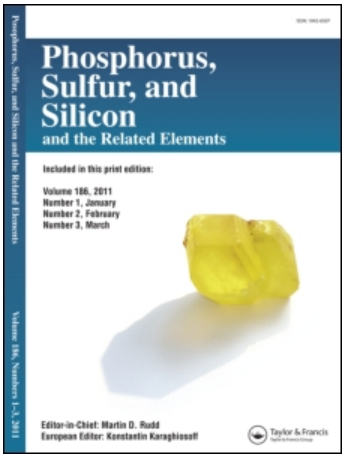

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Hui-Ying Li[a]; Ru-Yu Chen[a]; Kang-Tai Ren[a]
[a] Institute of Elemento-Organic Chemistry Nankai University, Tianjin, China

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HYDROLYSIS OF N-(METHOXYCARBONYL-OR ISOPROPYLCARBAMOYL-METHOXYPHOSPHONYL)-α-AMINO ACID ESTERS

HUI-YING LI*, RU-YU CHEN and KANG-TAI REN

Institute of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, China

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The hydrolysis of the title compounds was studied in order to investigate the possibility of their usage as drugs or pesticides. It was found that there were two different pathways of hydrolysis according to the pH region of the solution. In the acidic pH region, the P-N bond cleaves for the both compounds. In the basic pH region, the P-C and P-O bonds would cleave for the compound of N-(methoxycarbonyl-methoxyphosphonyl)-α-amino acid ester (I). While for the compound of N-(isopropylcarbamoyl-methoxyphosphonyl)-α-amino acid ester (II), only the P-O bond cleaves. The possible mechanism is discussed.

Keywords: Methoxycarbonyl-methoxyphosphonyl-; isopropylcarbamoylmethoxyphosphonyl; amino acid esters; hydrolysis; mechanism

Phosphonoformic acid (PFA) is an effective anti-viral agent with potential application in AIDS therapy [1]. The utility of PFA is restricted by its poor membrane permeability [2]. To overcome this disadvantage; a series of amino acid derivatives N-(methoxycarbonyl- and N-(isopropylcarbamoyl-methoxyphosphonyl)-α-amino acid esters; have been synthesized [3]. Since the derivatives possess a labile P-C bond; the success of these compounds as drugs or pro-drugs depends on knowledge of the lability and reactivity pattern. Here; we have studied the hydrolysis of the title compounds I and II in acetone-water or ethanol-water mixed solvent at $1 < pH < 14$.

*Corresponding author.

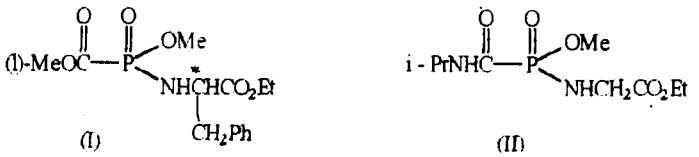

FIGURE 1

RESULTS AND DISCUSSION

The stability of hydrolysis of compounds I and II in various pH regions is studied by means of TLC. At 25 °C, in the regions of pH < 2 or pH > 13, the two compounds undergo rapid hydrolysis with compound I completely disappearing in 2 h and compound II in 30 min. At pH 3 ~ 4 and pH 9 ~ 11, the rate of hydrolysis for both compounds decreases. After 2 days, the compounds could still be detected. At pH 5 ~ 7, after 2 days, only a little product of hydrolysis for compound I was detected, while no product of hydrolysis was found for compound II. Four days later, there was no farther change.

The products of hydrolysis of compounds I and II at pH < 2 or pH > 13 have been isolated and determined. It was found that there were different pathways for the two compounds at various pH regions. The main patterns of hydrolysis is shown below:

In the low pH region, the P-N bond for the two compounds cleaves to yield the amino acid ester hydrochlorides, respectively, and the structure of the products had been confirmed by ^{1}HNMR and their melting points. The phosphorus residue was confirmed by ^{31}PNMR.

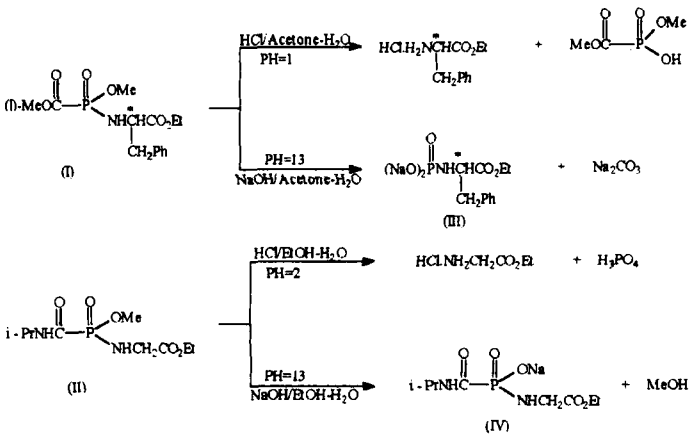

FIGURE 2

In the high pH region, the P-O and P-C bonds for compound I cleave and the ester of amino acid was not hydrolyzed. The ^{13}CNMR spectra of the hydrolyzed products was determined so as to confirm the cleavage of the P-C bond rather than the C-O bond. From the ^{13}CNMR spectra, it was found that the product had a single peak at the δ value of 177.1 ppm. If the peak was the C=O absorption adjacent to P atom, it should be a double peak due to the coupling effect of the P atom. Therefore, it could be confirmed that the single peak resulted from the carbonyl group in the amino acid ester. There were two peaks at the chemical shifts of 14.45 and 63.16 ppm for the ethyl ester group. The δ values for the phenyl group were 128.2, 129.8, 130.8, and 138.1 ppm, respectively. It was at δ of 57.55 for the α-C atom.

From the ^{1}HNMR spectra, the peaks for -OH and -NH were not observed due to the rapid exchange of the proton. There was one peak at δ (^{31}P) of 2.93, corresponding to compound (III). IR spectra showed that there were absorption peaks at 1715.0 cm^{-1} and 1192.7 cm^{-1} for C=O and P=O, respectively.

In high the pH region, only P-O bond cleavage was found for compound II. The ^{1}HNMR spectra of the hydrolyzed product indicated that the peak for the OCH_3 group adjacent to the P atom was not observed. There was one peak at δ (^{31}P) of 4.22 ppm, corresponding to compound (IV). In IR spectra there were absorptions at 1731.4, 1588.9 cm^{-1} for C=O and at 1203.3 cm^{-1} for P=O.

It was reported that the mechanism for the hydrolysis of phosphonoamidates varies with the pH of the solution [4,5]. So, two mechanisms for compounds I and II were suggested in high pH region and in low pH region, respectively.

Under acidic conditions, the compounds undergo a $S_N2(P)$ mechanism in which H_2O as a nucleophile attack the cation (A). Compound I (R^1 = OMe, R = phenylalanine residue) was hydrolyzed to give phosphonate (B) and compound II (R^1 = i-PrNH, R = glycine residue) to give phosphoric acid.

Under basic conditions, the hydrolysis of the compounds proceeds through an Addition-Elimination mechanism in which a monomeric metaphosphate ion (D) is formed. Compound I may go directly to the hydrolyzed product from (C) via a monomeric metaphosphate ion (E).

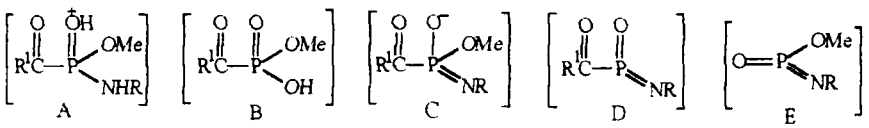

FIGURE 3

EXPERIMENTAL

The compounds I and II were prepared by the reported method [3].

1). The Hydrolysis of N-(methoxycarbonyl-methoxyphosphonyl)-(1)-α-phenylalanine ethyl ester (I)

To compound I (0.5mmol) and acetone (5 ml) was added 1N NaOH (aq.) (1.5 ml) and the mixture was stirred mildly at 25 °C. After 15 min, it was tracked by TLC and found that compound I vanished to give a solid 8h later. It was filtered and washed with acetone to obtain 0.10 g white solid(III), m.p. > 300 °C. Yield 57.9%. ^{1}H-NMR (D_2O as solvent): 1.23(t,3H,CH_3, $^3J_{HH}$ = 7.2Hz), 3.07(d,2H,CH_2Ph), 4.16(q,2H,OCH_2), 4.35(m,1H,CH), 7.15 ~ 7.30(m,5H,Ph). ^{31}PNMR(δ): 2.93 ppm. ^{13}C-NMR(δ): 177.1(CO_2^-), 128.2, 129.8, 130.8, 138.1(Ph); 42.05(CH_2Ph), 57.55(α-C), 63.16, 14.45(OCH_2CH_3). IR(cm^{-1}): $\nu_{C=O}$1715.0, $\nu_{P=O}$1192.7.

In the same way as above with 1N HCl (aq.) to replace 1N NaOH(aq.) and after removal of the solvent, a viscous substance was obtained. It solidified after standing and was washed with some ethyl acetate giving needle-like crystals, m.p. 150 ~ 152 °C. 1-phenylalanine ethyl ester hydrochloride was confirmed by ^{1}HNMR spectra. The filtrate was concentrated to obtain a little viscous substance which was phosphonoformic acid dimethyl ester with δ(^{31}P) = 7.95, 9.29 ppm.

2). The Hydrolysis of N-(isopropylcarbamoyl-methoxyphosphonyl)-glycine ethyl ester (II)

To 1mmol compound II and 5 ml ethanol, was added 1.5 ml 1N NaOH(aq.). The mixture was stirred at 25 °C. After 15 min, completion of the reaction was traced by TLC. After removal of the solvent, 3 ml acetone was dropped in and the reaction mixture was filtered to give 0.2 g of a white solid(IV), m.p. 145 ~ 150. ^{1}H-NMR(D_2O as solvent): 1.14(d,6H,$(CH_3)_2$, $^3J_{HH}$ = 6.6Hz), 3.96(m,1H,CH), 3.69(d,2H,NCH_2, $^3J_{PNCH}$ = 11.3 Hz), 1.23(t,3H,CH_3,$^3J_{HH}$ = 7.2Hz), 4.17(q,2H,OCH_2). ^{31}PNMR(δ): 4.22 ppm. IR(cm^{-1}): $\nu_{C=O}$1731.4, 1588.9; $\nu_{P=O}$1203.3.

1N HCl(aq.) was used instead of 1N NaOH(aq.) in the reaction, when the completion of the reaction, the solvent was removed to give a viscous substance. It solidified after standing and washing with acetone giving 0.11 g of white needle crystals, m.p. 143–145 °C. It was glycine ethyl ester hydrochloride con-

firmed by ^{1}H-NMR. The filtrate was concentrated to give 0.14 g of pale yellow solid, which was deliquated easily, with $\delta(^{31}P) = 0.15$ ppm.

Acknowledgment

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