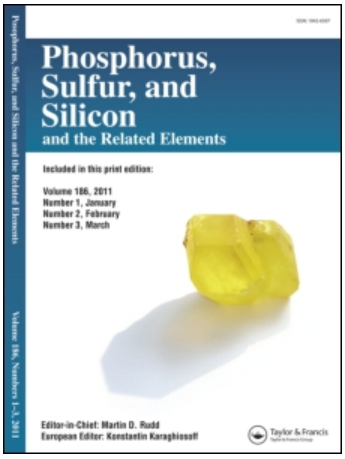

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Addition of Hypophosphorous Acid to *N,N'*-Terephthalylidene-bis[1-(alkoxycarbonyl)alkylamines]

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ADDITION OF HYPOPHOSPHOROUS ACID TO *N,N′*-TEREPHTHALYLIDENE-BIS[1-(ALKOXYCARBONYL)ALKYLAMINES]

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The preparation of 1,4-phenylene-bis[1-(alkoxycarbonyl)alkylamino-methanephosphonous acids] by the addition of hypophosphorous acid to terephthalylidene-bis[1-(alkoxycar bonyl)alkylamines] is described. Despite expectations, no chiral assistance of the amino acid ester moiety is observed.

Keywords Amino acid esters; azomethine bond; chiral assistance; chiral terephthalic imines; hypophosphorous acid

INTRODUCTION

The addition of hypophosphorous acid to terephthalic Schiff bases was stereoselective in a majority of cases. The addition of hypophosphorous acid to achiral *N*-alkyl terephthalic imines has been reported[1,2] to be diastereoselective to 100% and to lead to a *meso*-form, while the reaction performed on *N*-aryl imines has been noted to depend on the nature of a substituent at the aromatic ring.[2] Similar results have been reported for the addition of dialkyl phosphites to achiral *N*-alkyl and *N*-aryl terephthalic Schiff bases.[1,3–7]

The addition of dialkyl phosphites as well as hypophosphorous acid to a chiral *N*-(*R*)-α-methylbenzyl Schiff base led to the formation of all three possible diastereoisomers. This was rather unexpected in the case of the addition of hypophosphorous acid, because the addition of hypophosphorous acid to chiral mono (*R*)-*N*-α-methylbenzyl Schiff bases was demonstrated to be diastereoselective to 100%,[8,9] and we hoped that the influence of the chiral substituent at nitrogen would work in this case also. But evidently, that influence was in competition with the phenomenon determining the stereochemistry of the addition to terephthalic Schiff bases.

That is why we have reached for more efficient chiral auxiliaries, i.e., L-α-amino acid esters. We supposed that their chiral assistance would force the system to form one diastereoisomer, which was necessary for further synthesis of some macrocyclic systems.

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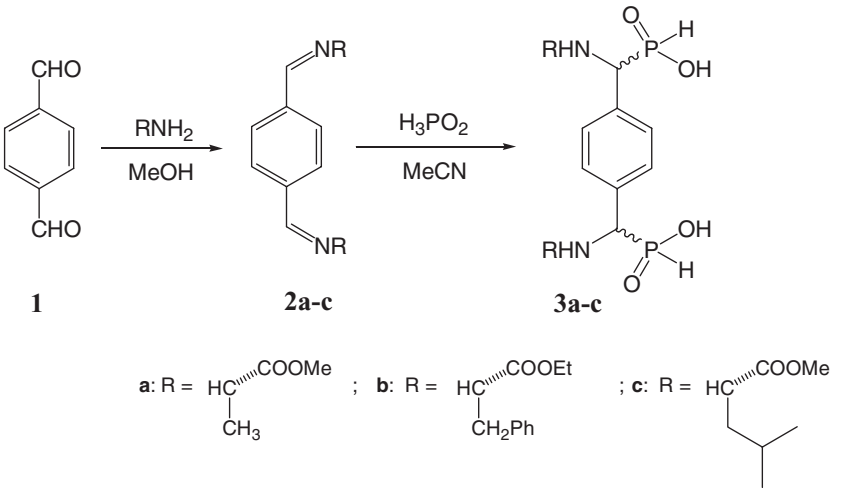
RESULTS AND DISCUSSION

We have chosen three model amino acid esters: L-alanine methyl ester, L-phenylalanine ethyl ester, and L-leucine methyl ester and prepared their imines **2a–c** with terephthalic aldehyde. Imines **2a–h** were prepared following a modification of the commonly known procedure for the condensation of corresponding hydrochlorides of amino acid esters with terephthalic aldehyde **1** in methanol in the presence of triethylamine at room temperature. After precipitation of the formed triethylamine hydrochloride from dichloromethane-hexane, the imines were obtained in almost quantitative yields.

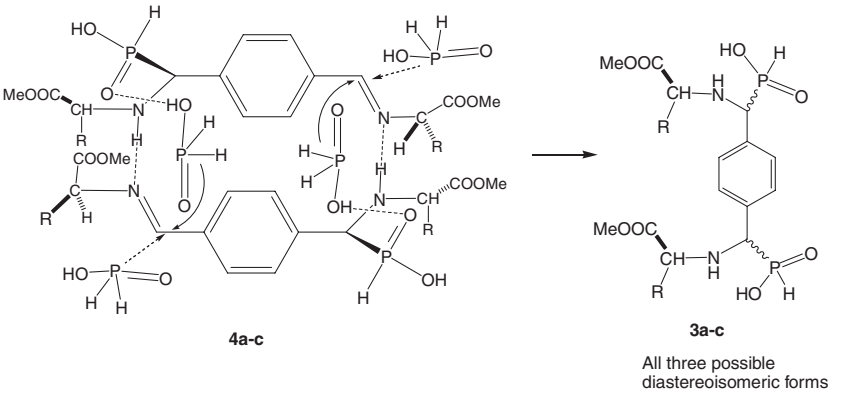
The preparation of terephthalic bis-aminophosphonous acids **3a–c** has been performed based on the previously published procedure.[2] Reactions were carried out in boiling acetonitrile for 5 h and subsequent stirring overnight at room temperature (Scheme 1). The acids were obtained as powder solids in moderate yields fluctuating around 45%, which was expected, as Barycki et al.[1] suggested much lower conversion rates for the addition to two azomethine groups.



Scheme 1

Unfortunately, the ^{1}H and ^{31}P NMR spectroscopy demonstrated that each of all three acids **3a–c** occurred as a mixture of all three possible diastereoisomeric forms in a 2:1:1 ratio; therefore no chiral assistance occurred. Evidently, the chiral assistance of L-α-amino acid esters interferes with the "natural" stereochemistry of the addition to terephthalic imines, as was demonstrated in the case of addition to *N*-α-methylbenzyl Schiff bases.[2] The problem is depicted in Scheme 2. Considering the formation of intermediate **4a–c**, the occurrence of which we have postulated in a case of nonchiral Schiff bases,[2] the "natural" action within the complex **4a–c** is in competition with the action of the amino acid chiral moiety, which may force the attack of the hypophosphorous acid molecule from the completely opposite direction. Therefore, the resultant stereoselectivity became zero, and the formation of the stoichiometrically equal amounts of all possible diastereoisomers occurred. The phenomenon is obvious from the ^{31}P NMR spectra. In the case of the leucine (**3c**) and phenylalanine (**3b**) derivatives, the magnetic nonequivalence of two phosphorus nuclei has been demonstrated for two of the three diastereoisomers, as their ^{31}P NMR

signals occurred as two-peak systems but not as single peaks, which was rather expected. However, such a phenomenon has not been noticed in the case of the alanine derivative **3a**.



Scheme 2

EXPERIMENTAL

All solvents (POCh-Poland) were routinely distilled and dried prior to use. Hypophosphorous acid 50% (Aldrich) was dehydrated following the published procedure.[2] Amino acid ester hydrochlorides and terephthalic aldehyde (Aldrich) were used as received. NMR spectra were recorded on a Varian Gemini 200 BB apparatus operating at 200 MHz (^{1}H NMR) and 81 MHz (^{31}P NMR). Elemental analyses were performed in the Centre for Molecular and Macromolecular Science of the Polish Academy of Science in Łódź, Poland.

Preparation of 1,4-Phenylene-bis[1-(alkoxycarbonyl)alkylamino]-methanephosphonous acids] 3a–c: General Procedure

In a 250-mL flask, terephthalic aldehyde (1.34 g, 10 mmol) was dissolved in methanol, then amino acid ester hydrochloride (20 mmol) and triethylamine (20 mmol) were added. The mixture was stirred at room temperature for 24 h, the solvent was removed in vacuo, and the residue was dissolved in dichloromethane. To this solution, hexane was added portionwise until white precipitate stopped occurring. The white precipitate was filtered off and discarded, and the filtrate was evaporated to give the corresponding imine. The imine (5 mmol) was dissolved in acetonitrile, hypophosphorous acid (0.66 g, 10 mmol) was added, and the mixture was refluxed for 5 h. Then the solvent was removed in vacuo to afford the crude acid, which was purified by dissolving in aqueous sodium hydroxide and subsequent precipitation with hydrochloric acid.

1,4-Phenylene-bis[1-(methoxycarbonyl)ethylaminomethanephosphonous acid] (3a). Yield: 0.85 g (39%); Mp: 101–105°C. Calcd. for $C_{16}H_{26}N_2O_8P_2$: C, 44.04; H, 6.01; N, 6.42. Found: C, 43.92; H, 5.87; N, 6.47. ^{1}H NMR (NaOD/D_2O, 200 MHz): δ 7.26 (s, C_6H_4, 4H); 6.97 and 6.80 (2d, $^1J_{PH}$ = 518.4 and 506.4 Hz, PH, 2H); 3.77 and 3.65 (2d, $^2J_{PH}$ = 15.1 and 15.4 Hz, PCH, 2H); 3.28 (s, OCH_3, 6H); 3.15 (q, J = 6.5 Hz, $\underline{CH}CH_3$, 2H); 1.12 (d, J = 6.5 Hz, $CH\underline{CH_3}$, 6H). ^{31}P NMR (NaOD/D_2O, 81 MHz): δ 27.96; 26.31; 26.29 (2:1:1).

1,4-Phenylene-bis[1-(ethoxycarbonyl)-2-phenylethylaminomethanephosphonous acid] (3b). Yield: 1.42 g (46%); Mp: 159–163°C. Calcd. for $C_{30}H_{38}N_2O_8P_2$: C, 58.44; H, 6.21; N, 4.54. Found: C, 58.43; H, 5.98; N, 4.18. ^{1}H NMR (NaOD/D_2O, 200 MHz): δ 7.15 (s, C_6H_4, 4H); 7.09-6.92 (m, PhH, 10H); 6.64 and 6.63 (2d, $^1J_{PH}$ = 522.6 Hz, PH, 2H); 3.77 and 3.65 (2d, $^2J_{PH}$ = 15.1 and 15.4 Hz, PCH, 2H); 3.49 (q, J = 7.1 Hz, $O\underline{CH_2}CH_3$, 4H); 2.95 (m, $\underline{CH}CH_2Ph$, 2H); 2.81-2.69 (m, $CH\underline{CH_2}Ph$, PCH, 6H); 1.03 (t, J = 7.1 Hz, $OCH_2\underline{CH_3}$, 6H). ^{31}P NMR (NaOD/D_2O, 81 MHz): δ 27.40; 27.15; 27.08; 26.10; 25.81 (4:1:1:1:1).

1,4-Phenylene-bis[1-(methoxycarbonyl)isopentylamino)methanephosphonous acid] (3c). Yield: 1.22 g (47%); Mp: 155–158°C. Calcd. for $C_{22}H_{38}N_2O_8P_2$: C, 50.77; H, 7.36; N, 5.38. Found: C, 51.92; H, 7.48; N, 5.05. ^{1}H NMR (NaOD/D_2O, 200 MHz): δ 7.22 (s, C_6H_4, 4H); 6.93, 6.75 and 6.68 (3d, $^1J_{PH}$ = 518.4 and 520.4 and 523.1 Hz, PH, 2H); 3.69 and 3.53 (2d, $^2J_{PH}$ = 14.2 and 17.6 Hz, PCH, 2H); 3.23 (s, OCH_3, 6H); 3.14 (t, J = 5.7 Hz, $\underline{CH}CH_2$, 2H); 2.81 (dd, J = 5.7 and 6.0 Hz, $CH\underline{CH_2}$, 4H); 1.32 (m, $\underline{CH}(CH_3)_2$, 2H); 0.67 (d, J = 5.4 Hz, $CH(\underline{CH_3})_2$, 12H). ^{31}P NMR (NaOD/D_2O, 81 MHz): δ 28.10; 28.02; 27.95; 26.70; 26.64 (4:1:1:1:1).

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