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Amino Acids

1-(*N*-Trifluoroacetylamino)alkylphosphonic acids: synthesis and properties

Z. H. Kudzin[1], **R. Depczyński**[1], **M. H. Kudzin**[1,2], **J. Łuczak**[3], and **J. Drabowicz**[3]

[1] Institute of Chemistry, University of Łódź, Łódź, Poland
[2] Textile Research Institute, Brzezińska, Łódź, Poland
[3] Centre of Molecular and Macromolecular Studies, Polish Academy of Sciences, Łódź, Poland

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Summary. The 1-(*N*-trifluoroacetylamino)alkylphosphonic acids (TFA-AA^P) – sub-products in the synthesis of *O,O*-dialkyl 1-(*N*-trifluoroacetylamino)alkylphosphonates and *O,O*-diethyl 1-aminoalkylphosphonates, were synthesized in two-stage transformations of 1-aminoalkylphosphonic acids including: trifluoroacetylation of 1-aminoalkylphosphonic acids (AA^P) using a trifluoroacetic anhydride/trifluoroacetic acid reagent (AA^P + TFAA/TFA→**2**) and subsequent hydrolysis of the intermediary compounds **2** into desired TFA-AA^P (**2**→TFA-AA^P). These intermediates **2** presented mixtures of the type of mixed anhydrides of TFAA and 1-(*N*-trifluoroacetylamino)alkylphosphonic, pyrophosphonic and polyphosphonic acids, which underwent rapid and quantitative conversion to corresponding TFA-AA^P during treatment with an excess of water. The title acids were isolated by direct evaporation of the corresponding post-reaction mixtures, and their physicochemical proprieties, including deacylation abilities, were determined. TFA-AA^P compounds can be re-converted into the starting amino acids AA^P under respectively mild conditions (AA^P→TFA-AA^P→AA^P).

Keywords: Acylation – Trifluoroacetylation – Mixed anhydrides – Aminophosphonic acids – 1-Aminoalkylphosphonic acids – 1-(*N*-Trifluoroacetylamino)alkylphosphonic acids

Introduction

The 1-(*N*-trifluoroacetylamino)alkylphosphonic acids (TFA-AA^P) belong to an interesting (Kafarski and Mastalerz, 1984; Kafarski and Lejczak, 1991; Kukhar and Hudson, 2000), although almost not explored group of *N*-acyl derivatives of aminophosphonic acids (AA^P), as until now only TFA-Val^P was synthesized and partly characterized (Khomutov et al., 1979).

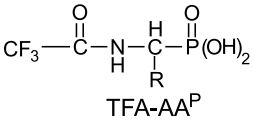
These 1-(*N*-trifluoroacetylamino)alkylphosphonic acids are sub-products in the synthesis of *O,O*-dialkyl 1-(*N*-trifluoroacetylamino)alkylphosphonates (Kudzin and Łuczak, 1995) and *O,O*-diethyl 1-aminoalkylphosphonates (Kudzin et al., 1997), important key-substrates in the preparation of phosphonopeptides (Kafarski et al., 1984). 1-(*N*-Trifluoroacetylamino)alkylphosphonic acids, due to liability of the TFA-NH linkage are also potentially atractive substrates in the synthesis of optically active 1-aminoalkylphosphonic acids (Dahvan and Redmore, 1987; Kukhar and Hudson, 2000).

In this communication we present a simple and quantitative method of conversion of 1-aminoalkylphosphonic acids into the title 1-(*N*-trifluoroacetylamino)alkylphosphonic acids (AA^P→**2**→TFA-AA^P) and tentative results on the course of trifluoroacetylation (AA^P→**2**). In addition, also results on conditions of the re-conversion of 1-(*N*-trifluoroacetylamino)-alkylphosphonic acids into the starting 1-aminoalkylphosphonic acids, i.e. on deprotections of the amine function in TFA-*N*-protected amino acids (AA^P→TFA-AA^P→AA^P).

Materials and methods

Materials

1-Aminoalkylphosphonic acids were prepared according to Kudzin and Stec [1978 (Ala^P, Val^P, $Pgly^P$ and Phe^P)] and Soroka [1989 (Gly^P)]. All other reagents were purchased from Aldrich (Milwaukee, IL, USA). Acetate buffer solution contained 10 mmol AcOH and 10 mmol of AcONa in 5 ml of aqueous solution.



TFA-AA^P

Fig. 1. Structure of 1-(*N*-trifluoroacetylamino)alkylphosphonic acids TFA-AA^P (**3**)

Equipment

All melting points were determined using a MEL-TEMP II capillary melting point apparatus (Laboratory Devices Inc., USA) and are uncorrected. NMR spectra were recorded on a Brucker AC 200 spectrometer operating at 200 MHz for ^{1}H NMR, at 188.3 MHz for ^{19}F NMR and at 81.01 MHz for ^{31}P NMR. Elemental analyses (C, H) were recorded on an Elemental Analyzer Euro EA (Eurovector, Italy). The chemical shift data for each signal on ^{1}H NMR are taken in units of δ relative to $CHCl_3$ (δ 7.26) for TFA-$CDCl_3$ solutions and H_2O (δ 4.72) for aqueous solutions, The chemical shifts of ^{31}P are recorded relative to external 85% H_3PO_4 (δ 0.0) with broad-band ^{1}H decoupling.

General procedure of N-trifluoroacetylation of 1-aminoalkylphosphonic acids

A sample of AA^P (1 mmol) was added to a solution of TFA (0.5 ml) and TFAA (1 ml, 1.51 g; 7.2 mmol), and the mixture was stirred at ambient temperature until homogenization, and then for additional 1 h. The formed solution was evaporated (20 °C, 10–20 mmHg), an oily residue was dissolved in cold water (5 ml), and evaporated again *to dryness* (50 °C, 10–20 mmHg). The residues presented pure 1-(*N*-trifluoroacetylamino)-alkylphosphonic acids, which were stored in a vacuum desiccator over solid KOH.

TFA-Gly^P (**3a**)

Yield: 96–98% (100% according to ^{31}P NMR). Colorless, hygroscopic crystals; mp 66–68 °C. ^{31}P NMR (δ_P, ppm): 18.1 (2 M HCl/D_2O), 16.8 (D_2O), 19.3 ($DMF/CDCl_3$). ^{19}F NMR (δ_F, ppm): −74.88 (D_2O). ^{1}H NMR (δ_H, ppm): δ_H ($CDCl_3$): 3.71 (1H, dd, J 5.6, 13.1 Hz, TFANHC$\underline{H}_2$P(O)$(OH)_2$], 7.91–8.07 (1H, m, TFAN$\underline{H}$CH_2P), 11.0–11.31 [2H, br s, CH_2P(O)(O$\underline{H}_2$)]; δ_H [$CDCl_3$-TFA (3:2)]: 4.05 [2H, d, J 6.1 Hz, TFANHC$\underline{H}_2$P(O)$(OH)_2$], 7.00–7.50 (1H, br s, TFAN$\underline{H}$CH_2P). Found: C 17.37, H 2.57, P 14.65. Calc. for $C_3H_5F_3NPO_4$ [207.1]: C 17.40, H 2.42, P 14.96.

TFA-Ala^P (**3b**)

Yield: 96–98% (100% according to ^{31}P NMR). Colorless, hygroscopic crystals; mp 102–104 °C. ^{31}P NMR (δ_P, ppm): 21.2 (2 M HCl/D_2O), 20.3 (D_2O), 19.3 ($DMF/CDCl_3$). ^{19}F NMR (δ_F, ppm): δ_F −74.81 (D_2O). ^{1}H NMR (δ_H, ppm): δ_H ($CDCl_3$): 1.43 [3H, dd, J 7.2, 16.2 Hz, TFANHCH(C$\underline{H}_3$)P(O)$(OH)_2$], 4.25–4.50 (1H, m, CH_3C$\underline{H}$P), 7.56 (1H, d, J 8.3 Hz, TFANHCH), 8.25–8.50 [2H, br s, CHP(O)(O$\underline{H}_2$)]; δ_H [$CDCl_3$-TFA (3:2)]: 1.60 [3H, d, J 13.6 Hz, TFANHCH(C$\underline{H}_3$)P(O)$(OH)_2$], 2.10–2.60 (1H, m, CH_3CHP), 7.55–7.85 (1H, m, TFAN$\underline{H}$CHP). Found: C 21.50, H 3.40, P 14.30. Calc. for $C_4H_7F_3NPO_4$ [221.1]: C 21.73, H 3.19, P 14.01.

TFA-Val^P (**3c**)

Yield: 96–98% (100% according to ^{31}P NMR). Colorless, hygroscopic crystals; mp 164–166 °C [235–238 °C (Khomutov et al., 1979)]. ^{31}P NMR (δ_P, ppm): 19.8 (2 M HCl/D_2O), 18.9 (D_2O), 18.2 ($DMF/CDCl_3$); ^{19}F NMR (δ_F, ppm): −74.40 (D_2O). ^{1}H NMR (δ_H, ppm): δ_H [$CDCl_3$-TFA (3:2)]: 1.12 {6H, dd, J 7.0, 8.7 Hz, TFANH[(C$\underline{H}_3$)$_2$CH]CHP(O)$(OH)_2$}, 2.12–2.40 [1H, m, $(CH_3)_2$C$\underline{H}$CHP], 4.24–4.56 [1H, m, $(CH_3)_2$CHC$\underline{H}$P], 7.65 (1H, d, J 7.0 Hz, TFAN$\underline{H}$CHP). Found: C 28.90, H 4.43, P 12.07. Calc. for $C_6H_{11}F_3NPO_4$ [249.1]: C 28.93, H 4.45, P 12.43.

TFA-$Pgly^P$ (**3d**)

Yield: 96–98% (100% according to ^{31}P NMR). Colorless, hygroscopic crystals; mp 184–186 °C. ^{31}P NMR (δ_P, ppm): 16.1 (2 M HCl/D_2O), 14.8 (D_2O), 15.0 ($DMF/CDCl_3$). ^{19}F NMR (δ_F, ppm): −74.56 (D_2O). ^{1}H NMR (δ_H, ppm): δ_H ($CDCl_3$); 5.36 [1H, dd, J 9.0, 21.2 Hz, TFANHC$\underline{H}$(C_6H_5)-P(O)$(OH)_2$], 7.22–7.50 [(5H, m): 7.22–7.32 ($3H_{ar}$, m); 7.32–7.50 ($2H_{ar}$, m)], 8.26 (1H, dd, J 5.0, 8.6 Hz, TFA-N$\underline{H}$CH), 11.86–12.16 [2H, br s, CHP(O)(O$\underline{H}_2$)]; δ_H [$CDCl_3$-TFA (3:2)]: 5.66 [1H, dd, J 7.9, 20.5 Hz, TFANHC$\underline{H}$(C_6H_5)P(O)$(OH)_2$], 7.32–7.50 ($5H_{ar}$, m), 8.0–8.25 (1H, br s, TFAN$\underline{H}$CHP). Found: C 38.58, H 3.46, P 11.15. Calc. for $C_9H_9F_3NPO_4$ [283.1]: C 38.18, H 3.20, P 10.94.

TFA-Phe^P (**3e**)

Yield: 96–98% (100% according to ^{31}P NMR). Colorless, hygroscopic crystals; mp 146–150 °C. ^{31}P NMR (δ_P, ppm): 18.9 (2 M HCl/D_2O), 17.9 (D_2O), 17.8 ($DMF/CDCl_3$). ^{19}F NMR (δ_F, ppm): −74.69 (D_2O) ^{1}H NMR (δ_H, ppm): δ_H ($CDCl_3$): 2.91–5.08 [1H, m, TFA-NH(C_6H_5C$\underline{H}_2$)-CHP(O)$(OH)_2$], 3.20–3.37 (1H, m, C_6H_5C$\underline{H}_2$CHP), 4.46–4.65 (1H, m, PhCH_2C$\underline{H}$P); 7.08–7.25 (m, $5H_{ar}$), 8.04 (1H, d, J 9.7 Hz, TFAN$\underline{H}$CH), 11.40–11.70 [2H, br s, CHP(O)(O$\underline{H}_2$)]; δ_H [$CDCl_3$-TFA (3:2)]: 2.90–3.10 [1H, m, TFANH(C_6H_5C$\underline{H}_2$)CH-P(O)$(OH)_2$], 3.25–3.45 (1H, m, C_6H_5C$\underline{H}_2$CHP), 4.60–4.90 (1H, m, PhCH_2C$\underline{H}$P), 7.11–7.45 [(5H): 7.11–7.25 ($3H_{ar}$, m); 7.30–7.45 ($2H_{ar}$, m)], 7.54–7.90 (1H, br s, TFA-N$\underline{H}$CHP); Found: C 40.24, H 3.95, P 10.43. Calc. for $C_{10}H_{11}F_3NPO_4$ [297.2]: C 40.23, H 3.72, P 10.42.

Deacylation investigations of 1-(N-trifluoroacetylamino) alkylphosphonic acids

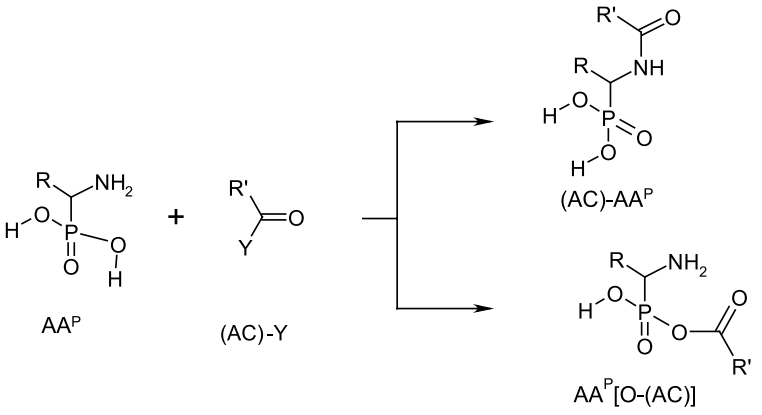
Samples of TFAA-AA^P (1 mmol) were dissolved in 10 ml of appropriate solution (water, 2 M HCl, AcOH/AcONa buffer, 2 M NaOH) containing 10% D_2O and 1 mmol of phosphoric(V) acid or its salts and kept in a thermostat at 20 ± 0.5 °C (or in the thermoregulated oil bath, in the case of exposition at elevated temperatures). Temporarily ^{31}P NMR spectra of corresponding reaction mixtures were recorded.

Results and discussion

Trifluoroacetylation of 1-aminoalkylphosphonic acids

The acylation reaction of aminoalkylphosphonic acids, despite of the advantage of monitoring by ^{31}P NMR, still belongs to scarcely explored domains of the chemistry of organophosphorus compounds. As a matter of fact, the complicated mechanism of the reactions of AA^P with acylation reagents was the subject of only a few literature reports (Soroka, 1987; Hirschmann et al., 1995, 1997). These revealed competitive course of the acylation, namely *N*-acylation [$AA^P \rightarrow$(AC)-AA^P] vs. *O*-acylation of AA^P, {$AA^P \rightarrow AA^P$[O-(AC)]}, occurring as result of the so-called *active sterical hindrance* of the phosphonic function (Scheme 1) (Soroka, 1987).

Tentative investigations on the reaction course of AA^P with anhydrides carried out by us (Kudzin et al., 2005), especially those with an application of the TFAA/TFA reagent (Depczyński, 2006), revealed unexpectedly even far more complex mechanism of these reactions. This is demonstrated in the ^{31}P NMR spectra of reaction mixtures of TFAA/TFA with representative 1-aminoalkylphosphonic acids, namely: Ala^P and $Pgly^P$, presented in Figs. 2 and 3.



Scheme 1. Reaction course of 1-aminoalkylphosphonic acids with acyl chlorides

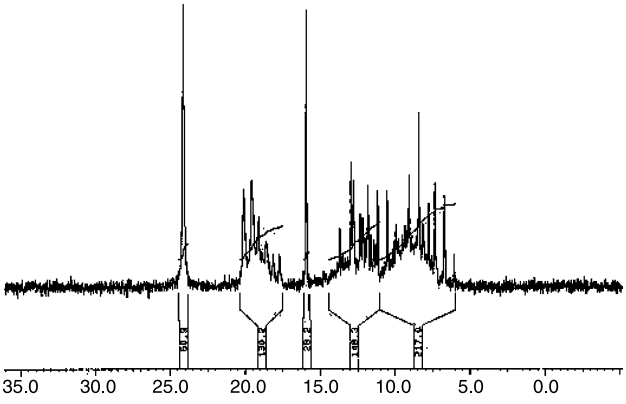


Fig. 2. ^{31}P NMR spectrum of the reaction mixture of Ala^P and TFAA/TFA

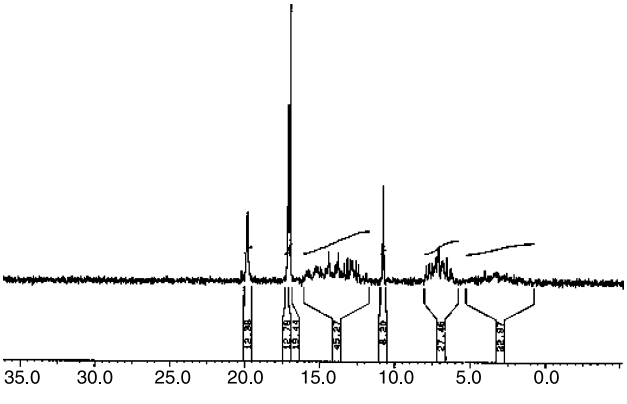


Fig. 3. ^{31}P NMR spectrum of the reaction mixture of Pgly^P and TFAA/TFA

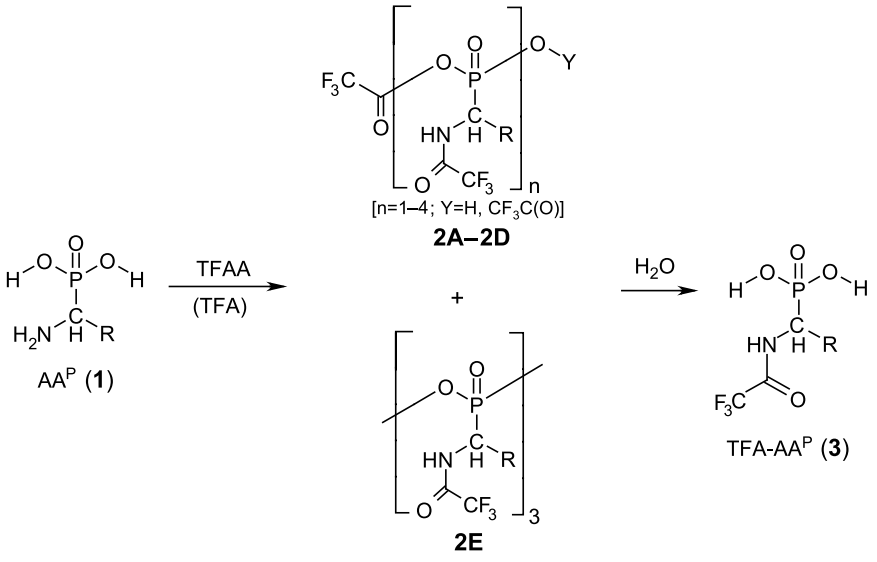
Discussed spectra present the multicomponent mixtures containing intermediary compounds **2** – products of *N*-trifluoroacetylation and *O*-trifluoroacetylation of AA^P (as singlets), as well as products of their dimerization (singlets and/or dublets) and polycondensation (multiplets) (Scheme 2: AA^P→**2**) (Depczyński, 2006). Corresponding trimers presumably can exist in both acyclic (**2C**) and cyclic (**2E**) forms (Ohms et al., 1992; Diemert et al., 1998).

All investigated reaction mixtures of AA^P with TFAA/TFA converted rapidly into the one ^{31}P signal solutions, containing corresponding TFA-AA^P, during their pretreatment with water (Scheme 2: AA^P→**2**→TFA-AA^P). This enabled a quantitative conversion of 1-aminoalkylphosphonic acids into their TFA-AA^P derivatives, which were isolated in an analytically pure state after direct evaporation of the corresponding post-reaction mixtures. The analytical properties of 1-(*N*-trifluoroacetyl-amino) alkylphosphonic acids obtained are described under Materials and methods.

Deacylation of 1-(N-trifluoroacetylamino) alkylphosphonic acids

Since the trifluoroacetyl function belongs to common amine-protecting groups applied in the peptides chemistry (Weygand and Frauendorfer, 1970; Wunsch, 1994; Kociensky, 1994), we undertook some investigations on its application in the field of phosphonopeptides. In preliminary approach, we started with a search on stability of the trifluoroacetyl-amide function of TFA-AA^P.

Our investigations were performed in 0.1 M aqueous solutions of TFA-AA^P, strongly differing in respect to the pH. These included solutions of TFA-AA^P in water (pH ~3.5), in 2 M HCl (pH ~0) and 2 M NaOH (pH ~14), and also in acetate buffer (pH ~4.54) aqueous solutions. All stock solutions were fortified with internal standards consisting of phosphoric acid or appropriate phosphate salts ($Na_nH_{3-n}PO_4$). The progress of TFA-AA^P deacylations was monitored by ^{31}P NMR. Identification of the deacylation products was performed on the basis of chemical shift data of the starting TFA-AA^P and final



Scheme 2. Reaction course of 1-aminoalkylphosphonic acids with trifluoroacetic anhydride with subsequent hydrolysis of intermediary anhydrides **2**

Table 1. Chemical shifts δ (^{31}P) of 1-aminoalkylphosphonic and 1-(*N*-trifluoroacetyl-amino)alkylphosphonic acids

Acids		^{31}P NMR; δ (ppm)			
1 or **3**	AA^P/TFA-AA^P	2 M HCl[a]	Buffer[a]	H_2O[a]	2 M NaOH[a]
1a	Gly^P	13.9	10.6	11.0	19.3
1b	Ala^P	16.8	13.9	14.3	22.3
1c	Val^P	15.7	12.7	13.0	21.2
1d	$Pgly^P$	12.5	10.2	10.5	18.0
1e	Phe^P	14.8	12.1	12.5	20.4
3a	TFA-Gly^P	18.1	14.1	16.8	
3b	TFA-Ala^P	21.2	17.5	20.3	
3c	TFA-Val^P	19.8	16.0	18.9	
3d	TFA-Pgl^P	16.1	12.9	14.8	
3e	TFA-Phe^P	18.9	15.5	17.9	
IS	H_3PO_4/ $Na_nH_mPO_4$	−0.54	+0.12	−0.10	5.39

[a] Aqueous solutions of AA^P or TFA-AA^P (0.1 mmol per ml) containing 10% D_2O and phosphoric (V) acid (0.05 mmol per ml) or phosphates (V) (0.05 mmol per ml), applied as internal standards (IS)

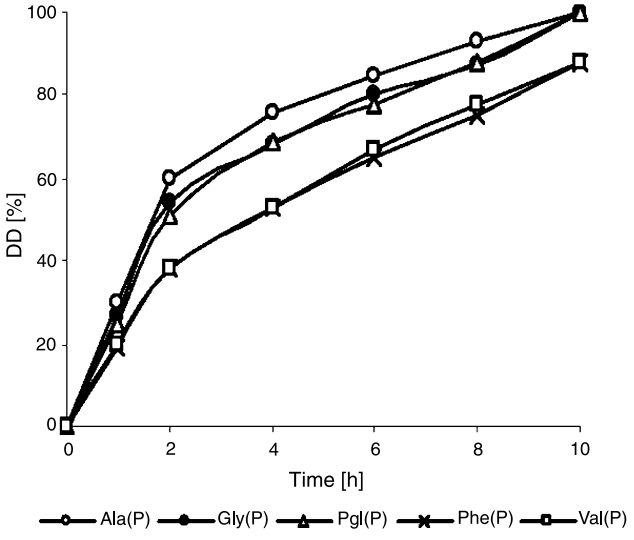


Fig. 4. Deacylation course of 1-(*N*-trifluoroacetylamino)alkylphosphonic acids TFA-AA^P (TFA-Gly^P, TFA-Ala^P, TFA-Val^P, TFA-$Pgly^P$ and TFA-Phe^P) in 2 M HCl_{aq} solutions (temp. 100 ± 0.5 °C)

AA^P, determined in appropriate solutions and listed in Table 1.

Deacylation results of representative TFA-AA^P, are illustrated graphically in Figs. 4 and 5.

The graphs represent the plots of corresponding, so the called, deacylation degree (***DD***) values in function of the reaction time. ***DD*** factors, defined by Eq. (1), were directly determined from corresponding ^{31}P NMR spectra:

$$\boldsymbol{DD} = \frac{\boldsymbol{S}_{(AAP)}}{\boldsymbol{S}_{(AAP)} + \boldsymbol{S}_{(TFA\text{-}AAP)}} \times 100\% \qquad (1)$$

where: ***DD*** – deacylation degree factor; $\boldsymbol{S}_{(AAP)}$ and $\boldsymbol{S}_{(TFA\text{-}AAP)}$ – ^{31}P peak areas of starting TFA-AA^P and final AA^P, determined from ^{31}P NMR spectra of corresponding reaction mixtures.

The results obtained exhibited the substantial stability of TFA-AA^P in water and buffer solutions at ambient temperatures (no changes up to 24 h), gradual deacylations in 2 M HCl solutions (Fig. 4) and rapid deacylations in 2 M NaOH solution (100% of deacylation of TFA-AA^P in 15 min). Compounds TFA-AA^P present also the moderate stability in aqueous solutions at elevated temperatures (Fig. 5). These observations can be useful for the protection/deprotection sequences concerning AA^P ($AA^P \rightarrow$TFA-$AA^P \rightarrow AA^P$), and applied in the chemistry of aminophosphonates and phosphonopeptides. Moreover,

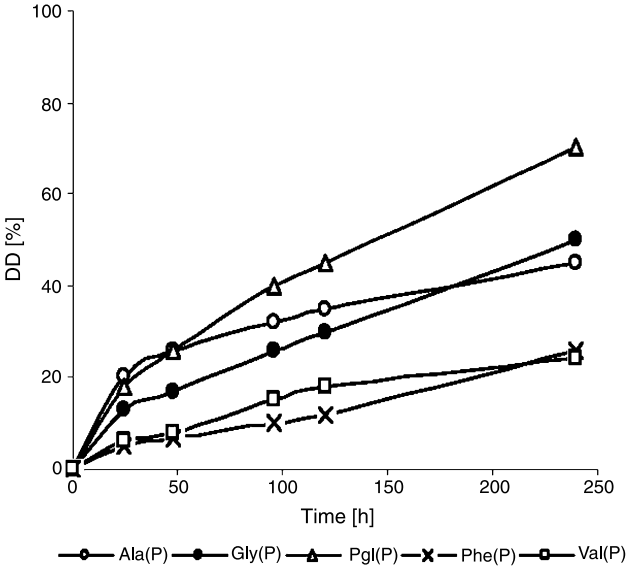


Fig. 5. Deacylation course of 1-(*N*-trifluoroacetylamino)alkylphosphonic acids (TFA-AA^P: TFA-Gly^P, TFA-Ala^P, TFA-Val^P, TFA-Pgly^P and TFA-Phe^P) in aqueous solutions (temp. $20 \pm 0.5\,^\circ$C)

they have to be taken also into consideration during routine work-up procedures of TFA-AA^P (e.g. purifications with active carbon, neutralizations, evaporations of aqueous solutions, etc.).

Conclusion

In summary, the trifluoroacetylation procedure of 1-aminoalkylphosphonic acids we describe, is quantitative, completely general and simple. They make 1-(*N*-trifluoroacetylamino)-alkylphosphonic acids, compounds so far not described (excluding TFA-Val^P), readily available.

The reaction of 1-aminoalkylphosphonic acids with TFAA proved to occur through complex, not described earlier mechanism, postulating the formation of intermediary mixed anhydrides **2**, derived from TFAA and phosphonic, pyrophosphonic and polyphosphonic amino acids (AA^P→**2A**–**2D**). These intermediates **2** underwent quantitative conversion to the title 1-(*N*-trifluoroacetylamino)-alkylphosphonic acids during subsequent treatment with water (**2**→TFA-AA^P). 1-(*N*-Trifluoroacetylamino)alkylphosphonic acids contain labile amide function which can be easily removed during exposition in 2 M NaOH solutions or in boiling water solution (TFA-AA^P→AA^P).

A study on antibacterial activities of representative 1-(*N*-trifluoroacetylamino)alkylphosphonic acids is underway.

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Authors' address: Zbigniew H. Kudzin, Institute of Chemistry, University of Łódź, Narutowieza 68, Łódź 91-136, Poland,
Fax: +48-042-6362860; E-mail: zhk@chemul.uni.lodz.pl