture was stirred for 24 h. *N,N'*-Dicyclohexylurea was filtered off and the filtrate was diluted with ethyl acetate (200 ml) and water (200 ml). The organic layer was separated and treated as in Method (B). Recrystallization of the

residue from benzene–petroleum ether gave the acetyl ester: 5.06 g (53.8%); mp 69 °C.

Found: C, 60.38; H, 5.18; N, 7.88%. Calcd for $C_9H_9NO_3$: C, 60.33; H, 5.06; N, 7.82%.

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