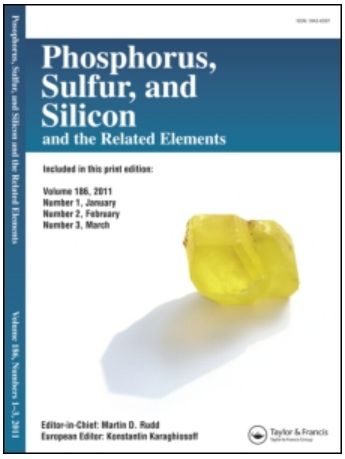

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Addition of Dialkyl and Diaryl Phosphites to *N*-(ortho-Substituted Phenyl) Terephthalic Schiff Bases: The Stereochemical Behavior

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Addition of Dialkyl and Diaryl Phosphites to *N*-(ortho-Substituted Phenyl) Terephthalic Schiff Bases: The Stereochemical Behavior

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The synthesis of bis-aminophosphonates via the phosphite addition to N-aryl terephthalic Schiff bases is reported here. The influence of methoxy and methyl groups in the ortho position on the stereoselectivity of this reaction is also discussed.

Keywords Addition of phosphites; imino-ester intermediates; ortho-substituent; stereoselectivity; terephthalic Schiff bases

INTRODUCTION

A study on the synthesis of bis-aminophosphonates derived from terephthalic aldehyde started in the late 1960s, when Pudovik and Pudovik[1] published the synthesis of 1,4-phenylene-bis-(N-phenylamino)-bis-phosphonates by the addition of phosphite to the azomethine bond of N,N′-terephthalylidene-bis-aniline. Later on, Failla and Finocchiaro[2,3] reported the syntheses of several N-aryl and N-alkyl bis-aminophosphonates derivatives of terephthalic aldehyde; then Barycki et al.[4] and Gancarz[5] reported that the addition of diethyl phosphite to N,N′-terephthallilidene-bis-benzylamine was stereoselective, leading nearly exclusively to one diastereoisomeric form.

We have also contributed to this topic reporting that the synthesis of N-alkyl derivatives was always stereoselective and led exclusively

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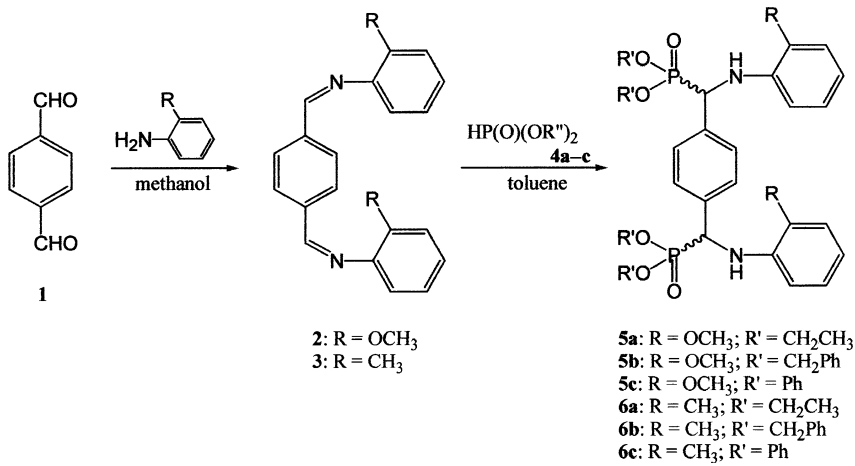
to the *meso*-form,[6] and that the formation of N-aryl derivatives sometimes was and sometimes was not diastereoselective.[7,8] We suggested that the stereoselectivity of the reaction depended on the possibility of the formation of the imino-aminophosphonate intermediate. Moreover, we proved that the nature of the substituent of the N-aryl group plays a key role in the reaction orientation. The influence of the methoxy and methyl group in the *para* position depended on the kind of phosphite; the methoxy group in the *meta* position led exclusively to the formation of the *meso* form, while the methyl group in the *meta* position made the reaction to be completely non-stereoselective. Previously, we have published results concerning the stereochemical behavior of the addition of phosphites to N-(*m*- or *p*-substituted phenyl) terephthalic Schiff bases, where we discussed the mechanism. In this article, we wish to report the influence of methoxy and methyl groups in the *ortho* position on the stereoselectivity of this reaction.

RESULTS AND DISCUSSION

For the purpose previously mentioned, we synthesized three model 1,4-phenylene-bis-(*o*-methoxyphenylaminomethane)-bis-phosphonates **5a–c** and 1,4-phenylene-bis-(*o*-methylphenyl-aminome-thane)-bis-phosphonates **6a–c**. They were prepared by the classical method of the addition of three model phosphites, diethyl, dibenzyl, and diphenyl ones **4a–c**, respectively, to the azomethine bond of terephthalic Schiff bases, N,N′-terephthalylidene-bis-*o*-anisidine **2** and N,N′-terephthalylidene-bis-*o*-toluidine **3**. The reaction was carried out in toluene and afforded products in fair yields (Scheme 1).

Terephthalic Schiff bases N,N′-terephthalylidene-bis-*o*-anisidine **2** and N,N′-terephthalylidene-bis-*o*-toluidine **3** were obtained by the use of the commonly known method of the condensation of terephthalic aldehyde **1** with o-anisidine and o-toluidine in nearly quantitative yields (Scheme 1). All products were characterized by elemental analyses and ^{1}H and ^{31}P NMR spectroscopy.

As we previously mentioned, the addition of phosphites to N,N′-terephthalylidene-bis-*p*-anisidine and to N,N′-terephthalylidene-bis-*p*-toluidine was, in the case of diethyl and diphenyl phosphite, stereoselectively, leading exclusively to bis-aminophosphonates in the *meso*-form.[8] In the case of dibenzyl phosphite, the addition led to the formation of both diastereoisomeric forms of appropriate bis-aminophosphonate. The addition of three model phosphites to N,N′-terephthalylidene-bis-*m*-anisidine led exclusively to bis-aminophosphonates,[8] and



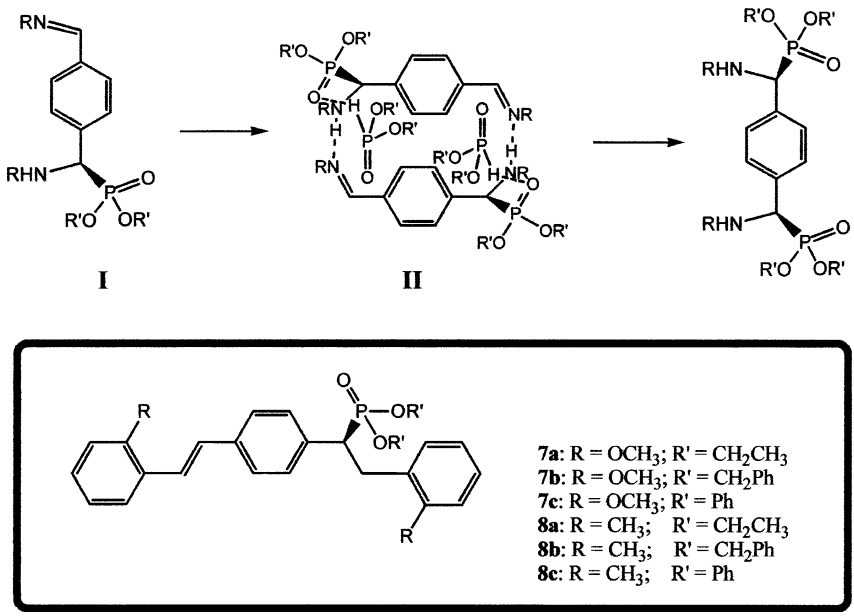
SCHEME 1

N,N′-terephthalylidene-bis-*m*-toluidine led to both diastereoisomeric forms of the appropriate bis-aminophosphonate.

The similar addition to N,N′-terephthalylidene-bis-*o*-anisidine **2** and N,N′-terephthalylidene-bis-*o*-toluidine **3** demonstrated behavior contrary to our expectations. The NMR spectra analysis of products demonstrated that the addition of diethyl and diphenyl phosphites to both Schiff bases **2** and **3** were completely nonstereoselective. Spectra of isolated products **5a**, **5c**, **6a**, and **6c** contained 2 sets of doublets of a coupling constant ~23 Hz attributed to the CHP protons, which suggests univocally the formation of two diastereoisomeric forms. Although each ^{31}P NMR spectrum showed only one signal, when the signals were enlarged, it suggested the existence of overlapping two signals.

The addition of dibenzyl phosphite to N,N′-terephthalylidene-bis-*o*-anisidine **2** was diastereoselective because two diastereoisomeric forms of aminophosphonate **5b** appeared in a 20:1 ratio, which was demonstrated by NMR spectroscopy. The addition of dibenzyl phosphite to N,N′-terephthalylidene-bis-*o*-toluidine **3** led exclusively to the *meso* form of **6b**.

In one of our previous works,[6] we have proposed the hypothetical reason of such a highly stereoselective reaction starting from completely achiral reagents. According to this hypothesis, the reaction is controlled kinetically, and the key step is the formation of such an active complex **II** consisting of two molecules of an iminoester **I** and two molecules of phosphite linked to each other by hydrogen bonding (Scheme 2), which forced the attack of the phosphite molecule from the strictly defined



SCHEME 2

side. The applied semi-empirical AM1 Mulliken population analysis rather confirmed our hypothesis.[8]

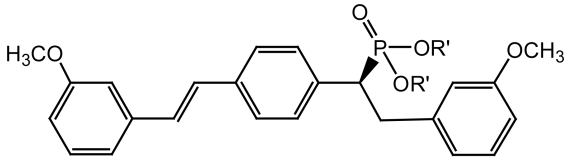
The preliminary semi-empirical AM1[9] Mulliken population analysis demonstrated that charge distribution in iminoesters **7a**, **7c** and **8a**, **8c** on an azomethine nitrogen atom and on an amine group hydrogen atom have values, which make the formation of hydrogen bonding less favorable in comparison to values of **7b**, and **8b**, which have azomethine nitrogen atoms slightly more negative and amine hydrogen atoms—more positive (Table I). And effectively, only the benzyl phosphite addition to Schiff bases **2** and **3** was diastereoselective.

We compared this case to the addition of three model phosphites to N,N′-terephthalylidene-bis-m-anisidine, which was totaly diastereoselective[8] and where values of charge distribution in iminoester **11** seemed to favor the formation of hydrogen bonding. In reference to these values, it is clearly visible why the corresponding complexes of type **II** should not form. In some sense, these data seem to confirm our hypothesis presented previously[6,8] and reminded in Scheme 2.

These are preliminary results. We are going to study the behavior of *o*-substituted aniline-derived series, and in this article, we wish to communicate that this behavior seems to be different.

TABLE I Charges (Mulliken) of Iminoesters 7a–c and 8a–c

		$R' = CH_2CH_3$ **(a)**		$R' = CH_2Ph$ **(b)**		$R' = Ph$ **(c)**	
		HC═**N**	**H**—N	HC═**N**	**H**—N	HC═**N**	**H**—N
7	$R = OCH_3$	−0.15460	+0.18080	−0.16620	+0.19280	−0.13670	+0.18260
8	$R = CH_3$	−0.15190	+0.18600	−0.15250	+0.18670	−0.13260	+0.18810
11		−0.15570	+0.21260	−0.15580	+0.21330	−0.15610	+0.20930



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EXPERIMENTAL

All solvents were routinely dried and distilled prior to use. Terephthalic aldehyde (Aldrich) as well as all three phosphites (Aldrich) and amines (Aldrich) were used as received. NMR measurements were recorded on a Varian Gemini 200 BB at 200 MHz (^{1}H NMR) and 81 MHz (^{31}P NMR) apparatus. Melting points were measured on a MelTemp II apparatus and were not corrected. Elemental analyses were made in the Center for Molecular and Macromolecular Studies in Łódź, Poland. All computations were performed on a PC with a Celeron® 1 GHz processor and 128 MB RAM. Minima of all hypothetical intermediates **7** or **8** were searched by the use of Molecular Dynamics protocol in an MM2 packet included in the ChemOffice 7.0 Ultra pack with 10,000 steps and 2 fs intervals. The generated conformational families were examined by the use of the MM2 force field packet included in the ChemOffice 7.0 Ultra pack. Geometries of resulting models with global minima were optimized by the use of the AM1 method, and their geometries were minimized, and their charge distributions were computed. Semi-empirical RHF AM1 computations were performed by the use of the GAMESS[9] for ChemOffice 7.0 pack. Tight convergence criteria have been used.

Synthesis of Terephthalic Schiff Bases—General Procedure

In a 250-mL round-bottom flask, 1.34 g (10 mmol) of terephthalic aldehyde was placed in 100 mL of benzene. To this solution was added 20 mmol of amine. Then it was stirred for 24 h at r.t. The precipitate was collected by filtration.

N,N′-Terephthalylidene-bis-o-anisidine (3)

Y = 2.58 g (75%); m.p. = 177–179°C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ8.54 (s, CH=N, 2H); 8.03 (s, C_6H_4, 4H); 7.22 (m, o-C_6H_4, 1H); 7.19 (m, o-C_6H_4, 1H); 7.08–6.94 (m, o-C_6H_4, 6H); 3.91 (s, OCH_3, 6H).

Elemental analysis. Calcd. for $C_{22}H_{20}N_2O_2$: C, 76.72; H, 5.85; N, 8.13; found: C, 76.79; H, 5.91; N, 8.19.

N,N′-Terephthalylidene-bis-o-toluidine (4)

Y = 2.94 g (94%); m.p. = 124–125°C; lit.[10] = 128–129°C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ8.42 (s, CH=N, 2H); 8.02 (s, C_6H_4, 4H); 7.25–7.13 (m, o-C_6H_4, 6H); 6.99–6.92 (m, o-C_6H_4, 2H); 2.38 (s, CH_3, 6H).

Synthesis of 1,4-Phenylene-bis-(N-arylaminomethane)-bis-phosphonates—General Procedure

5 mmol of the Schiff base and 10 mmol of dialkyl (diaryl) phosphite were placed in a 250-mL round-bottom flask equipped with a condenser. Then, 50 mL of toluene was added and stirred for 5 h at the boiling temperature. The precipitate was filtered, the filtrate was concentrated, and the re-precipitated solid was collected by filtration. Crude products were recrystallized from toluene.

Tetraethyl 1,4-Phenylene-bis-(N-o-methoxyphenylaminomethane)-bis-phosphonate (6a)

Y = 2.94 g (95%); m.p. = 144–145°C. ^{1}H NMR (200 MHz, $CDCl_3$) : δ7.43 (s, C_6H_4, 4H); 6.21 (m, o-C_6H_4, 2H); 6.74 (m, o-C_6H_4, 2H); 6.30 (m, o-C_6H_4, 2H); 6.34 (m, o-C_6H_4, 2H); 4.74 and 4.73 (2d, $^2J_{PH}$ = 23.0 Hz, C $\underline{H}$P, 2H); 4.05 (m, O$\underline{CH_2}CH_3$, 4H); 3.62 (m, O$\underline{CH_2}CH_3$, 4H); 3.87 (s, OCH_3, 6H); 1.23 and 1.21 (2t, J = 6.9 Hz, OCH_2 $\underline{CH_3}$, 6H); 1.07 and 0.99 (2t, J = 7.1 Hz, $OCH_2\underline{CH_3}$, 6H). ^{31}P NMR (81 MHz, $CDCl_3$): δ22.48.

Elemental analysis. Calcd. for$C_{30}H_{42}N_2O_8P_2$: C, 58.06; H, 6.82; N, 4.51; found: C, 57.83; H, 6.64, N, 4.64.

Tetrabenzyl 1,4-Phenylene-bis-(N-o-methoxyphenylaminomethane)-bis-phosphonate (6b)

Y = 4.14 g (95%); m.p. = 95–98°C. ^{1}H NMR (200 MHz, $CDCl_3$): δ7.44 (s, C_6H_4, 4H); 7.29–7.11 (m, C_6H_5, 20H); 7.04 (m, o-C_6H_4, 2H); 6.74 (m, o-C_6H_4, 2H); 6.61 (m, o-C_6H_4, 2H); 6.35 (m, o-C_6H_4, 2H); 4.86 and 4.48 (2m, O$\underline{CH_2}$Ph, 8H); 4.81 (d, $^2J_{PH}$ = 22.8 Hz, C$\underline{H}$P, 2H); 3.85 (s, OCH_3, 6H). ^{31}P NMR (81 MHz, $CDCl_3$) : δ22.68 and 21.82 (10:1).

Elemental analysis. Calcd. for $C_{50}H_{50}N_2O_8P_2$: C, 69.12; H, 5.80; N, 3.22; found: C, 69.33; H, 5.98; N, 3.20.

Tetraphenyl 1,4-Phenylene-bis-(N-o-methoxyphenylaminomethane)-bis-phosphonate (6c)

Y = 2.91 g (72%); m.p. = 158–160°C. ^{1}H NMR (200 MHz, $CDCl_3$): δ7.55 (s, C_6H_4, 4H); 7.20–7.01 (m, C_6H_5, 16H); 6.75 (m, C_6H_5, o-C_6H_4, 8H); 6.45 (m, o-C_6H_4, 2H); 5.46 (m, o-C_6H_4, 2H); 5.14 and 5.10 (2d, $^2J_{PH}$ = 23.3 Hz, C<u>H</u>P, 2H, 3:2); 3.88 and 3.86 (2s, OCH_3, 6H, 3:2). ^{31}P NMR (81 MHz, $CDCl_3$) : δ14.66.

Elemental analysis. Calcd. for $C_{46}H_{42}N_2O_8P_2$: C, 67.98; H, 5.21; N, 3.45; found: C, 68.09; H, 5.32; N, 3.28.

Tetraethyl 1,4-Phenylene-bis-(N-o-methylphenylaminomethane)-bis-phosphonate (7a)

Y = 2.46 g (84%); m.p. = 137–138°C. ^{1}H NMR (200 MHz, $CDCl_3$) : δ7.44 (s, C_6H_4, 4H); 7.04 (d, J = 7.1 Hz, o-C_6H_4, 2H); 6.88 (dd, J = 7.1 and 7.3 Hz, o-C_6H_4, 2H); 6.62 (dd, J = 7.3 and 7.8 Hz, o-C_6H_4, 2H); 6.32 (d, J = 7.8 Hz, o-C_6H_4, 2H); 4.78 and 4.77 (2d, $^2J_{PH}$ = 23.3 Hz, C<u>H</u>P, 2H, 1:1); 4.23–3.96 (m, O<u>C</u>H_2CH_3, 4H); 3.92–3.78 (m, O<u>C</u>H_2CH_3, 2H); 3.68–3.46 (m, O<u>C</u>H_2CH_3, 2H); 2.26 (s, OCH_3, 6H); 1.26 and 1.21 (2t, J = 6.9 Hz, OCH_2<u>C</u>H_3, 6H); 1.06 and 0.97 (2t, J = 6.9 Hz, OCH_2 <u>C</u>H_3, 6H). ^{31}P NMR (81 MHz, $CDCl_3$): δ22.63.

Elemental analysis. Calcd. for $C_{30}H_{42}N_2O_6P_2$: C, 61.22; H, 7.19; N, 4.76; found: C, 61.38; H, 7.15; N, 4.56.

Tetrabenzyl 1,4-Phenylene-bis-(N-o-methylphenylaminomethane)-bis-phosphonate (7b)

Y = 3.16 g (76%); m.p. = 144–145°C. ^{1}H NMR (200 MHz, $CDCl_3$): δ7.42 (2s, C_6H_4, 4H); 7.30–7.11 (m, C_6H_5, 20H); 7.02 (m, o-C_6H_4, 2H); 6.82 (m, o-C_6H_4, 2H); 6.57 (m, o-C_6H_4, 2H); 6.30 (m, o-C_6H_4, 2H); 4.95 (m, O<u>C</u>H_2Ph, 4H); 4.81 (d, $^2J_{PH}$ = 22.5 Hz, C<u>H</u>P, 2H); 4.77 (Part of AMX system, $^3J_{PH}$ = 7.1 Hz, $^2J_{HH}$ = 11.6 Hz, O<u>C</u>H_2Ph, 2H); 4.36 (Part of AMX system, $^3J_{PH}$ = 8.2 Hz, $^2J_{HH}$ = 11.6 Hz, O<u>C</u>H_2Ph, 2H); 2.20 (s, CH_3, 6H). ^{31}P NMR (81 MHz, $CDCl_3$): δ22.91.

Elemental analysis. Calcd. for $C_{50}H_{50}N_2O_6P_2$: C, 71.76; H, 6.02; N, 3.35; found: C, 71.47; H, 5.86; N, 3.07.

Tetraphenyl 1,4-Phenylene-bis-(N-o-methylphenylaminomethane)-bis-phosphonate (7c)

Y = 2.00 g (51%); m.p. = 131–132°C. ^{1}H NMR (200 MHz, $CDCl_3$): δ7.56 (s, C_6H_4, 4H); 7.21–6.95 (m, C_6H_5, 16H); 6.80–6.74 (m, C_6H_5, 4H); 6.70 (m, o-C_6H_4, 2H); 6.66 (m, o-C_6H_4, 2H); 6.45 (m, o-C_6H_4, 4H); 5.19 and 5.16 (2d, $^2J_{PH}$ = 23.4 Hz, C<u>H</u>P, 2H); 2.20 and 2.19 (2s, CH_3, 6H). ^{31}P NMR (81 MHz, $CDCl_3$): δ14.66.

Elemental analysis. Calcd. for $C_{46}H_{42}N_2O_6P_2$: C, 70.76; H, 5.42; N, 3.59; found: C, 70.49; H, 5.11; N, 3.29.

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