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1-Aminothiaalkanephosphonic Acids and Their Sulfinyl and Sulfonyl Derivatives: Synthesis and Acidic Properties

Zbigniew H. Kudzin*

Department of Organic Chemistry, University of Łódź, Łódź 90-136, Poland

Grzegorz Andrijewski

Department of General and Inorganic Chemistry, University of Łódź, Łódź 90-136, Poland

Józef Drabowicz

Centre of Molecular and Macromolecular Studies, Polish Academy of Sciences, Łódź 90-362, Poland

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ABSTRACT

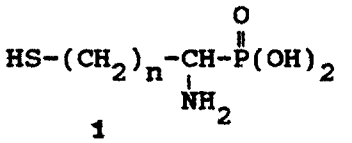
*Several 1-aminothiaalkanephosphonic acids **2** were synthesized and selectively oxidized to their sulfinyl **3** and sulfonyl **4** derivatives. For the compounds **2**, **3**, and **4**, their dissociation properties were determined potentiometrically.*

INTRODUCTION

Aminoalkanephosphonates have attracted much attention in recent years, mainly as phosphonic components of mixed phosphono-carbonic peptides, which have been found to possess strong antibacterial activity [1–3]. The other reason that these compounds have been an object of intensive investigations stems from their very interesting chelating and flame retardant properties [4–7].

As a result, the synthesis of new aminoalkanephosphonic acids has been the subject of extensive studies, and a number of synthetic procedures are now available [8].

Recently, we reported the synthesis of phosphonocysteine (**1a**; $n = 1$) and phosphonohomocysteine (**1b**; $n = 2$) and their S-substituted derivatives represented by the structure **2** [9–11].



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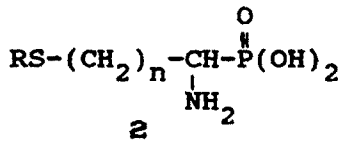

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Taking into account the well-known fact that the biological activity of organic sulfur compounds is strongly modified by the oxidation state of the sulfur atom [12,13], it is interesting to check such activity in sulfinyl **3** and sulfonyl **4** derivatives of **2**.

Dedicated to Prof. J. C. Martin on the occasion of his retirement from the Department of Chemistry, Vanderbilt University.

*To whom correspondence should be addressed.

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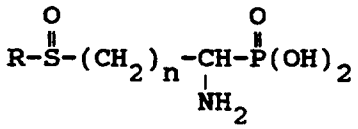

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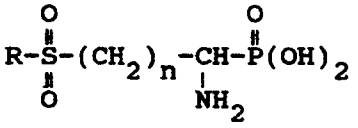

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Moreover, our interest in the preparation of compounds **3** and **4** was augmented by the expectation that they would also possess good chelating properties [14].

DISCUSSION AND RESULTS

Synthetic Investigations

In this section, we present the synthesis of the sulfinyl **3** and sulfonyl **4** derivatives of the amino acids **2**, based on the selective oxidation of the latter compounds. Hydrogen peroxide was found to be useful as a selective oxidant of thioethers in the case of simple sulfides [15]. However, application of this reagent for the oxidation of sulfides bearing an acidic function is limited by the fact that, in the presence of such a group, the subsequent oxidation of the sulfoxides initially formed to sulfones is facilitated. For this reason, the oxidations of amino acids related to methionine have been carried out using hydrogen peroxide in nearly stoichiometric amounts and/or carrying out the reaction at low temperature with careful TLC monitoring of the reaction's progress [16–20].

We have found that the addition of DMSO, used in excess to the oxidant, to the reaction mixture of the amino acids **2**, and hydrogen peroxide, enables the selective course of oxidation **2** → **3**, at ambient temperature, in spite of a large excess of oxidant used. The opposite effect was observed with the use of selenium (IV) dioxide [21] as a catalyst.

The acceleration of the second oxidation stage (**3** → **4**) results in a fast and almost quantitative conversion of the amino acids **2** to their sulfonyl derivatives **4**.

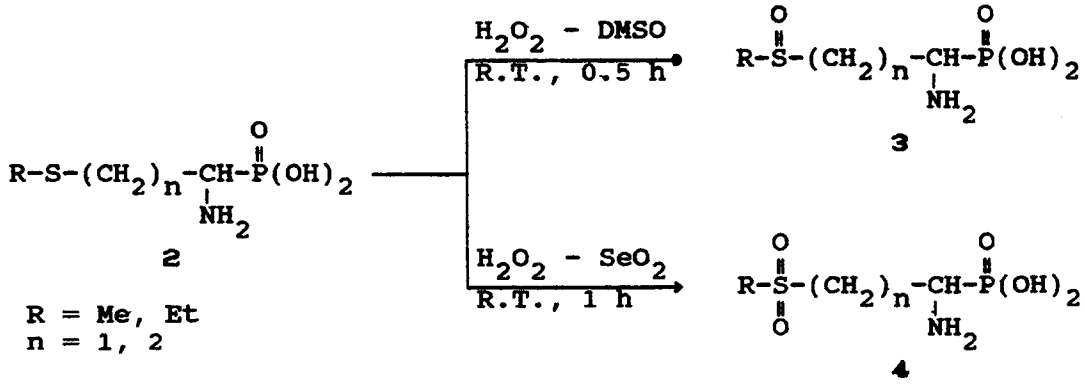
The latter reagent has also been successfully applied in the oxidation system TFA-H_2O_2-SeO_2 for oxidation of surfactant derivatives of 1-aminothiaalkanephosphonic acids to their sulfonyl analogs [20]. The yields and physical and analytical properties of the amino acids **3** and **4** are summarized in Tables 1 and 2, respectively.

Potentiometric and ^{31}P NMR Spectroscopic Investigations of Protonation Equilibria of the Aminophosphonic Acids **2–4**

The acid dissociation constants of the amino acids **2** and their sulfinyl **3** and sulfonyl analogs **4** are presented in Table 3.

These results are in accord with those reported earlier for other 1-aminoalkanephosphonic acids [23–25]. Thus, the first dissociation constants (pk_1) have been found to lie in the domain $1 < pk_1 < 2$, illustrating the strong acidic character of these compounds. The second and the third dissociation constants (pk_2 and pk_3) of 1-aminothiaalkanephosphonic acids are lower in comparison with those observed for the corresponding 1-aminoalkanephosphonic acids. This effect results from the presence of the thioalkyl group of the amino acids **2**. It is higher for the S-alkyl derivatives of phosphonocysteine (n = 1) and lower for the corresponding derivatives of phosphonohomocysteine (n = 2), obviously due to the inductive effect. Therefore, dissociation constants of derivatives **2a**, **2b**, **3b**, and **4b** are lower than those determined for derivatives of **2c**, **2d**, **3d**, and **4d**. Since the electron withdrawing effect of thioether, sulfinyl, and sulfonyl functions increases in the order, R-S- < R-S(O)- < R-S(O)$_2$, the aminophosphonic acids **2** being weaker acids than their corresponding sulfinyl derivatives **3**. The latter amino acids **3**, in turn, are weaker acids than their sulfonyl analogs **4**.

It is obvious that, due to the nature of the aminophosphonic acids being considered, the ioniza-



(1)

TABLE 1 Yields and Analytical Data of Amino Acids **2** and Their Sulfinyl **3** and Sulfonyl **4** Derivatives: R-S/0/$_m$/CH_2/$_n$CH/NH_2/PO_3H_2 **2** (m = 0), **3** (m = 1), and **4** (m = 2)

Compound						Molecular	Microanalysis Data (Calcd./found)						
Nr	R	n	m	Yield[a] (%)	Mp (°C)	Formula (weight)	C (%)	H (%)	N (%)	P (%)	S (%)	TLC[b] (R_f)	
2a	CH_3	1	0	—	258–260[10]	$C_3H_{10}NPO_3S$	21.02	5.92	8.19	18.10	18.70	0.69[c]	0.40[e]
						(171.2)	21.15	6.16	8.07	17.86	19.10	0.62[d]	1.00[f]
2b	C_2H_5	1	0	—	257–259[10]	$C_4H_{12}NPO_3S$	25.90	6.55	7.57	16.75	17.30	0.77[c]	0.52[e]
						(185.2)	26.07	6.60	7.65	16.76	17.46	0.70[d]	0.92[f]
2c	CH_3	2	0	—	270–272[9]	$C_4H_{12}NPO_3S$	25.90	6.55	7.57	16.75	17.30	0.83[c]	0.50[e]
						(185.2)	26.00	6.49	7.57	16.76	17.30	0.73[d]	0.92[f]
2d	C_2H_5	2	0	—	261–263[9]	$C_5H_{14}NPO_3S$	30.40	7.03	7.05	15.58	16.10	0.87[c]	0.55[e]
						(199.2)	30.05	7.04	7.29	15.66	16.30	0.74[d]	0.76[f]
3a	CH_3	1	1	88	194–196	$C_3H_{10}NPO_4S$	19.30	5.78	7.53	16.56	17.15	0.40[c]	0.22[e]
						(187.2)	19.64	5.73	7.63	16.89	17.21	0.30[d]	0.74[f]
3b	C_2H_5	1	1	86	192–194	$C_4H_{12}NPO_4S$	23.90	6.02	6.96	15.40	15.93	0.49[c]	0.34[e]
						(201.2)	23.89	6.26	6.82	15.60	15.75	0.33[d]	0.71[f]
3c	CH_3	2	1	85	185–187	$C_4H_{12}NPO_4S$	23.90	6.02	6.96	15.40	15.93	0.45[c]	0.24[e]
					188–190[13]	(201.2)	23.94	6.26	6.74	15.56	15.86	0.35[d]	0.62[f]
3d	C_2H_5	2	1	93	194–196	$C_5H_{14}NPO_4S$	28.08	6.57	6.53	14.32	14.90	0.57[c]	0.39[e]
						(215.2)	27.70	6.80	6.83	14.41	14.68	0.40[d]	0.59[f]
4a	CH_3	1	2	90	250–252	$C_3H_{10}NPO_5S$	17.79	4.96	6.90	15.28	15.79	0.54[c]	0.24[e]
						(203.2)	17.80	5.20	6.70	15.10	15.80	0.43[d]	0.81[f]
4b	C_2H_5	1	2	89	258–260	$C_4H_{12}NPO_5S$	22.18	5.58	6.46	14.29	14.80	0.61[c]	0.41[e]
						(217.2)	22.30	6.00	6.40	14.30	14.90	0.48[d]	0.74[f]
4c	CH_3	2	2	86	254–256	$C_4H_{12}NPO_5S$	22.18	5.58	6.46	14.29	14.80	0.61[c]	0.27[e]
					258–260[13]	(217.2)	22.40	6.00	6.40	14.00	14.85	0.50[d]	0.64[f]
4d	C_2H_5	2	2	93	255–257	$C_5H_{14}NPO_5S$	26.10	6.10	6.06	13.41	13.85	0.75[c]	0.41[e]
						(231.2)	26.50	6.30	6.30	13.60	—	0.57[d]	0.64[f]

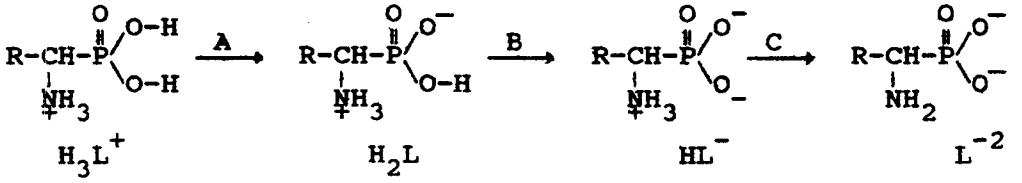
[a]The yields were calculated on the base of amino acids **2**.
[b]Cellulose plates DC (E. Merck, Darmstadt, Germany); indicator—0.5% ninhydrin in ethanol. Solvents: [c]pyridine-acetic acid-water-dimethylsulphoxide (8:9:3:5); [d]pyridine—acetic acid-water (10:7:3); and [e]*n*-butanol-acetic acid-water (12:3:5).
[f]Electrophoretic data: buffer solution, pH = 7.3; U = 40 (V cm^{-1}), t = 1 h, and standard compound **2a**.

tion state of the phosphonic group should exert a strong influence on the chemical shift of the phosphorus nucleus. The pH dependence of the phosphorus chemical shift [δ(P) = f(pH)] for several of the amino acids **2**, **3**, and **4**, depicted in Figure 1, clearly supports such an assumption. The observed complex character of these curves, different from those for ethanephosphonic acid (Figure 1) and/or for those reported by Maier for bis(aminomethyleno)phosphinic acid [22], results from their protonation sequences presented in Equation 2.

Similar shapes have characterized the curves δ(P) = $f(a)$ (where a is the titration degree) presented by Hagele et al. [26,27] for 1-aminoethanephosphonic and 1-aminopropanephosphonic acid, respectively. The complex course of these curves results from the subsequent deprotonation:

Thus, the subsequent dissociation of two protons from H_3L^+, which leads via H_2L to HL^- structures, is accompanied by a decrease of chemical shifts δ(P) of the aminophosphonic acids **2–4**. These conversions are illustrated on the graph as two declining parts of curves: (A) in the region of pH 1–3 and (B) in the region of pH 4–6.5. The characteristic V-shape of the curves appearing at the region of pH 6–8 can be considered to be the result of intersection of two different curves: the first one (descending) attributed to the conversion $H_2L \xrightarrow{(B)} HL^-$, and the second (ascending) attributed to the conversion of $HL^- \xrightarrow{(C)} L^{-2}$.

The examination of these dependencies in more acidic medium (e.g., 2.0 N HCl) revealed the further strong increase of chemical shifts δ(P) of ami-



(2)

TABLE 2 Spectral Characteristics of Amino Acids **2**, **3**, and **4**

Compound	^{31}P NMR δ (ppm)	IR (KBr) ν_{max} (cm^{-1})	^{1}H NMR[a] δ (ppm)	Mass Spectrometry (m/e vs. Intensitivity (%)[b]) Molecular formula (weight)	M	M-RS $(O)_m$	M-PTMS[c]	
2a	18.3[d] 13.3[e]	Ref. 10	Ref. 10	$C_{12}H_{34}NPO_3SSi_3$ (387)	387 (1.9) (0.1)	340 (0.6) (0.9)	162 (2.9) (4.2)	211 (14.3) (13,6)
2b	18.3[d] 13.2[e]	Ref. 10	Ref. 10	$C_{13}H_{36}NPO_3SSi_3$ (401)	401 (0.2) (0.1)	340 (0.3) (0.3)	176 (1.9) (1.4)	211 (100) (64)
2c	20.6[d] 15.3[e]	Ref. 9	Ref. 9	$C_{13}H_{36}NPO_3SSi_3$ (401)	401 (0.2) (0.1)	354 (0.1) (0.1)	176 (2.0) (2.0)	211 (100) (71)
2d	20.5[d] 15.3[e]	Ref. 9	Ref. 9	$C_{14}H_{38}NPO_3SSi_3$ (415)	415 (0.5) (0.1)	354 (3.8) (2.9)	190 (13.0) (6.7)	211 (76) (85)
3a	16.5; 17.1[d] 10.9; 11.2[e]	broad 3700–2000, 1615, 1530, 1390–1400 bs, 1300–1200 bs, 1170, 1070, 1000, 915	3.0 (s, 3H, CH_3); 4.0–3.5 (m, 2H, CH_2CH); 4.3–5.0 (m, 1H, CH); 7.4–8.25 (bs, 3H, NH_3)	$C_{12}H_{34}NPO_4SSi_3$ (403)	403 (0.3) (0.1)	340 (0.5) (0.0)	178 (6.4) (4.8)	211 (91) (62)
3b	16.6; 17.3[d] 10.9; 11.3[e]	broad 3700–2000, 1630, 1530, 1465, 1370–1200 bs, 1180, 1120, 1025, 910	1.45 (t, 3H, CH_3CH_2SO); 2.7–4.1 (2.7–3.5 (m, 2H, CH_3CH_2SO); 3.5–4.1 (m, 2H, $S(O)CH_2CH$)); 4.3–5.0 (m, 1H, CH); 7.2–8.4 (m, 3H, NH_3)	$C_{13}H_{36}NPO_4SSi_3$ (417)	417 (0.1) (0.2)	340 (100) (30)	192 (92) (66)	211 (15) (21)
3c	19.0; 19.5[d] 14.0[e]	broad 3630–2000, 1640, 1530, 1450–1400 bs, 1370–1100 bs, 1070, 1025, 910	2.4–4.55 (2.4–3.1 (m, 2H, CH_2CH); 3.2 (s, 3H, $CH_3S(O)$); 3.3–3.9 (m, 2H, $S(O)CH_2CH_2CH$); 3.9–4.6 (m, 1H, CH)); 7.1–8.1 (bs, 3H, NH_3)	$C_{13}H_{36}NPO_4SSi_3$ (417)	417 (0.9) (0.9)	354 (1.4) (2.4)	192 (3.8) (7.8)	211 (18) (5.6)
3d	19.4[d] 14.0[e]	broad 3630–2000, 1630, 1540, 1230, 1180, 1060, 990, 920	1.45 (t, 3H, $CH_3CH_2S(O)$); 2.4–4.6 (2.4–3.0 (m, 2H, CH_2CH); 3.0–3.3 (m, 2H, $CH_3CH_2S(O)$); 3.3–3.75 (m, 2H, $CH_3CH_2S(O)CH_2$); 3.75–4.6 (m, 1H, CH)); 7.25–8.0 (bs, 3H, NH_3)	$C_{14}H_{38}NPO_4SSi_3$ (431)	431 (0.3) (0.1)	354 (0.1) (9.1)	206 (0.3) (0.0)	211 (24) (31)
4a	16.1[d] 10.1[e]	broad 3600–2000, 1615, 1530, 1305, 1275, 1180, 1140, 1090, 1020, 940, 920	2.55 (s, 3H, CH_3); 3.3 (d, 2H, $S(O)_2CH_2CH$); 3.85–4.25 (m, 1H, CH); 7.3–8.0 (bs, 3H, NH_3)	$C_{12}H_{34}NPO_5SSi_3$ (419)	419 (0.2) (0.1)	340 (0.3) (0.0)	194 (2.5) (1.9)	211 (100) (100)
4b	16.2[d] 10.2[e]	broad 3260–2200, 1610, 1530, 1290, 1250–1200 bs, 1180, 1125, 1025, 910	1.35 (t, 3H, CH_3); 2.7–4.2 (2.7–3.8 (m, 4H, $CH_2S(O)_2CH_2$); 3.8–4.2 (m, 1H, CH)); 7.2–8.0 (bs, 3H, NH_3)	$C_{13}H_{36}NPO_5SSi_3$ (433)	433 (0.5) (0.2)	340 (7.7) (11.0)	208 (74) (73)	211 (12) (2.0)
4c	19.0[d] 13.6[e]	broad 3720–2200, 1700–1570 bs, 1540, 1450, 1315, 1290, 1230, 1175, 1030, 930	2.4–3.1 (m, 2H, CH_2CH); 3.2 (s, 3H, CH_3); 3.5–3.9 (t, 2H, $CH_3S(O)_2CH_2$); 4.0–4.5 (m, 1H, CH); 7.2–7.9 (bs, 3H, NH_3)	$C_{13}H_{36}NPO_5SSi_3$ (433)	433 (1.2) (1.2)	354 (1.0) (1.1)	208 (51) (62)	211 (36) (2.0)
4d	19.0[d] 13.6[e]	broad 3250–2200, 1615, 1535, 1285, 1260, 1230, 1180, 1130, 1110, 1065, 1000, 990, 920	1.45 (t, 3H, $CH_3CH_2S(O)_2$); 2.4–4.5 (2.4–3.0 (m, 2H, CH_2CH); 3.0–3.3 (m, 2H, $CH_3CH_2S(O)_2$); 3.65 (t, 2H, $S(O)_2CH_2CH_2CH$); 3.9–4.5 (m, 1H, CH)); 7.2–8.1 (bs, 3H, NH_3)	$C_{14}H_{38}NPO_5SSi_3$ (447)	447 (0.3) (0.6)	354 (1.0) (0.8)	222 (2.8) (3.8)	211 (18) (76)

[a]Approximately 5% solutions of amino acids **2**, **3**, and **4** in trifluoroacetic acid.
[b]Intensitivity (%) of ions were taken at 15 eV (upper bracket values) and at 70 eV (lower bracket values) of ionizing energy.
[c]P TMS presents $(TMSO)_2P(O)$ (m/e = 225) fragment.
[d]Approximately 5% solutions of amino acids **1**, **2**, and **3** in 1.5 N aqueous sodium hydroxide.
[e]Approximately 5% solutions of amino acids in 2.0 N aq hydrochloric acid.

nophosphonic acids **2d**, **3d**, and **4d**, caused presumably by the protonation and/or subsequent hydration of the P=O function. The investigation of the titration curve for 1-amino-3-ethylsulfonylpropanephosphonic acid (**3d**) revealed the existence of two separable peaks ($\Delta\delta$(P) ~ 0.1 ppm), due to the formation of diasteroisomeric compounds. The tentative examination of curves δ(P) = f(pH) at their deflection points suggests the possibility of application of these plots for the investigation of the dissociation (protonation) equilibria of aminophosphonic acids.

EXPERIMENTAL

All melting points were taken on a Boetius apparatus and are uncorrected. ^{31}P NMR spectra were

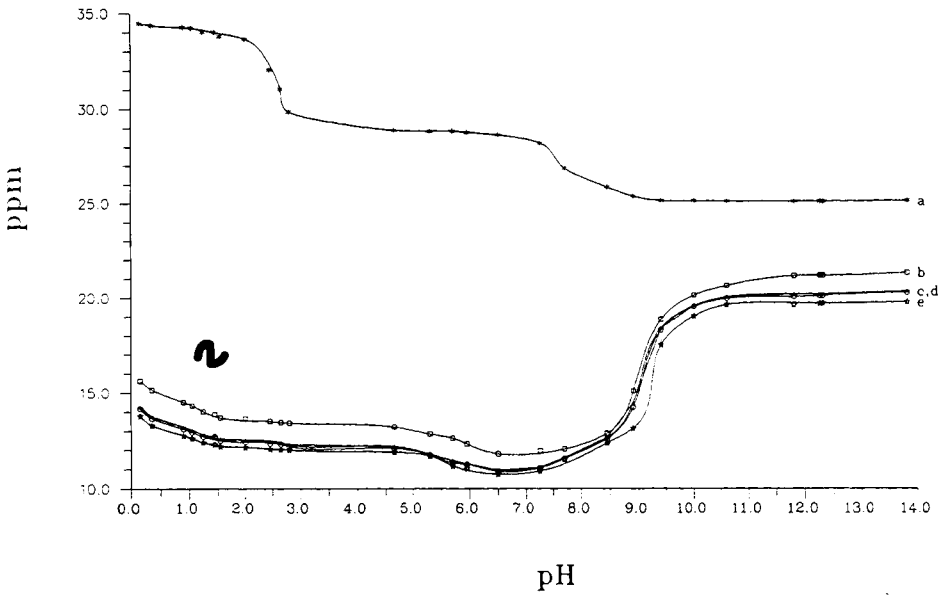


FIGURE 1 The pH dependence of phosphorus chemical shifts [δ(P)] of the 0.01 molar aqueous solutions (20% of D_2O) of (a) ethanephosphonic acid and aminoalkanephosphonic acids (b) **2d**, (c) and (d) **3d**, and (e) **4d**. (Proton decoupled spectra were recorded on a Bruker AC 200 spectrometer operating at 81.01 MHz.)

TABLE 3 Dissociation Constants of the Amino Acids **2**, **3**, and **4**

Amino Acids [*R'–CH(NH₂)P(O)(OH)₂*]		*Negative Logarithm of Dissociation Constants*[a,b]	
Nr	*R'*	pk_2	pk_3
2a	CH_3–S–CH_2–	5.32	9.51
2b	C_2H_5–S–CH_2–	5.38	9.52
2c	CH_3–S–$(CH_2)_2$–	5.65	9.74
2d	C_2H_5–S–$(CH_2)_2$–	5.68	9.73
3b	C_2H_5–S(O)–CH_2–	5.02	8.18
3d	C_2H_5–S(O)–$(CH_2)_2$–	5.43	9.17
4b	C_2H_5–$S(O)_2$–CH_2–	5.00	8.07
4d	C_2H_5–$S(O)_2$–$(CH_2)_2$–	5.33	8.91

[a]Dissociation constants k (or protonation constants K) are determined for the corresponding equilibria:

$$L^{-2} + H^+ \underset{k3}{\overset{K_1}{\rightleftarrows}} HL^-; \quad HL^- + H^+ \underset{k2}{\overset{K_2}{\rightleftarrows}} H_2L; \quad H_2L + H^+ \underset{k1}{\overset{K_3}{\rightleftarrows}} H_3L^+$$

Thus, $K_1 = \dfrac{[HL^-]}{[L^{-2}][H^+]}$; $K_2 = \dfrac{[HL^-]}{[L^{-2}][H^+]}$; $K_3 = \dfrac{[HL^-]}{[L^{-2}][H^+]}$; and $k_1 = 1/K_3$; $k_2 = 1/K_2$; $k_3 = 1/K_1$.

[b]For all compounds in the table the value of dissociation constants have been found to lie in domain $1 < pk_1 < 2$.

recorded on a Bruker AC 200 spectrometer operating at 81.01 MHz. Negative chemical shift values are reported for compounds absorbing at higher fields than H_3PO_4. ^1H NMR spectra were taken at 80 MHz on a Tesla BS 487 spectrometer, and IR spectra (KBr) were measured on a Zeiss-Jena UR-10 spectrometer. Mass spectra were obtained on a LKB 2091 spectrometer at 15 and 70 eV ionizing energy. Samples were introduced via a Direct Inlet System. Product purities were determined from integration of NMR spectra.

S-alkylderivatives (R = Me, Et) of phosphonocysteine (**1a**, n = 1) and phosphonohomocysteine (**1b**, n = 2) were prepared by hydrolytic degradation of the corresponding thioureidoalkanephosphonates (obtained from triphenylphosphite, *N*-phenylthiourea, and thiaaldehydes) according to Refs. [9] and [10].

The dissociation (protonation) constants of the amino acids **2**, **3**, and **4** were determined by pH-metric titration by means of a Mettler DL 40 RC Memotitrator fitted with a combined glass-calomel electrode. The electrode system was calibrated by use of 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 25°C + 0.2°C. The exact concentrations of amino acids solutions were determined by titration, these concentrations in the samples (50 cm^3) being approximately 3.5×10^{-3} mol dm^3. The ionic strength was adjusted to 0.1 mol dm^{-3} with potassium nitrite. The titrations (150–200 measurements with increments equal to 0.05 cm^3) were performed over the pH range 1–11, with 0.1 mol dm^{-3} HCl solution ($1 < pH < 3$) and with 0.1 mol dm^{-3} KOH solution ($3 < pH < 11$), respectively.

Preparation of the Sulfinyl Derivatives **3** *of the Amino Acids* **2**

General Procedure. Each of the amino acids **1** (5 mmol) was added in one portion into a cooled

(10°C) and well-stirred mixture of hydrogen peroxide (30% aq, 2 cm^3), water (2 cm^3), and dimethyl sulfoxide (3 cm^3), and the reaction mixture was stirred for 0.5 hours at room temperature. After dilution with acetone (30 cm^3), the mixtures were left in the refrigerator for 2 hours. The solvent layer was removed, and the residue was dissolved in distilled water (25 cm^3). The aqueous solutions of the amino acids **3** were passed through a Dowex 50W × 2 column, the fractions containing the amino acids (ninhydrin test) being collected and evaporated to dryness. The amino acids **3** were recrystallized from water-ethanol mixtures.

Preparation of the Sulfonyl Derivatives **4** *of the Amino Acids* **2**

General Procedure. Each of the amino acids **2** (5 mmol) was added in one portion into a cooled (10°C) and well-stirred solution of hydrogen peroxide (30% aq, 2 cm^3), water (3 cm^3), and selenic acid (0.01 g). The reaction mixture was stirred at room temperature for 0.5 hours, diluted with acetone (30 cm^3), and left in the refrigerator for 2 hours. The precipitated amino acids **4** were isolated by decantation, dissolved in distilled water (25 cm^3), and purified on a Dowex 50W × 2 column. The fractions containing the amino acids (ninhydrin test) were collected and evaporated to dryness, and the pure compounds **4** were recrystallized from water-ethanol mixtures.

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