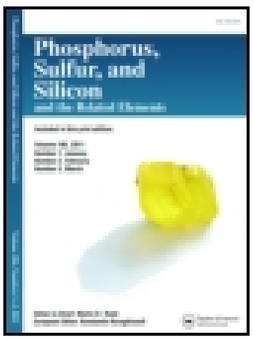

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Addition of Dimethyl Phosphite to *N*,*N'*-dialkyl- and -diaryl Terephthalaldimines and Its Stereochemistry Contrary to Behavior of Other Analogues

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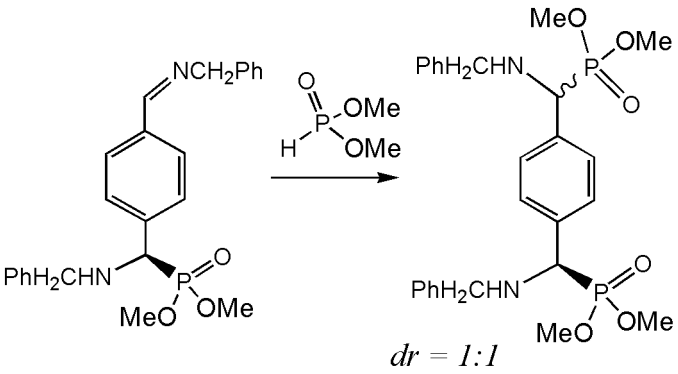
Abstract: The addition of dimethyl phosphite to *N*,*N*'-terephthalylidene-alkyl- (or aryl-) amines resulted in new tetramethyl 1,4-phenylene-bis-(*N*-alkylaminomethyl)-phosphonates in moderate yields. The stereochemical behaviour of these reactions was studied by NMR demonstrating, that the reactions lead to the formation of both possible diastereomeric forms in 1:1 up to 1:2 ratios. This was unexpected considering that previously investigated additions of diethyl, dibenzyl and diphenyl phosphites to terephthalaldimines were diastereoselective up to 100 %. Attempts were made to find reasonable explanation for the phenomenon using semi-empirical and DFT calculations.



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Keywords: Diaminophosphonates; terephthalic moiety; stereochemistry; dimethyl phosphite

INTRODUCTION

During routine literature studies, we have found to our great surprise, that tetramethyl 1,4-phenylene-di-(*N*-alkylaminomethylphosphonates) have been mentioned only once in the literature and that this was nearly 50 years ago. Pudovik and Pudovik[1] reported the synthesis of two such compounds, but, as it was published in mid-sixties, no spectral characterisation had been reported.

Therefore, in the name of scientific routine, we decided to synthesize these tetramethyl 1,4-phenylene-di-(*N*-alkylaminomethylphosphonates) and to investigate *pro forma* the stereo-chemistry of their formation. Our team investigated the addition of phosphorus nucleophiles to azomethine bond in many aspects, inspired by the excellent work of Failla and Finocchiaro group[2-4] and by the studies of Gancarz and Tyka[5]. They found, that the addition of diethyl phosphite to achiral terephthalic Schiff bases was diastereoselective up to 100 % and found also, that this phenomenon was not easy to explain. It is to note, that these 1,4-phenylene-bis-(*N*-alkylaminomethyl)-phosphonic acid derivatives have been found to have coordination abilities towards Cu(II) ions[6] or diaminophosphonate peptide receptor for lysine and arginine.[7]

We have discovered that the addition of diethyl, dibenzyl and diphenyl phosphites to achiral *N*-alkyl terephthalic Schiff bases[2-5,8] was diastereoselective to 100 %, but similar addition to *N*-aryl ones was in some cases also highly stereoselective, while in other cases not stereoselective at all, and it depended on the nature of the substituents at the aromatic ring[9,10]. The predominant or exclusive diastereoisomer was found to adopt a *meso*-form.

Similar results have been reported for the addition of hypophosphorous acid to terephthalic Schiff bases.[11] This addition has been reported[5,11] to be diastereoselective to 100 % for

N-alkylaryl imines and to lead to a *meso*-form too, while the reactions performed on *N*-aryl imines showed similar tendencies as described above.[11] The surprising exception has been noticed in this report,[11] namely the addition of hypophosphorous acid to *N*-furfuryl terephthalic Schiff base, did not show any evidence of diastereoselectivity, leading to the formation of both diastereomeric forms in a 1:1 ratio.

Similar tendencies have been noticed in a case of the addition of di-(trimethylsilyl) phosphite to achiral terephthalic Schiff bases, which led to the formation of 1,4-phenylene-bis-(*N*-alkylaminomethyl)-phosphonic acids.[12] The stereochemical behaviour of such processes demonstrated, that - for several examples - this reaction led to the exclusive formation of only one diastereomeric form, which was identified to be the racemic mixture.

When we thought that all is well explained, our routine examination of the tetramethyl 1,4-phenylene-di-(*N*-alkylaminomethylphosphonate) formation revealed some astonishing facts, which made our previous conclusions rather questionable. Addition of dimethyl phosphite to a variety of achiral terephthalic Schiff bases was found to be either only slightly diastereoselective or not diastereoselective at all!

RESULTS AND DISCUSSION

Terephthalaldimines **2a-h** were prepared by the condensation of amines **1a-h** with terephthalic aldehyde in methanol at room temperature (Scheme 1). As this method is commonly known,[8,9,11,12] we found useless to report it here. Imines with *N*-alkylaryl (**2a-c**), *N*-aliphatic (**2d**) and *N*-aryl groups (**2e-h**) were selected for the investigations, so that imines with all kinds of *N*-substituents were studied.

The preparation of tetramethyl 1,4-phenylene-bis(*N*-alkylaminomethyl)-phosphonates **3a-h** was carried out following the previously published procedures[8,9,11,12] by the addition of dimethyl phosphite to azomethine bond of terephthalic Schiff bases **2a-h** in toluene for 5 hours (Scheme 1). Tetramethyl aminophosphonates **3a-h** have been obtained as crystalline powder in moderate to low yields. This is not unusual, as Barycki and coworkers[5] suggested, that the conversion rate for the addition to two azomethine groups is lower than that to one azomethine group. Tetramethyl aminophosphonates **3a-h** were purified by recrystallization and appropriate results of spectroscopic and elemental analysis are given in the Experimental Part.

The ^{1}H, ^{13}C and in some cases ^{31}P NMR spectroscopic data demonstrated, that all investigated tetramethyl aminophosphonates **3a-h** were formed with very low diastereoselectivities or even with a complete lack of distereoselectivity. The formation of *N*-benzyl and *N*-furfuryl derivatives was not stereoselective; NMR investigation showed the presence of the two diastereosisomers in a 1:1 ratio. In the other cases investigated (formation of **3c** and **3e-h**) only a low stereoselectivity ranging from 14 % *de* up to 43 % *de* was observed. Only the addition to *N*-*t*-butylaldimine **2d** was much more stereoselective giving diastereoisomeric products in 67 % *de* (Table 1). This phenomenon was greatly unexpected in the light of previous results,[2-5,8-9] which were discussed in the introductory part. Additions of diethyl, dibenzyl and diphenyl phosphites led in most cases to the exclusive formation of a *meso*-form.

The question appeared what might be the difference between these three phosphites and dimethyl phosphite, so that the addition of the latter displays different stereochemistry. In order to put light on the nature of this difference theoretical analysis was done.

In previous papers[8-12] we followed the Gancarz's suggestion[5] that addition of phosphites to terephthalic Schiff bases proceeds through a two-step mechanism, where the first step is the addition of a phosphite to the first azomethine bond resulting in the imino-aminophosphonate derivative **4b**. We have drawn a hypothesis[8,9] that two molecules of imino-aminophosphonate derivative **4b** are able to form a dimer linked by hydrogen bonds. This dimer coordinates to phosphite molecules and such a system is able to determine the stereochemistry of the addition to the next azomethine bond to afford the *meso* form of bis-aminophosphonate **5** (Scheme 2). However, considering the high similarity between diethyl phosphite and dimethyl phosphite, the formation of bis-aminophosphonate **3a** from the intermediate **4a** should be characterised by a similar stereoselectivity (Scheme 2). Taking into account, that the resolution of the problem in an experimental way is extremely difficult (we did not manage to isolate any intermediate), we used theoretical methods, which would help us to find the reason of such stereochemical behaviour. In our computations, we followed Gancarz's suggestion[5] of a two-step reaction mechanism mentioned above.

First we have performed PM6 and PM7 semi-empirical calculations for the addition of dimethyl phosphite and diethyl phosphite to *N,N'*-terephthalilidenedibenzylamine. We computed the total energies of equilibrium states of the structures formed at particular steps of both reactions, the hypothetical iminoaminophosphonate intermediate **4a**-**b** and 1,4-phenylene-bis-(*N*-benzylaminomethylphosphonates) **3a** and **5**. Then the calculated values were compared. We have chosen the addition to *N,N'*-terephthalilidenebenzylamine as a model for our computations because of its typical behaviour and the relatively simple structure of the substrates.

The calculations of the hypothetical dimethyl iminoaminophosphonate intermediate **4a** were performed separately for the *cisoid* and the *transoid* (with respect to the positions of the N atoms) conformations, which, if differences in energies between them were high enough, might play a key role in the stereochemistry of the reaction. The ground state structures found with the PM6 method differ significantly from those obtained from the PM7 calculations, but the energy differences between the most stable conformational states found with both methods for the *cisoid* and the *transoid* form are so small, that they should be considered as insignificant. Similar results were obtained for diethyl iminoaminophosphonate intermediate **4b**. The differences between the *cisoid* and the *transoid* forms of both **4a** and **4b** intermediates oscillate around 0.1 kcal / mol (Table 2). However, it is to note that in both cases, the *transoid* forms are more privileged.

Semi-empirical methods are essentially approximate and may lead to erroneous representation of reality. Therefore to verify these findings we applied a more advanced methodology, namely the DFT method, using the B3LYP functional with a 6-31G(d,p) basis set. The energy differences between *cisoid* and *transoid* conformations of the hypothetical imino amino-phosphonate intermediates **4a** and **4b** at the B3LYP/6-31G(d,p) level of theory (see Table 2) appear to be even smaller (≤0.05 kcal/mol) than those found with the semi-empirical methods. The DFT results show also, that the structural properties of this system are somewhat better reproduced by the PM6 method, but it predicts incorrectly the orientation of the phosphonate groups.

Since stability of the intermediates does not explain the phenomena observed in the experiment, we performed similar study for the final products. The total energies of equilibrium states of dimethyl and diethyl 1,4-phenylene-bis-(*N*-benzylaminomethyl-phosphonates) **3a** and **5,**

respectively, were calculated for (*R*,*S*) and (*S*,*S*) diastereomers, as by definition the (*R*,*R*) diastereomer behaves identically as the (*S*,*S*) one. As for the intermediates, the *cisoid* and *transoid* forms were considered for each diastereoisomer. As can be seen in Table 3, all methods predict that for both final products **3a** and **5** there is no significant difference between the energies of the most stable conformers of (*S*,*S*) and (*R*,*S*) isomers. One may note some inconsistency in the lowest energy structures pointed out by the methods PM6 and PM7. The other corresponding conformers (analogues of the B3LYP structures) appear to be higher in energy by up to 1 kcal/mol.

Obviously, the above computations did not allow us to approach to the reason of the phenomena observed experimentally. Therefore we turned our attention to substrates of the studied reaction. We found only one difference, which we show in Table 4, namely both dimethyl and diethyl phosphites show tendencies to form dimers and the dimer of dimethyl phosphite is more stable, because its dissociation energy is higher by about 0.6 kcal/mol according to the DFT results. It is then probable that the higher stability of the dimethyl phosphite dimer as compared to that of the diethyl phosphite dimer plays a key role in explaining such a great difference in stereochemistry of discussed reactions.

If we consider the previously suggested mechanism[8-12] to be true, such a difference between tendencies of dimer formation of both phosphites should be critical for the formation of active complexes **AC-4a** and **AC-4b** (Figure 1) Because the diethyl phosphite dimer is less stable, the formation of the active complex **AC-4b** is much more probable, while the higher stability of dimethyl phosphite dimer may disfavour the formation of the **AC-4a** complex. However, it is to stress that the formation of active complexes **AC-4a** and **AC-4b** is hypothetical. We did not

succeed in isolating intermediates **4a**,**b**, the characterization of which would confirm experimentally the formation of complexes **AC-4a** and **AC-4b**. Also, considering the discrepancies between the semiempirical and DFT results presented in Tables 2-4, as well as the large number of variables involved, verification of our hypothesis at a reliable theoretical level would be a very long task, therefore could not be done at the moment.

Summarizing, the thorough analysis performed in the present work allowed us to eliminate the possibility that different stability of single intermediate or final products is responsible for the phenomenon of different diastereoselectivity. We managed however to find another factor that hypothetically could be its source. An important achievement of our study is also the detailed knowledge of specific properties of the compounds participating in these reactions, which constitutes a good starting point for further investigations.

EXPERIMENTAL

All solvents (POCh-Poland) were routinely distilled and dried prior to use. Amines, dimethyl phosphite and terephthalic aldehyde (Aldrich) were used as received. NMR spectra were recorded with a Bruker Avance III 600 MHz apparatus operating at 600 MHz (^{1}H), 150 MHz (^{13}C) and 243 MHz (^{31}P). Elemental analyses were performed in the Centre for Molecular and Macromolecular Science of the Polish Academy of Science in Łódź. Melting points were measured on a MelTemp II apparatus and are not corrected. The Supplemental Materials contains sample ^{1}H, ^{13}C and ^{31}P NMR spectra for 3a-3d (Figures S 1 – S 11)

Tetramethyl 1,4-phenylene-bis-(aminomethylphosphonates) (3a-h). General procedure.

Terephthalic aldehyde (1.34 g, 10 mmol) was dissolved in methanol (40 mL) and then the corresponding amine (20 mmol) was added. The mixture was stirred at room temperature for 24

h and the precipitated solid was then collected and dried. The thus obtained Schiff base **2a-f** was used for the next step without further purification.

The Schiff base (**2a-f**) (5 mmol) was dissolved in toluene (30 mL) and then the dimethyl phosphite (10 mmol, 1.10 g) was added. The mixture was refluxed for 5 to 7 h. After cooling to room temperature the solid precipitate was collected by filtration, washed, and dried. Products were purified by recrystallization. A separation of the diastereoisomers *via* column chromatography or crystallization failed.

Tetramethyl 1,4-phenylene-bis-(N-benzylaminomethylphosphonate) (3a)

Yield: 85 % (2.13 g); mp: 103-104 °C (dichloromethane). ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 7.26 (s, 4H, C_6H_4); 7.14-7.11 (m, 4 H, PhH); 7.08-7.07 (m, 6 H, PhH); 3.90 (d, $^{2}J_{PH}$ = 19.4 Hz, 1H, CHP) and 3.89 (d, $^{2}J_{PH}$ = 19.6 Hz, 2H, CHP), (1:1); 3.63 (d, $^{2}J_{HH}$ = 13.3 Hz, 2H, C$\underline{H_A}H_B$); 3.56 (d, $^{3}J_{PH}$ = 10.5 Hz, 3H, P-O-CH3), 3.55 (d, $^{3}J_{PH}$ = 10.5 Hz, 3H, P-O-CH_3); 3.38 (d, $^{2}J_{HH}$ = 13.3 Hz, 2H, C$\underline{H_A}H_B$); 3.36 (d, $^{3}J_{PH}$ = 10.5 Hz, 3H, P-O-CH_3), 3.35 (d, $^{3}J_{PH}$ = 10.5 Hz, P-O-CH_3, 3H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ = 139.2 (C_{ipso}); 135.5 (C_{ipso}); 128.9 (C_{para}); 128.4 (C_{arom}); 128.2 (C_{arom}); 127.2 (C_{arom}); 59.1 (d, $^{1}J_{PC}$ = 153.2 Hz, CP); 53.6 (m, COP); 53.3 (m, COP); 51.32 (d, $^{3}J_{PC}$ = 9.0 Hz, $\underline{C}$NCP); 51.26 (d, $^{3}J_{PC}$ = 9.0 Hz, $\underline{C}$NCP). ^{31}P NMR ($CDCl_3$, 243 MHz): δ = 25.6. Anal. Calcd. for $C_{26}H_{34}N_2O_6P_2$: C, 58,64; H, 6,44; N, 5,26. Found: C, 58.46; H, 6.51; N, 5.23 %.

Tetramethyl 1,4-phenylene-bis-(N-furfurylaminomethylphosphonate) (3b)

Yield: 61 % (1.49 g); mp: 103-107 °C (dichloromethane). ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 7.44 (s, 4H, C_6H_4); 7.35-7.34 (m, 2H, CH^{5}_{fur}); 6.29 (dd, *J* = 1.5 Hz, 3.0 Hz, 2H, H^{4}_{fur}); 6.11-6.10 (m, 2H, H^{3}_{fur}); 4.10 (d, $^{2}J_{PH}$ = 18.4 Hz, 2H, CHP), 4.09 (d, $^{2}J_{PH}$ = 18.4 Hz, 2H, CHP); 3.81 (d, $^{2}J_{HH}$ = 14.3 Hz, 2H, C$\underline{H_A}H_B$); 3.71 (d, $^{3}J_{PH}$ = 10.6 Hz, 6H, P-O-CH_3); 3.59 (d, $^{2}J_{HH}$ = 14.3 Hz, 2H,

$CH_A\underline{H_B}$); 3.58 (d, $^3J_{PH}$ = 10.2 Hz, 3H, P-O-CH_3), 3.57 (d, $^3J_{PH}$ = 10.2 Hz, 3H, P-O-CH_3). ^{13}C NMR ($CDCl_3$, 150 MHz): δ = 152.8 (C_{ipso}); 142.0 (C_{fur}); 135.1 (C_{ipso}); 128.9 (C_{para}); 110.1 (C_{fur}); 107.7 (C_{fur}); 58.86 (d, $^1J_{PC}$ = 153.5 Hz, CP); 58.83 (d, $^1J_{PC}$ = 153.5 Hz, CP); 53.53 (d, $^2J_{PC}$ = 35.5 Hz, COP); 53.51 (d, $^2J_{PC}$ = 35.5 Hz, COP); 43.8 (d, $^3J_{PC}$ = 8.8 Hz, $\underline{C}$NCP); 43.7 (d, $^3J_{PC}$ = 8.9 Hz, $\underline{C}$NCP). ^{31}P NMR ($CDCl_3$, 243 MHz): δ = 25.3 (br s). Anal. Calcd. for $C_{22}H_{30}N_2O_8P_2$: C, 51,57; H, 5,90; N, 5,47. Found: C, 51.59; H, 6.10; N, 5.31 %.

Tetramethyl 1,4-Phenylene-bis-(N-benzhydrylaminomethylphosphonate) (3c)

Yield: 53 % (1.91 g); mp: 181-183 °C (toluene / hexane 1:1). ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 7.36-7.33 (m, 12H, Ph, C_6H_4); 7.29-7.24 (m, 10H, Ph); 7.21-7.19 (m, 2H, Ph); 4.71 (s, 1H, C$\underline{H}$$Ph_2$); 4.69 (s, 1H, C$\underline{H}$$Ph_2$); 4.02 (d, $^2J_{PH}$ = 21.8 Hz, 1H, CHP), 4.00 (d, $^2J_{PH}$ = 21.8 Hz, 2H, CHP); 3.87 (d, $^3J_{PH}$ = 10.6 Hz, 3H, P-O-CH_3); 3.86 (d, $^3J_{PH}$ = 10.6 Hz, 3H, P-O-CH_3); 3.52 (d, $^3J_{PH}$ = 10.1, 3H, P-O-CH_3); 3.51 (d, $^3J_{PH}$ = 10.6 Hz, 3H, P-O-CH_3). ^{13}C NMR ($CDCl_3$, 150 MHz): δ = 143.5 (C_{ipso}); 141.8 (C_{ipso}); 135.6 (C_{tereph}); 128.9 (m, C_{ipso}); 128.7 (C_{arom}); 128.5 (C_{arom}); 127.8 (C_{arom}); 127.5 (C_{arom}); 127.24 (C_{arom}); 127.21 (C_{arom}); 63.9 (d, $^3J_{PC}$ = 8.7 Hz, $\underline{C}$NCP); 63.9 (d, $^3J_{PC}$ = 8.5 Hz, $\underline{C}$NCP); 57.5 (d, $^1J_{PC}$ = 154.5 Hz, CP); 53.9 (m, COP); 53.2 (m, COP). ^{31}P NMR ($CDCl_3$, 243 MHz): δ = 25.9 (br s). Anal. Calcd. for $C_{38}H_{42}N_2O_6P_2$: C, 66,66; H, 6,18; N, 4,09. Found: C, 66.33; H, 6.26; N, 3.83 %.

Tetramethyl 1,4-Phenylene-bis-(N-t-butylaminomethylphosphonate) (3d)

Yield: 57 % (1.25 g); mp: 145-149 °C (dichloromethane). ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 7.15 (s, 4H, C_6H_4); 4.18 (d, $^2J_{PH}$ = 24.1 Hz, 1H, PCH); 4.17 (d, $^2J_{PH}$ = 24.1 Hz, 2H, PCH); 3.79 (d, $^3J_{PH}$ = 10.2 Hz, 3H, P-O-CH_3); 3.78 (d, $^3J_{PH}$ = 10.2 Hz, 3H, P-O-CH_3); 3.41 (d, $^3J_{PH}$ = 10.1 Hz, 3H, P-O-CH_3); 3.40 (d, $^3J_{PH}$ = 10.1 Hz, 3H, P-O-CH_3); 1.01 (s, 9H, $C(CH_3)_3$); 0.98 (s, 18H,

$C(CH_3)_3$). ^{13}C NMR ($CDCl_3$, 150 MHz): δ = 139.2 (C_{ipso}); 139.0 (C_{ipso}); 128.3 (m, C_{tereph}); 55.3 (d, $^1J_{PC}$ = 155.2 Hz, CP); 55.2 (d, $^1J_{PC}$ = 155.5 Hz, CP); 54.4 (m, COP); 53.2 (m, COP); 52.4 (d, $^3J_{PC}$ = 8.2 Hz, <u>C</u>NCP); 52.3 (d, $^3J_{PC}$ = 7.8 Hz, <u>C</u>NCP); 29.9 (<u>C</u>H_3); 29.8 (<u>C</u>H_3). ^{31}P NMR ($CDCl_3$, 243 MHz): δ = 26.3, 25.5 (5:1). Anal. Calcd. for $C_{20}H_{38}N_2O_6P_2$: C, 51,72; H, 8,25; N, 6,03. Found: C, 51.98; H, 8.38; N, 5.83 %.

Tetramethyl 1,4-Phenylene-bis-(N-(p-methylphenyl)aminomethylphosphonate) (3e)

Yield: 35 % (0.84 g); mp: 197-200 °C (dichloromethane). ^1H NMR ($CDCl_3$, 600 MHz): δ = 7.44 (s, 4H, C_6H_4); 6.89 (A part of AA'XX' spectrum, ^3J = 8.3 Hz, ^4J = 3.4 Hz, 4H); 6.49 (X part of AA'XX' spectrum, 4H); 4.75 and 4.74 (2d, $^2J_{PH}$ = 22.9 and 23.4 Hz, PCH, 2H); 3.73 and 3.72 (2d, $^3J_{PH}$ = 10.6 Hz, P-O-CH_3, 6H); 3.42 and 3.34 (2d, $^3J_{PH}$ = 10.5 Hz, P-O-CH_3, 6H); 2.18 and 2.17 (2s, CH_3, 6H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 143.65 (m, C_{ipso}); 135.74 (C_{tereph}); 129.60 (C_{arom}); 129.57 (C_{arom}); 128.20 (d, $^3J_{CP}$ = 7.5 Hz, <u>*C_{ipso}*</u>NCP); 127.87 (C_{arom}); 127.86 (C_{arom}); 114.10 (C_{arom}); 114.06 (C_{arom}); 55.83 (d, $^1J_{CP}$ = 150.7 Hz, CP); 55.78 (d, $^1J_{CP}$ = 150.4 Hz, CP); 53.75 (m, COP); 53.63 (m, COP); 20.27 (<u>C</u>H_3); 20.26 (<u>C</u>H_3). ^{31}P NMR ($CDCl_3$, 243 MHz): δ 24.90 and 24.86 (3:4). Anal. Calcd. for $C_{26}H_{34}N_2O_6P_2 \bullet {}^1/_4CH_2Cl_2$: C, 56,94; H, 6,28; N, 5,06. Found: C, 56.82; H, 6.00; N, 4.90 %.

Tetramethyl 1,4-Phenylene-bis-(N-(p-methoxyphenyl)aminomethylphosphonate) (3f)

Yield: 16 % (0.4 g); mp: 195-197 °C (dichloromethane). ^1H NMR ($CDCl_3$, 600 MHz): δ = 7.47 (s, 4H, C_6H_4); 7.45 (s, 4H, C_6H_4); 6.68-6.65 (A-part of AA'XX' spectrum, 2H); 6.58-6.55 (X-part of AA'XX' spectrum, 2H); 4.72 (d, $^2J_{PH}$ = 24.0 Hz, 1H, PCH); 4.71 (d, $^2J_{PH}$ = 24.0 Hz, 1H, PCH); 3.74 (d, $^3J_{PH}$ = 10.8 Hz, 3H, P-O-CH_3); 3.71 (d, $^3J_{PH}$ = 10.8 Hz, 3H, P-O-CH_3); 3.69 (s, OCH_3, 3H); 3.68 (s, OCH_3, 3H); 3.41 (d, $^3J_{PH}$ = 10.8 Hz, 3H, P-O-CH_3); 3.36 (d, $^3J_{PH}$ = 10.8

Hz, 3H, P-O-CH_3) (4:9). ^{13}C NMR (DMSO-D_6, 150 MHz): δ = 151.4 (C_{ipso}); 140.8 (d, $^3J_{PC}$ = 15.0 Hz, $\underline{C_{ipso}}$NCP); 135.9 (C_{arom}); 127.9 (C_{arom}); 114.63 (C_{arom}); 114.59 (C_{arom}); 114.2 (C_{arom}); 114.10 (C_{arom}); 114.06 (C_{arom}); 55.1 (O$\underline{C}$H$_3$); 54.04 (d, $^1J_{PC}$ = 151.5 Hz, CP); 53.97 (d, $^1J_{PC}$ = 151.4 Hz, CP); 53.2 (m, COP); 52.8 (m, COP). ^{31}P NMR ($CDCl_3$, 243 MHz): δ = 24.6. Anal. Calcd. for $C_{26}H_{34}N_2O_8P_2$: C, 55,32; H, 6,07; N, 4,96. Found: C, 55.11; H, 6.11; N, 4.81 %.

Tetramethyl 1,4-Phenylene-bis-(N-(m-methylphenyl)aminomethylphosphonate) (3g)

Yield: 35 % (0.96 g); mp: 171-174 °C (dichloromethane / hexane 1:1). ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 7.46 (s, 4H, C_6H_4); 6.97-6.94 (s, 2H, *m*-C_6H_4); 6.52 (dd, *J* = 7.8 Hz, 7.2 Hz, 2H, *m*-C_6H_4); 6.40 (br s, 2H, *m*-C_6H_4); 6.36 (dd, ^3J = 7.8 Hz, ^4J = 2.6 Hz, 2H, *m*-C_6H_4); 4.78 (d, $^2J_{PH}$ = 23.3 Hz, 1H, PCH); 4.77 (d, $^2J_{PH}$ = 23.3 Hz, 1H, PCH); 3.73 (d, $^3J_{PH}$ = 10.6 Hz, 3H, P-O-CH_3); 3.72 (d, $^3J_{PH}$ = 10.6 Hz, 3H, P-O-CH_3); 3.42 (d, $^3J_{PH}$ = 10.5 Hz, 3H, P-O-CH_3); 3.35 (d, $^3J_{PH}$ = 10.5 Hz, 3H, P-O-CH_3); 2.19 (s, 3H, CH_3); 2.18 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 150 MHz): δ = 146.0 (m, C_{ipso}); 138.91 (C_{ipso}); 138.88 (C_{ipso}); 135.7 (C_{tereph}); 128.97 (C_{arom}); 128.94 (C_{arom}); 128.2 (m, $\underline{C_{ipso}}$NCP); 119.53 (C_{arom}); 119.50 (C_{arom}); 114.77 (C_{arom}); 114.74 (C_{arom}); 110.94 (C_{arom}); 110.91 (C_{arom}); 55.50 (d, $^1J_{PC}$ = 150.6 Hz, CP); 55.45 (d, $^1J_{PC}$ = 150.0 Hz, CP); 53.7 (m, COP); 21.4 ($\underline{C}$H$_3$). ^{31}P NMR ($CDCl_3$, 243 MHz): δ = 24.83; 24.78 (5:2). Anal. Calcd. for $C_{26}H_{34}N_2O_6P_2$: C, 58,64; H, 6,44; N, 5,26. Found: C, 58.37; H, 6.51; N, 5.34 %.

Tetramethyl 1,4-Phenylene-bis-(N-(m-methoxyphenyl)aminomethylphosphonate) (3h)

Yield: 62 % (1.75 g); mp: 145-148 °C (toluene). ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 7.45 (s, 4H, C_6H_4); 6.99-6.96 (m, 2H, *m*-C_6H_4); 6.25-6.23 (m, 2H, *m*-C_6H_4); 6.19-6.17 (m, 2H, *m*-C_6H_4); 6.09-6.08 (m, 2H, *m*-C_6H_4); 4.77 (d, $^2J_{PH}$ = 23.4 Hz, 1H, PCH); 4.75 (d, $^2J_{PH}$ = 23.4 Hz, 1H, PCH); 3.73 (d, $^3J_{PH}$ = 10.6 Hz, 3H, P-O-CH_3); 3.72 (d, $^3J_{PH}$ = 10.6 Hz, 3H, P-O-CH_3); 3.66 (s,

3H, OCH_3); 3.65 (s, 3H, OCH_3); 3.40 (d, $^3J_{PH}$ = 10.4 Hz, 3H, P-O-CH_3); 3.35 (d, $^3J_{PH}$ = 10.4 Hz, 3H, P-O-CH_3). ^{13}C NMR ($CDCl_3$, 150 MHz): δ = 160.7 (C_{ipso}); 147.3 (m, C_{ipso}); 135.7 (C_{tereph}); 129.90 (C_{arom}); 129.88 (C_{arom}); 128.2 (m, $\underline{C}_{ipso}$NCP); 106.93 (C_{arom}); 106.91 (C_{arom}); 103.84 (C_{arom}); 103.79 (C_{arom}); 100.17 (C_{arom}); 100.13 (C_{arom}); 55.57 (d, $^1J_{PC}$ = 150.2 Hz, CP); 55.53 (d, $^1J_{PC}$ = 150.2 Hz, CP); 55.0 (O$\underline{C}H_3$); 53.8 (m, COP). ^{31}P NMR ($CDCl_3$, 243 MHz): δ = 24.62; 24.59 (2:3). Anal. Calcd. for $C_{26}H_{34}N_2O_8P_2$: C, 55,32; H, 6,07; N, 4,96. Found: C, 55.29; H, 6.27; N, 4.76 %.

Quantumchemical Calculations

The first series of our calculations has been performed using the MOPAC2012 program.[13] The structures of dimethyl and diethyl iminoaminophosphonate intermediates **4a**,**b,** as well as tetramethyl and tetraethyl 1,4-phenylene-bis-(*N*-benzylamino-methylphosphonates) **3a** and **5,** were fully optimized (no constraints) at the semi-empirical levels PM6 and PM7. No symmetry was imposed on the molecules geometry (C1) in all calculations. The potential energy surface of these systems is expected to have many local minima, but the systematic scan of all possible conformers is impossible because of an excessive number of torsional angles in these structures. Therefore the following strategy was used to find the most stable structures: first a large number of various conformers (taking into account rotations of different parts of the molecules around bonds C-C, C-P or C-N) were tested as starting structures for the PM6 and PM7 optimization. The lowest energy structures were then used as starting geometries in the conformational search performed using the stochastic dynamic method via the Verlet velocity algorithm, available in the program Gabedit.[14] In the simulation the conformational space was explored at a certain simulation time and temperature. During this search 50 lowest energy structures were selected

and saved, and subsequently optimized. The procedure was repeated with different simulations conditions: for two different friction parameters of 40 and 80 ps^{-1}, as well as for different temperatures, which initially were set to 1000 K, but for the lowest energy structures found in the simulations an additional verification was made by performing a subsequent simulation in 500 K and in 300 K. The simulation time for small molecules and at the verification steps was usually set to 5-10 ps, while for larger structures, such as **3a** and **5**, it was increased up to 50-70 ps. In all simulations the timesetp of 1 fs was used. The procedure was repeated independently with the PM6 and PM7 methods.

At the second stage of this part of our work the full geometry optimization of the same compounds was repeated at the more accurate level using the density functional method B3LYP[15-17] combined with the basis set 6-31G(d,p). However, due to a relatively long computational time, these calculations were limited to the lowest energy structures indicated by the semi-empirical PM6 and PM7 results for two isomers (*cisoid* and *transoid* conformers with respect to the positions of atoms N) of the intermediates **4a-b** and for four isomers (*cisoid* (*R*,*S*), *cisoid* (*S*,*S*), *transoid* (*R*,*S*), and *transoid* (*S*,*S*)) of the final products **3a** and **5**. Additionally, for the final products, which were the most problematic, for each lowest energy structure found from the B3LYP optimization we tested all corresponding conformers, created by applying the appropriate symmetry operations. Some additional tests were performed taking into account an effect of rotation of methyl and ethyl groups. The same strategy was used for the dimers of dimethyl and diethyl phosphites. All DFT calculations were performed with the Gaussian 09 package.[18]

At both stages for the resulting lowest energy structures the vibrational analysis was performed to verify whether these geometries correspond to true energy minima, which was confirmed by the absence of imaginary frequencies. The pictures of the optimized structures shown in Tables 2-4 were made with the program Gabedit.[14]

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Table 1 Results of the addition of dimethyl phosphite to azomethine bond of imines **2a-h**

3	R	Yield [%]	Diastereomeric ratio (dr)	Diastereomeric excess (de) [%]
a	CH_2Ph	85	1:1	--
b	CH_2Fur	61	1:1	--
c	$CHPh_2$	53	2:1	33
d	$C(CH_3)_3$	57	5:1	67
e	*p*-CH_3-C_6H_4	35	3:4	14
f	*p*-OCH_3-C_6H_4	16	4:9	39
g	*m*-CH_3-C_6H_4	35	5:2	43
h	*m*-OCH_3-C_6H_4	62	2:3	20

Table 2 PM6, PM7 and DFT B3LYP/6-31G(d,p) total energies and ZPE corrected energies of equilibrium states of hypothetical intermediates **4a** and **4b** for *cisoid* and *transoid* forms

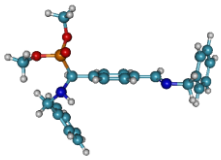
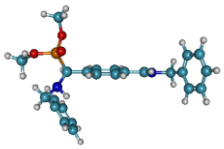
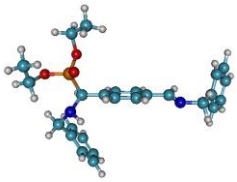
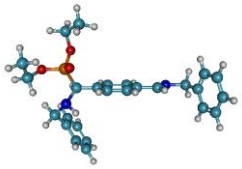
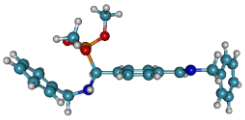
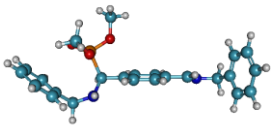
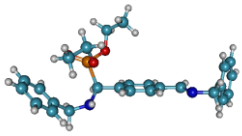
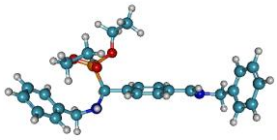
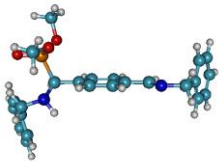
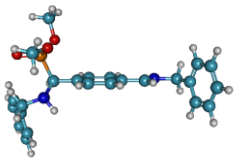
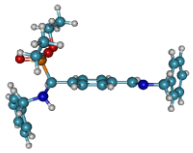
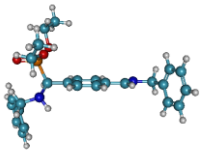
	Form	*cisoid* dimethyl **4a**	*transoid* dimethyl **4a**	*cisoid* diethyl **4b**	*transoid* diethyl **4b**
PM6					
	E [kcal/mol]	-107998.56	-107998.69	-114917.90	-114918.01
	E+ZPE [kcal/mol]	-107725.81	-107725.92	-114612.18	-114612.26
PM7					
	E [kcal/mol]	-109465.99	-109466.10	-116390.24	-116390.34
	E+ZPE [kcal/mol]	-109188.48	-109189.02	-116079.29	-116079.88
B3LYP/6-31G(d,p)					
	E [kcal/mol]	-1008670.552	-1008670.56	-1058021.10	-1058021.15
	E+ZPE [kcal/mol]	-1008376.24	-1008376.19	-1057691.15	-1057691.12

Table 3 PM7 and DFT B3LYP/6-31G(d,p) total energies of equilibrium states of tetramethyl and tetraethyl 1,4-phenylene-bis-(*N*-benzylamino-methylphosphonates) **3a** and **5** for (*R*,*S*) and (*S*,*S*) diastereomers, respectively

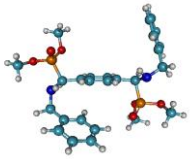
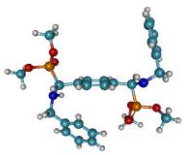
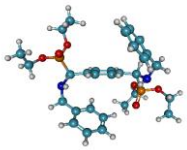
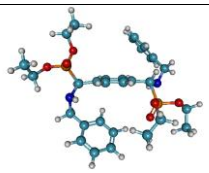
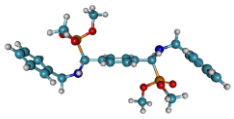
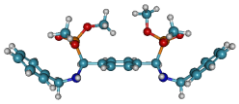
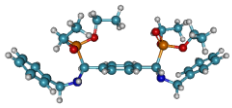
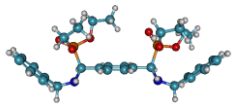
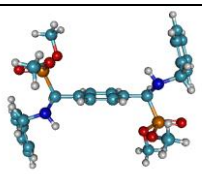
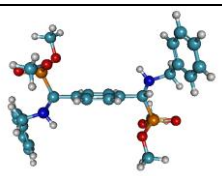
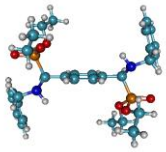
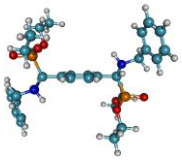
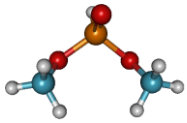
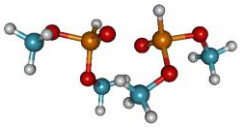
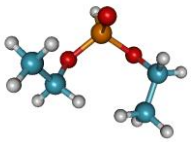
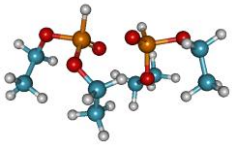
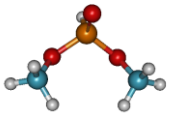
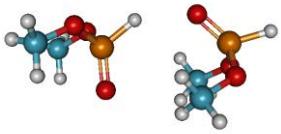
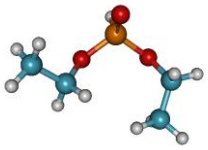
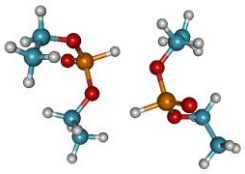
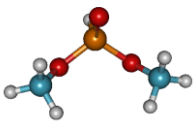
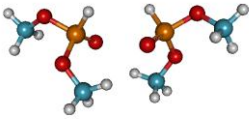
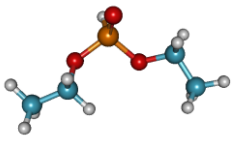
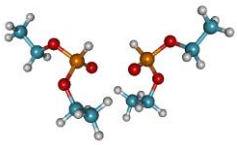
	Isomer	(*S*,*S*) tetramethyl **3a**	(*R*,*S*) tetramethyl **3a**	(*S*,*S*) tetraethyl **5**	(*R*,*S*) tetraethyl **5**
PM6					
	E [kcal/mol]	-139382.01	-139382.16	-153220.99	-153221.01
	E+ZPE [kcal/mol]	-139049.67	-139049.71	-152822.66	-152822.59
PM7					
	E [kcal/mol]	-141842.57	-141842.37	-155690.74	-155690.55
	E+ZPE [kcal/mol]	-141505.72	-141505.91	-155287.61	-155287.40
B3LYP/6-31G(d,p)					
	E [kcal/mol]	-1414996.23	-1414996.16	-1513697.2808	-1513697.3117
	E+ZPE [kcal/mol]	-1414635.38	-1414635.39	-1513265.1797	-1513265.0813

Table 4 DFT B3LYP/6-31G(d,p) total energies of dimethyl and diethyl phosphites of a single and a dimeric form. E_{dys} was calculated according to: E_{dys} (ZPE)= $2xE_{single}$ - E_{dimer} from values including the ZPE corrections.

	Form of a substrate	Dimethyl phosphite (single)	Dimethyl phosphite (dimer)	Diethyl phosphite (single)	Diethyl phosphite (dimer)
PM6					
	E [kcal/mol]	-31343.10	-62709.55	-38262.45	-76547.56
	E+ZPE [kcal/mol]	-31286.29	-62594.10	-38172.62	-76366.27
	E_{dys} (E+ZPE) [kcal/mol]	21.52		21.03	
PM7					
	E [kcal/mol]	-32368.58	-64743.35	-39292.91	-78590.79
	E+ZPE [kcal/mol]	-32311.96	-64629.64	-39202.87	-78410.50
	E_{dys} (E+ZPE) [kcal/mol]	5.72		4.76	
B3LYP/6-31G(d,p)					
	E [kcal/mol]	-406310.24	-812628.77	-455661.23	-911329.96
	E+ZPE [kcal/mol]	-406247.02	-812501.43	-455562.25	-911131.27
	E_{dys} (E+ZPE) [kcal/mol]	7.39		6.77	

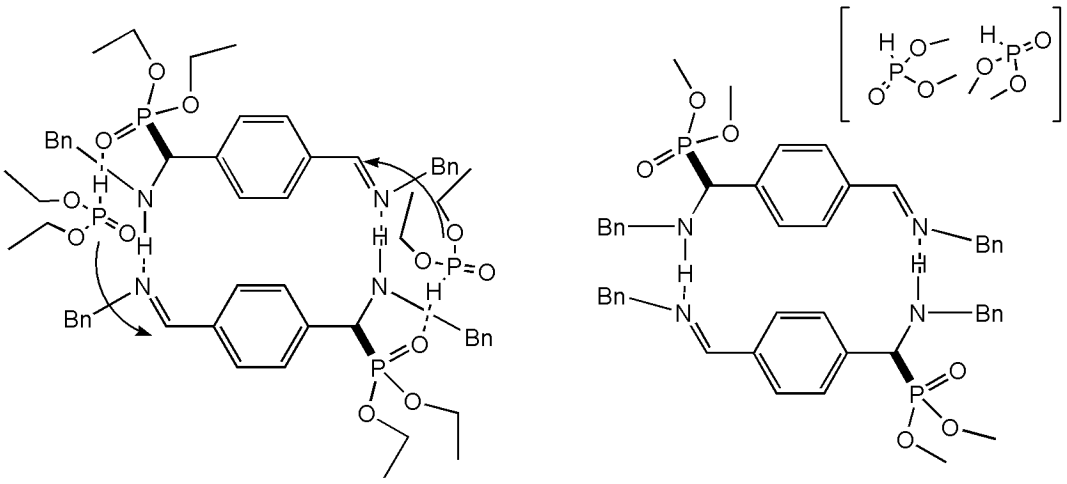
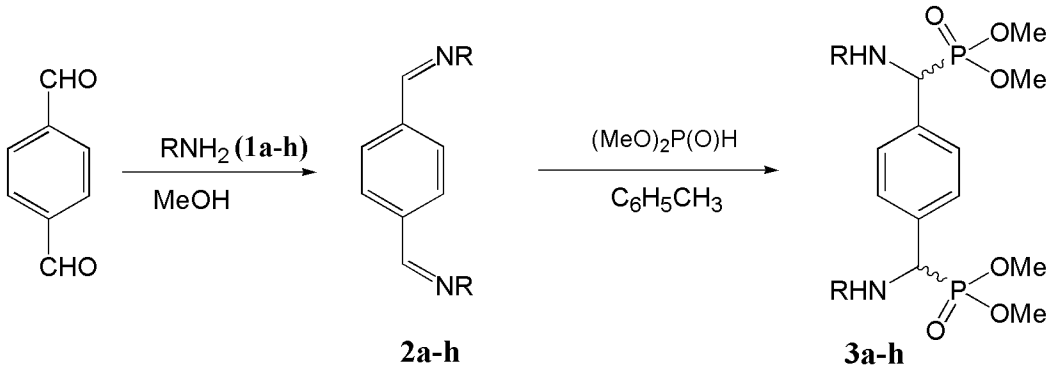
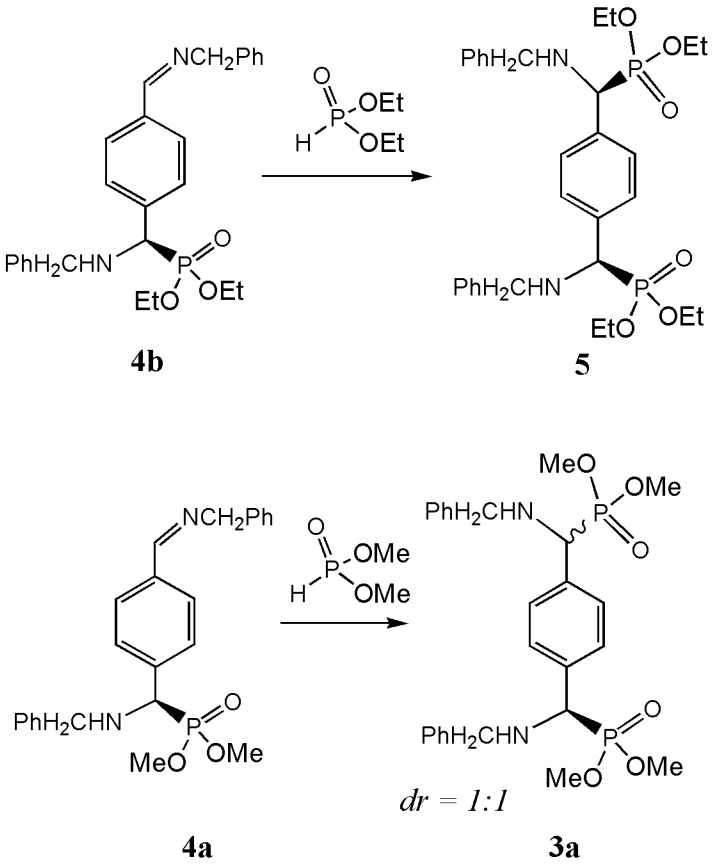


Figure 1 Structures of the active complexes **AC-4a** and **AC-4b**



a: R = CH_2Ph; **b**: R = CH_2Fur; **c**: R = $CHPh_2$; **d**: R = $C(CH_3)_3$; **e**: R = *p*-$CH_3C_6H_4$; **f**: R = *p*-$OCH_3C_6H_4$; **g**: R = *m*-$OCH_3C_6H_4$; **h**: R = *m*-$CH_3C_6H_4$

Scheme 1 Reaction of terephthalaldimines **2a - h** with dimethyl phosphite



Scheme 2 Formation of the bis(aminophosphonates) **3a** and **5**