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# 1-Aminoalkanediphosphonic acids. Synthesis and acidic properties *

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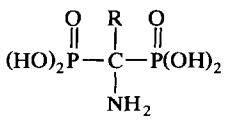
**Abstract**

The syntheses of 1-aminoalkane-1,*n*-diphosphonic acids ($n = 2$–4) by the thioureidoalkanephosphonate method are described. The acidities of these amino acids were determined potentiometrically.

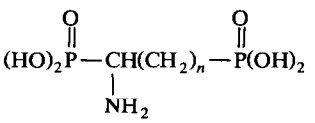
*Key words:* Phosphorus; Phosphonic acid; Aminoalkanephosphonic acids; Amino acids; Acidity

## 1. Introduction

Aminoalkanediphosphonic acids have attracted much interest because of the value of this type of compound in a variety of industrial applications [1,2]. However, the numerous reports are devoted mainly to the chemistry of aminoalkanediphosphonic acids **1a**, bearing two geminal functions [1–3], and there have been only two reports on the synthesis of derivatives **1** with phosphonic functions attached to terminal carbons [4,5].



**1a**



**1**

The aminoalkanediphosphonic acids (**1**) are phosphonic analogues of naturally occurring acidic amino acids. They also possess high chelating potential owing to the presence in the molecule of two phosphonic and one amino functions, with a molecular flexibility higher than their structural analogues **1a**. From these reasons the chemistry of this class of compounds represents a promising and relatively open field of exploration in both synthetic and fundamental aspects.

## 2. Results and discussion

### *2.1. Synthetic investigations*

In this section we present the new synthesis of 1-aminoalkanediphosphonic acids described by formula **1**. This procedure is based on the thioureidoalkanephosphonate method [7]. Thus, starting from aldehydes **2** ($n = 1$, 2, 3), N-phenylthiourea (**3**) and triphenyl phosphite (**4**) the corresponding thioureidoalkanephosphonates (**5**) were obtained in good yields (eqn. 1). The hydrolytic degradation of these derivatives (eqn. 2) led

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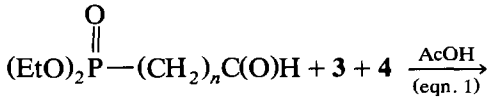
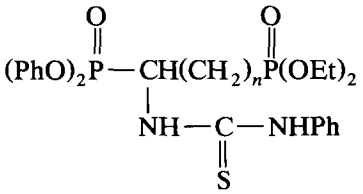
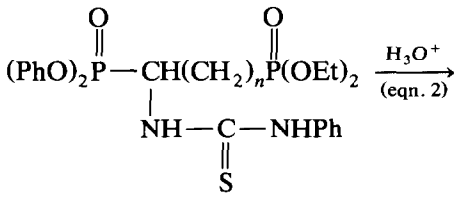
to satisfactory overall yields of the 1-aminoalkanediphosphonic acids (**1**).



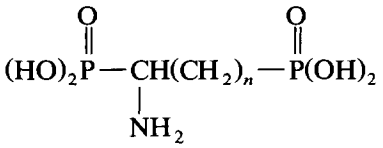
**2**



**5**



**5**



**1**

The good yields of **5** and **1** prompted us to apply a "one-pot" procedure for preparation of **1c** in which intermediate thioureidoalkanephosphonate (**5c**) could be isolated as an oil. Thus, treatment of product mixture from the reaction between **2c**, **3** and **4** in acetic acid directly with concentrated hydrochloric acid gave the desired amino acid **1c** in moderate yield (Procedure B).

The yields and physical properties of thioureidoalkanephosphonates **5** and aminoalkanediphosphonic acids **1** are summarized in Tables 1, 2 and 3, respectively. The dissociation constants of amino acids **1** are listed in Table 4.

We believe that the procedure described in this paper complements the multi-stage procedure based also on the phosphonoaldehydes (**2**) ($n = 1, 2$), described by Issbell [4], as well to the method we developed earlier [5,6] based on the corresponding halogenoalkanonitriles (practically limited to the synthesis of 1-aminoethane-1,2-diphosphonic acid).

### 2.2. *$^{31}$P-NMR spectroscopic investigations of the 1-aminoalkanediphosphonic acids (1)*

The results presented in Tables 2–4 revealed the distinct structural influence on physical properties of 1-aminoalkanephosphonic acids **1**. Examination of the $^{31}$P NMR spectra of amino acids **1a***, **1a**, **1b** and **1c** reveals a strong dependence of the chemical shifts $\delta$ ($^{31}$P) on the distance between the two phosphorus atoms in the molecule. Thus, $^{31}$P-NMR decoupled spectra of (aminomethylene)bisphosphonic acid (**1a***; $n = 0$, P–C–P) with two geminal phosphonic functions exhibit only singlets, whose chemical shifts are dependent on the solution pH. When the distance between

TABLE 1. Yields and analytical characteristics of the thioureidoalkanephosphonates (**5**) and amino acids **1**

| Compound | | Yield [a] (%) | M.p. (°C) | Molecular formula (wt.) | Mass spectrometry ($m/z$ *vs.* intensity (%)) | | Elemental analysis (%) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | M + 1 [b] | M − 1 [c] | C Calc. (Found) | H Calc. (Found) | N Calc. (Found) | P Calc. (Found) | S Calc. (Found) |
| **5a** | 1 | 75 | 150–151 | $C_{25}H_{30}N_2P_2O_6S$ (548.51) | 549 [b] (10%) | 547 [c] (55%) | 54.74 (54.53) | 5.51 (5.50) | 5.11 (4.90) | 11.29 (11.36) | 5.84 (5.84) |
| **5b** | 2 | 70 | 145–147 | $C_{26}H_{32}N_2P_2O_6S$ (562.53) | | | 55.51 (55.36) | 5.73 (5.73) | 4.98 (4.69) | 11.01 (11.09) | 5.70 (5.72) |
| **5c** | 3 | 58 | oil | $C_{27}H_{34}N_2P_2O_6S$ (576.55) | | | 56.24 (56.80) | 5.95 (5.80) | 4.86 (4.52) | 10.74 | 5.56 |
| **1a** | 1 | 70 | 233–235<br>233–235[4]<br>234–236[5] | $C_2H_9NP_2O_6$ (205.05) | 206 [b] (2%) | 204 [c] (12%) | 11.71 (11.82) | 4.42 (4.33) | 6.83 (6.71) | 30.21 (30.31) | |
| **1b** | 2 | 65 | 236–238<br>237–239[4] | $C_3H_{11}NP_2O_6$ (219.08) | 220 [b] (16%) | 218 [c] (71%) | 16.45 (16.55) | 5.06 (5.20) | 6.40 (6.26) | 28.28 (28.37) | |
| **1c** | 3 | 50 [d] | 235–237 | $C_4H_{13}NP_2O_6$ (233.12) | 234 [b] (9%) | 232 [c] (46%) | 20.61 (20.92) | 5.62 (5.69) | 6.01 (6.11) | 26.58 (26.66) | |

[a] The yields were calculated on the basis of aldehydes **2**. [b] Positive ions. [c] Negative ions. [d] The yield obtained in one-pot procedure without pre-isolation of the intermediary thioureidoalkanephosphonate (**5c**).

TABLE 2. Spectral characteristics of the thioureidoalkanephosphonates (**5**) and 1-aminoalkanediphosphonic acids (**1**)

| Compound | $^{31}$P-NMR $\delta$ [ppm] [b,c] | $^{1}$H-NMR $\delta$ [ppm] [b,c] |
|---|---|---|
| **5a** [b] | 15.6; 16.3; 26.0; 26.7 | 1.21 (t-t, 6H, $CH_3CH_2O$); 2.4–2.7 (m, 2H, $CH_2$–CH); 3.9–4.2 (m, 4H, $CH_2O$); 6.0–6.4 (m, 2H, P–CH); 7.1–7.3 (m, > 15H, Ar); 7.6–7.7 (m, 1H, N*H*–CH); 9.2–9.3 (m, 1H, N*H*Ph) |
| **5b** [b] | 17.3; 17.4; 31.2; 31.4 | 1.23 (t, 6H, $CH_3CH_2O$); 2.0–2.4 (m, 4H, $CH_2CH_2CH$); 3.7–4.1 (m, 4H, $CH_2O$); 5.6–5.9 (m, 1H, P–CH); 7.1–7.5 (m, > 15H, Ar, N*H*–CH); 8.8–9.0 (m, 1H, N*H*–Ph) |
| **5c** [b] | 18.3; 32.4 | 1.27 (t, 6H, $CH_3CH_2O$); 1.6–2.4 (m, 6H, $(CH_2)_3$–CH); 3.9–4.1 (q, 4H, $CH_2O$); 5.6–5.9 (m, 1H, P–CH); 6.8–6.9 (m, 1H, N*H*); 7.1–7.4 (m, > 15H, Ar); 8.4–8.5 (m, 1H, N*H*–Ph); |
| **1a*** [a,c] | 11.7 | 3.9–3.8 (m, 1H, CH); 6.0–6.5 (m, 3H, $NH_3$) |
| **1a** [c] | 19.1; 19.8; 33.6; 34.3 | 2.4–2.8 (m, 2H, $CH_2$); 3.9–4.2 (m, 1H, CH); 6.4–6.8 (m, 3H, $NH_3$) |
| **1b** [c] | 23.5; 41.0 | 1.9–2.2 (m, 4H, $CH_2CH_2$); 3.6–3.9 (m, 1H, CH); 6.4–6.7 (m, 3H, $NH_3$) |
| **1c** [c] | 24.8; 44.0 | 1.4–1.7 (m, 2H, $CH_2CH_2$–P); 1.8–2.1 (m, 4H, $CH_2$–$CH_2$–$CH_2$–P); 3.6–3.8 (m, 1H, CH); 6.39–6.60 (m, 3H, $NH_3$) |

[a] **1a*** = (aminomethelene)bisphosphonic acid ($n = 0$). The solutions of derivatives **1** or **5** in: [b] $CDCl_3$ or [c] trifluoromethanesulphonic acid (external lock on $CDCl_3$).

two phosphorus atoms is increased to three bonds, in **1a** ($n = 1$; P–C–C–P), the spectrum contains two doublets, one in the region 28–30 ppm (characteristic for the alkanephosphonic function; P–$C_\beta$), and the second at the region 14–16 ppm (characteristic for the 1-aminoalkanephosphonic function; P–$C_\alpha$). The spectra of **1a** also exhibited the highest coupling constants ($J_{P-P}$ reach the value 55.9 Hz). Further increase in the distance between phosphorus atoms on going to **1b** ($n = 2$; P–C–C–C–P) and then to **1c** ($n = 3$; P–C–C–C–C–P) reduces the inductive interaction between the phosphorus atoms and consequently lowers the coupling constants. The coupling constant for **1b** is observed in an alkaline solution ($J_{P-P} = 5.3$ Hz), whereas the spectra of **1c** do not exhibit coupling between phosphorus nuclei.

It is obvious that, owing to the nature of the 1-aminoalkanediphosphonic acids being considered, the ionization state of the phosphonic groups (P–$C_\alpha$ and P–$C_i$, $i = \alpha, \beta, \gamma, \omega$) should exert a strong influence on the chemical shift for the phosphorus nucleus. The pH dependence of the phosphorus chemical shift [$\delta$(P) = f (pH)] for amino acids **1a***, **1a**, **1b** and **1c**, shown in Table 3, is clearly consistent with this expectation. The complexity of this dependence resembles that of the dependence we described for 1-aminothiaalkanephosphonic acids and their sulphinyl and sulphonyl derivatives [8], and can be interpreted in a similar way. Investigations of amino acids **1a** and **1b** by monitoring of protolytic and complex formation equilibria by titration-dependent stopped-flow-NMR techniques [9] are in progress.

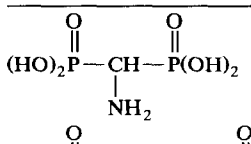
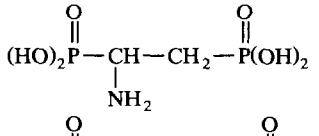
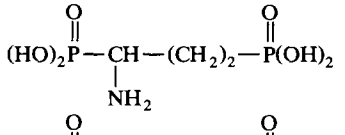
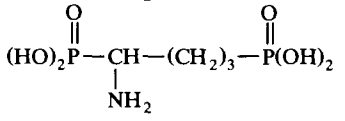
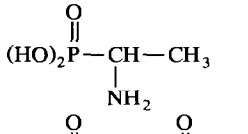
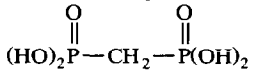
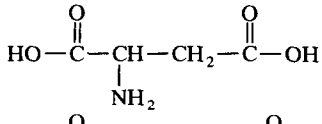
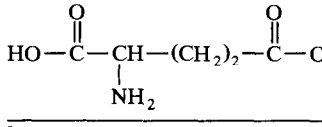
The $^{1}$H-NMR spectra of 1-aminoalkanediphosphonic acids (**1**) were measured in trifluoromethanesulfonic acid owing to their low solubility in other solvents. The application of trifluoromethanesulphonic

TABLE 3. The pH dependence of phosphorus chemical shift [$\delta$ (P)] of the 0.02 molar aqueous solutions (20% of $D_2O$) of 1-aminoalkanediphosphonic acids **1a***, **1a**, **1b** and **1c**. Proton decoupled spectra were recorded on a Bruker AC 200 spectrometer operating at 81.01 MHz

| pH | $^{31}$P-NMR chemical shifts (ppm) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **1a*** | **1a** | | | | **1b** | | **1c** | |
| | | P–$C_\alpha$ | | P–$C_\beta$ | | P–$C_\alpha$ | P–$C_\gamma$ | P–$C_\alpha$ | P–$C_\omega$ |
| *ca.* 0 [a] | 10.9 | 13.6, | 14.3, | 22.9, | 23.6 | 15.0, | 29.6 | 15.0, | 29.0 |
| 1.9 | 10.7 | 12.8, | 13.5, | 21.1, | 21.9 | 13.4, | 29.6 | 14.0, | 28.7 |
| 4.7 | 10.2 | 12.6, | 13.2, | 20.0, | 20.7 | 13.1, | 24.1 | 13.7, | 25.9 |
| 5.4 | 10.4 | 12.4, | 12.9, | 20.0, | 20.5 | 13.9, | 23.9 | 13.6, | 25.6 |
| 6.5 | 10.7 | 12.3, | 12.9, | 20.0, | 20.4 | 12.4, | 23.7 | 12.9, | 25.3 |
| 8.0 | 10.9 | 12.5, | 13.2, | 19.4, | 20.0 | 12.9, | 21.8 | 12.7, | 24.0 |
| 10.0 | 11.1 | 13.6, | 14.2, | 19.7, | 20.4 | 14.0, | 21.7 | 14.7, | 22.7 |
| *ca.* 14.0 [b] | 18.7 | 22.07 | | 22.12 | | 21.9, 22.0, | 23.3, 23.4 | 13.6, | 25.6 |

[a] Approximately 1.9 N aqueous solution of hydrochloric acid (20% $D_2O$). [b] Approximately 1.8 N aqueous solution of sodium hydroxide (20% $D_2O$).

TABLE 4. Comparison of dissociation constants of 1-aminoalkanediphosphonic acids (1), 1-aminoethanephosphonic acid, methanediphosphonic acid and 1-aminoalkanedicarboxylic acids (Asp, Glu)

| Acids [a] | Negative logarithm of dissociation constant [b] | | | | |
|---|---|---|---|---|---|
| | $pk_1$ | $pk_2$ | $pk_3$ | $pk_4$ | $pk_5$ |
|  | – | 1.7[10] | 5.59[10] | 8.06[10] | 10.42[10] |
|  | < 1 | 1.06 | 5.19 | 6.55 | 10.30 |
|  | < 1 | 1.07 | 5.56 | 6.92 | 10.43 |
|  | < 1 | < 1 | 5.66 | 7.55 | 10.68 |
|  | < 0.47[11,c] | 5.59[11]<br>5.55[12] | 10.19[11]<br>10.11[12] | | |
|  | | 2.87[13] | 7.45[13] | 10.96[13] | |
|  | 1.85[14] | 3.65[14] | 9.60[14] | | |
|  | 2.16[14] | 4.32[14] | 9.96[14] | | |

[a] Listed amino acids exist in the zwitter-ion forms.

[b] Dissociation constants $k$ (or protonation constants $K$) are determined for the corresponding equilibria.

(1) *for aminoalkanediphosphonic acids*

$$L^{-4} + H^+ \underset{k_5}{\overset{K_1}{\rightleftharpoons}} HL^{-3};\quad HL^{-3} + H^+ \underset{k_4}{\overset{K_2}{\rightleftharpoons}} H_2L^{-2};\quad H_2L^{-2} + H^+ \underset{k_3}{\overset{K_3}{\rightleftharpoons}} H_3L^-;\quad H_3L^- + H^+ \underset{k_2}{\overset{K_4}{\rightleftharpoons}} H_4L;\quad H_4L + H^+ \underset{k_1}{\overset{K_5}{\rightleftharpoons}} H_5L^+$$

(2) *for alkanediphosphonic acids*

$$L^{-4} + H^+ \underset{k_4}{\overset{K_1}{\rightleftharpoons}} HL^{-3};\quad HL^{-3} + H^+ \underset{k_3}{\overset{K_2}{\rightleftharpoons}} H_2L^{-2};\quad H_2L^{-2} + H^+ \underset{k_2}{\overset{K_3}{\rightleftharpoons}} H_3L^-;\quad H_3L^- + H^+ \underset{k_1}{\overset{K_4}{\rightleftharpoons}} H_4L;$$

(3) *for aminoalkanephosphonic acids*

$$L^{-2} + H^+ \underset{k_3}{\overset{K_1}{\rightleftharpoons}} HL^-;\quad HL^- + H^+ \underset{k_2}{\overset{K_2}{\rightleftharpoons}} H_2L;\quad H_2L + H^+ \underset{k_1}{\overset{K_3}{\rightleftharpoons}} H_3L^+;$$

[c] $\log \beta_{011} = 10.20$; $\log \beta_{021} = 15.78$ and $\log \beta_{031} = 16.25$.

acid as an NMR solvent also offers the advantage that a broad range of chemical shifts ($\delta$: 0–10.5 ppm) is free of solvent signals (except for small signals from trace impurities). These proton spectra of 1-aminoalkanediphosphonic acids (1) were structurally informative, revealing all the protons of the aliphatic chain and protons of the ammonium group.

The phosphorus spectra of amino acids 1 in trifluoromethanesulphonic (triflic) acid exhibit a very strong structural dependence. This is illustrated by the phos-

phorus spectrum of the mixture of amino acids **1a*** ($n = 0$), **1a** ($n = 1$), **1b** ($n = 2$) and **1c** ($n = 3$) (Fig. 1). Thus, strong protonation of phosphonic groups is accompanied by a substantial increase of their chemical shifts $\delta$ [P], increasing rapidly with the distance between the two phosphorus atoms in the molecule. Indeed, whereas the spectrum of (aminomethylene)bisphosphonic acid (**1a***, $n = 0$) in triflic acid exhibits a singlet at 11.7 ppm, that of 1-aminopropane-1,3-diphosphonic acid (**1c**, $n = 3$) exhibits two signals, at 24.8 (P–C–N) and at 45 ppm (P–$C_\omega$), respectively.

### *2.3. Potentiometric investigations of protonation equilibria of the 1-aminoalkanediphosphonic acids (1)*

The dissociation constants of aminoalkanediphosphonic acids (**1**), 1-aminoethanephosphonic acid ($Ala^P$), methanediphosphonic acid, asparagic (Asp) and glutamic (Glu) acid are listed in Table 4.

The first and the second dissociation constants of 1-aminoalkanediphosphonic acids (**1**) were found to lie in the domains $1 < pk_1$ and $1.1 < pk_2$, illustrating the strongly acidic character of these amino acids. The third ($5.2 < pk_3 < 5.7$) and the fourth ($6.6 < pk_4 < 7.6$) dissociation constants indicate that the larger structural influence resulted from the mutual inductive influence of the phosphonic and aminophosphonic functions, which depended on the distance between phosphorus atoms of these two entities. The values of $pk_3$ and $pk_4$ of 1-aminoalkanediphosphonic acids suggest that they can exist, as at least as triply ionized species at physiological pH (*ca.* 7.4). There is a relatively smaller difference in the $pk_5$ values.

These results suggest that 1-aminoalkanediphosphonic acids have higher acidities than methanediphosphonic acid ($pk_2$, $pk_3$ and $pk_4$) and of their carboxylic analogues (Asp and Glu) (compare $pk_1$, $pk_3$ and $pk_5$ for **1** with the corresponding values of $pk_1$, $pk_2$ and $pk_3$ of Asp or Glu).

1-Aminoalkanediphosphonic acids (**1**) possess more available protons than 1-aminoalkanephosphonic acids. In spite of this, these two groups of amino acids exhibit some similarity in the corresponding dissociation equilibria (compare the values of $pk_1$, $pk_3$ and $pk_5$ for **1** with the values of $pk_1$, $pk_2$ and $pk_3$ for $Ala^P$). The

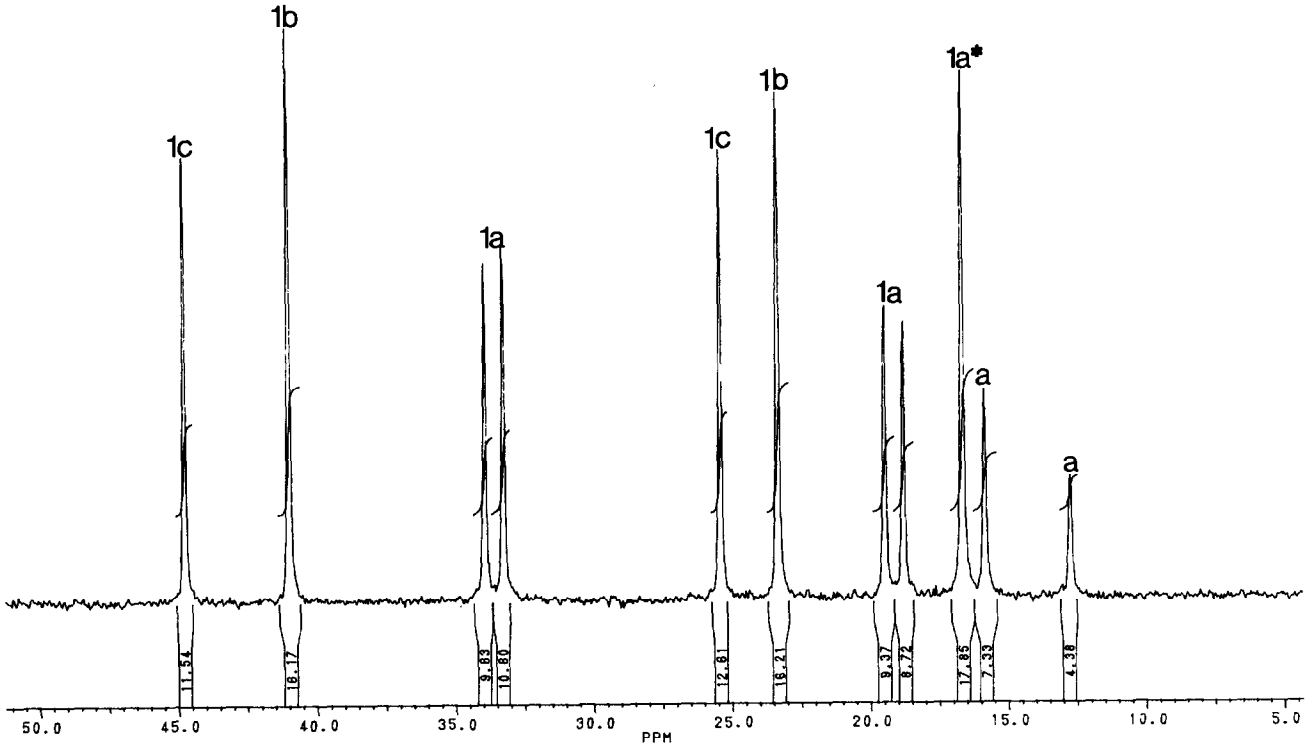



Fig. 1. The proton-decoupled phosphorus spectrum of the mixture of amino acids **1a*** ($n = 0$), **1a** ($n = 1$), **1b** ($n = 2$) and **1c** ($n = 3$) (the mixture contained 10 mg of each amino acids **1** in 1 ml of triflic acid.) Signals at 12.9 and 16.0 ppm reveal an impurity of (aminomethylene)bisphosphonic acid (**1a***).

comparison of dissociation constants of 1-aminoalkanediphosphonic acids (**1**) with those of their carboxylic analogues (Asp, Glu) exhibits the similar trend in respect of structural influences on the acidity.

The (aminomethylene)bisphosphonic acid (**1a***, $n = 0$), has the lowest acidicity ($pk_2$ and $pk_4$) among this type of amino acid.

## 3. Experimental section

All melting points (Boetius apparatus) are uncorrected. The $^{31}$P-NMR spectra were recorded with a Bruker AC 200 spectrometer at 81.01 MHz. Positive chemical shift values denote resonances at lower field than $H_3PO_4$. $^1$H-NMR spectra were recorded at 200 MHz. The low resolution mass spectra were obtained with Finnigan MAT 95 spectrometer by the fast atom bombardment (FAB) technique (mulls in glycerol matrix were bombarded with $Cs^+$ ions at 13 keV).

The acid dissociation (protonation) constants of the amino acids **1** were determined by pH-metric titration by means of an automatic titrator connected to an IBM PC computer (Elwro, Poland) fitted with a combined glass-calomel electrode OP-0808 P (Radelkis). The electrode system was calibrated using standard buffer solutions ($2 < pH < 10$), so that the pH-meter readings could be converted into hydrogen-ion concentrations. In all cases the temperature was $20.0 \pm 0.5$°C. The exact concentrations of amino acid solutions were determined by titration; the concentrations (in samples of 4 ml) were approximately $5 \times 10^{-3}$ mol dm$^{-3}$. The ionic strength was adjusted to 0.1 mol dm$^{-3}$ with potassium nitrite. The titrations (100 to 200 measurements with increment of 0.002 ml) were performed over the pH range 1–11, with a hydrochloric acid solution of known concentration (*ca.* 0.4 mol dm$^{-3}$; $1 < pH < 2$) and with a KOH solution of known concentration (*ca.* 0.4 mol dm$^{-3}$; $2 < pH < 11$), respectively.

N-Phenylthiourea (**3**), triphenyl phosphite (**4**) bromoacetal and 3-chloropropionaldehyde diethyl acetal were commercial products (Aldrich, Milwaukee, USA). The phosphonyl aldehydes **2a** and **2b** were prepared by the Arbusov reaction from the corresponding halogenoacetals and triethyl phosphite and subsequent deacetalization of intermediary acetals (*cf.* Ref. 15). 4-Bromobutyraldehyde diethyl acetal and/or 2-(3-bromopropyl)-1,3-dioxolane were prepared from tetrahydrofurane as described previously [16], and were used for synthesis of 4-phosphonylbutyraldehyde acetals (**2c**). (Aminomethylene)bisphosphonic acid (**1a***) was made as described previously [10].

Product purities were determined from integrated NMR spectra, by TLC or paper chromatography.

### *3.1. Synthesis of 4-(O,O-diethylphosphono)butanal. (O,O-Diethyl 4-oxo-butanephosphonate)*

A mixture of 2-(3-bromopropyl)-1,3-dioxolane (4.25 g, 0.22 mol) and triethyl phosphite (3.6 g, 0.22 mol) was stirred and heated at 110°C under argon for 10 h. Volatile components were evaporated off under reduced pressure (at 50°C under 20 hPs and 0.5 hPs) and the residue was passed through a silica column (eluent, hexane) to yield, after evaporation of the solvent, the acetal as a light pale oil (2.95 g, 0.0115 mol). (Physical characteristics of acetal: $^{31}$P-NMR ($CDCl_3$) $\delta = 32.2$ ppm; $^1$H-NMR ($CDCl_3$) $\delta$: 1.32 (t, 6H, $J = 7.1$ Hz, $CH_3CH_2O$); 1.6–2.1 (m, 4H, $P-CH_2CH_2CH_2$); 3.8–4.0 (m, 4H, $OCH_2CH_2O$); 4.0–4.25 (m, 6H, $P-CH_2$, $CH_3CH_2O$); 4.86 (t, 1H, $J = 4.2$ Hz, CH)).

Acetal (2.9 g, 0.011 mol) was then dissolved in a mixture of dioxane (10 ml) and a 1% aqueous solution of hydrochloric acid (30 ml) and the mixture was boiled under argon for 2 h. The solvents were evaporated off under reduced pressure (90°C, 20 hP), the residue was cooled down, and the aldehyde **2c** was extracted with methylene chloride in a Soxhlet apparatus for 8 h. The extract solution was concentrated by evaporation under reduced pressure (50°C, 20 hP) to give the crude aldehyde as a light yellow oil (2.4 g, 0.011 mol), which was used without purification in the synthesis of thioureidoalkanephosphonate (**5c**).

### *3.2. The synthesis of 1-aminoalkane-1,n-diphosphonic acids 1 (n = 1, 2, 3). General procedure A*

Triphenyl phosphite (**4**) (0.015 mol; 4.65 g) was added in one portion to a solution of aldehyde **2** (0.01 mol) and N-phenylthiourea (**3**) (0.015 mol; 2.26 g) in glacial acetic acid (20 ml). The mixture was stirred at 60°C for 1 h, left to stand overnight at room temperature and then diluted with water (2 ml). After 6 h the precipitate was filtered off and washed with AcOH-$H_2O$ (1 : 1) to give corresponding thioureidoalkanephosphonate **5a** or **5b** as crystalline compounds pure as indicated by their $^{31}$P NMR spectra. The products were purified for microanalysis by recrystallization from chloroform-methanol (5 : 1). Thioureidoalkanephosphonate (**5c**) was isolated as an oil by chromatography on a silica column (eluent : chloroform-methanol (10 : 1)). Thioureidoalkanephosphonates (**5**) were dissolved in glacial acetic acid (50 ml) and hydrochloric acid (100 ml, 1 : 1) and the solution was heated under reflux for 12 h. The mixture was then cooled to room temperature, diluted with water (100 ml), and extracted with toluene ($2 \times 50$ ml). The aqueous layer was evaporated to dryness under reduced pressure, and the solid residue was dissolved in water (10 ml). The solution was passed through Dowex 50 W × 8 column and fractions containing amino acids **1**

(ninhydrin test) were collected. The combined fractions containing **1a**, **1b** or **1c**, respectively, were concentrated under reduced pressure to *ca.* 5 ml and 1-aminoalkanediphosphonic acids were precipitated with ethanol (25 ml), and dried to constant weight in a desiccator under reduced pressure over solid phosphorus pentoxide and potassium hydroxide.

### *3.3. The synthesis of 1-aminoalkane-1,n-diphosphonic acids 1 (n = 1, 2, 3). Procedure B*

A mixture of **2c** (0.01 mol), **3** (0.015 mol) and **4** (0.015 mol) in glacial acetic acid (20 ml) was stirred for 1 h at 60°C (oil-bath), left to stand overnight at room temperature, and, then treated with concentrated hydrochloric acid. Work-up was as described for procedure A.

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