ISSN 1070-3632, Russian Journal of General Chemistry, 2012, Vol. 82, No. 8, pp. 1453–1454. © Pleiades Publishing, Ltd., 2012.
Original Russian Text © R.A. Cherkasov, A.R. Garifzyanov, S.A. Koshkin, N.V. Davletshina, 2012, published in Zhurnal Obshchei Khimii, 2012, Vol. 82, No. 8, pp. 1392–1393.

LETTERS TO THE EDITOR

Synthesis and Acid–Base Properties of Aminophosphine Oxides on the Basis of Natural Amino Acids

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Received March 27, 2012

DOI: 10.1134/S107036321208021X

In recent years aminophosphonate derivatives of the natural amino acids attracted a considerable interest because of their pronounced physiological activity and specific complexing properties [1, 2]. However, the phosphine oxide derivatives of amino acids, which can show high efficiency in liquid and membrane extraction processes [3], were not described up to day. Using the Kabachnik–Fields reaction [1] in a dioctylphosphine–formaldehyde–amino acid three-component system, we synthesized a series of α-aminomethylphosphine oxides containing structural fragments of glycine (**I**), β-alanine (**II**), and its *N*-butyl derivative (**III**) of the general formula $Oct_2P(O)\cdot CH_2NR(CH_2)_nC(O)OH$, R = $Oct_2P(O)CH_2$, n = 1 (**I**); R = $Oct_2P(O)CH_2$, n = 2 (**II**); R = C_4H_9, n = 2 (**III**).

The long-chain octyl substituents were attached to the phosphorus atom to achieve the necessary lipophilicity of the potential extractants [3]. In chloroform solutions the methylphosphorylation of the *N*-unsubstituted amino acids (glycine and β-alanine) proceeds sufficiently easily even at the equimolar ratio of the reagents and results in the bisphosphorylation products **I** and **II**. *N*-Butyl-β-alanine, obviously, forms a tertiary phosphorylamine **III**.

The dissociation constants pK_{BH^+} of the acids conjugated to phosphorylamines **I**–**III** and the corresponding amino precursors were determined in an aqueous propan-2-ol (50 vol%). The values of pK_{a1} corresponding to the ammonium proton dissociation for diphosphorylamines **I** and **II** are below the limits of the experimental sensitivity (<2) [3]. The found value of 5.85 for monophosphorylamine **III** lies in the range characteristic of the aminomethylphosphine oxides. The NH-acidity of the initial amino acid is 9.58, 10.19, and 9.76, respectively. The pK_{a2} values indicating the carboxy group dissociation are 5.02 (**I**), 5.42 (**II**), and 3.00 (**III**), and for the corresponding amine precursors they are 2.34, 3.60 and 4.01, respectively. Comparing the obtained values of the acid dissociation for the phosphorylated and non-phosphorylated amino acids it is possible to conclude that attaching the phosphorylmethylene acceptor groups to the nitrogen atom affects more the basicity of the amine moiety located close to the nitrogen center than the carboxylic acid fragment. This effect is naturally more pronounced in the diphosphorylated aminophosphine oxides.

The dissociation constants were determined by the method described in [3]. The ^1H and $^{31}P–\{H\}$ NMR spectra were recorded on a Varian XL-300 spectrometer operating at 300 and 122.4 MHz, respectively.

General procedure for the synthesis of the phosphorylated amino acids. A mixture of 0.0365 mol of amino acid, 0.0384 mol of paraformaldehyde, 0.009 mol of amino acid hydrochloride, and 0.0365 mol of dioctylphosphine oxide in 80 ml of chloroform was heated with stirring for 1 h. The unreacted amino acid was filtered off and the solvent was removed in a vacuum. The crystalline products **I** and **II** were purified by a double recrystallization from ethyl acetate. The oily product **III** was kept in a vacuum to the constant mass.

***N,N*-Bis(methylenedioctylphosphoryl)aminoethanoic acid (I)**. Yield 95%, mp 95°C. ^1H NMR spectrum ($CDC1_3$), δ, ppm: 0.81–1.85 m (68H, C_8H_{17}), 3.03 d.d (4H, PCH_2N, $^2J_{HH}$ 3, $^2J_{PH}$ 64 Hz), 3.18 s (2H, CH_2COO). $^{31}P–\{H\}$ NMR spectrum (CH_3CN), ppm: δ_P 50.12 ppm.

***N,N*-Bis(methylenedioctylphosphoryl)-3-aminopropanoic acid (II).** Yield 93%, mp 98°C. ^{1}H NMR spectrum ($CDC1_3$), δ, ppm: 0.85–1.89 m (68H, C_8H_{17}), 2.52 t (2H, NCH_2, $^3J_{HH}$ 9 Hz), 2.95 d.d (4H, PCH_2N, $^2J_{HH}$ 3, $^2J_{PH}$ 64 Hz), 3.13 t (2H, CH_2COO, $^3J_{HH}$ 9 Hz). ^{31}P–{H} NMR spectrum (CH_3CN), ppm: δ_P 49.2 ppm.

***N,N*-Bis(methylenedioctylphosphoryl)-*N*-butyl-3-aminopropanoic acid (III)**. Yield 83.6%, n_D^{20} 1.4750. ^{1}H NMR spectrum ($CDC1_3$), δ, ppm: 0.81–0.93 m (9H, $\underline{CH_3}C_7H_{14}$, $\underline{CH_3}C_3H_6$), 1.19–1.80 m {32H, $P[(\underline{CH_2})_7CH_3]_2$, $CH_3\underline{CH_2}\underline{CH_2}$}, 2.20–2.30 br.s (2H, $N\underline{CH_2}C_3H_6$), 2.40–2.50 br.s (2H, $N\underline{CH_2}CH_2COOH$), 2.69 d (2H, PCH_2N, $^2J_{PH}$ 5.62 Hz), 2.82–2.92 br.s (2H, $NCH_2\underline{CH_2}COO$). ^{31}P–{H} NMR spectrum (benzene), ppm: δ_P 55.4 ppm.

ACKNOWLEDGMENTS

This work was financially supported by the Russian Foundation for Basic Research (grant no. 10-03-00580).

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