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Stereochemical Aspects of the Hypophosphorous Acid Addition to Terephthalic Schiff Bases. Synthesis of New 1,4-Phenylene-bis-aminomethane-bis-phosphonous Acids

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ABSTRACT: *Terephthalic Schiff bases react with hypophosphorous acid to form 1,4-phenylene-bis-N-alkyl-aminomethanephosphonous acids in moderate yields. NMR studies demonstrated that—for several examples—this reaction led to the exclusive formation of only one diastereomeric form. NMR investigation of a chiral salt identified the meso form. In contrast hereto, a corresponding addition of hypophosphorous acid to a chiral Schiff base proved to be not stereoselective; all three possible diastereoisomers were formed in a 4:1:1 ratio.* © 2008 Wiley Periodicals, Inc. Heteroatom Chem 19:283–287, 2008; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20422

INTRODUCTION

Studies on the addition of phosphites to symmetrical bis-Schiff bases were performed previously, where particular attention was directed to reactions of terephthalic Schiff. The first report was published by Pudovik et al. [1], presenting the synthesis of a variety of 1,4-phenylene-bis-amino-methane-bis-phosphonates, and hence it has historical importance. Later papers authored by Finocchiaro et al. [2–4] and Gancarz et al. [5] presented the discussion on the stereochemical aspect of these reactions. Our group has also contributed to this topic reporting about the stereochemistry of addition reactions to various *N*-substituted terephthalic imines [6–9]. A comprehensive and detailed report on NMR spectroscopic and molecular modeling studies of 1,4-phenylene-bis-aminomethane-bis-phosphonates and related structures is given in [10].

In contrast to the 1,4-phenylene-bis-aminomethane-bis-phosphonates, the corresponding formation of aminophosphonous analogs was scarcely studied and described. Only Gancarz's paper [5] described the synthesis of 1,4-phenylene-bis-*N*-benzyl- and *N*-benzhydrylaminomethane-bis-phosphonous acid. These authors reported the exclusive formation of one diastereoisomeric form but did not point out its configuration.

In this paper, we would like to present results from our studies on the addition of hypophosphorous acid to terephthalic *N*-aliphatic and *N*-aromatic Schiff bases and the synthesis of several new 1,4-phenylene-bis-aminomethane-bis-phosphonous acids.

This work is dedicated to my mentor Professor Romuald Skowroński of the University of Łódź, Łódź, Poland on the occasion of his 80th birthday.

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RESULTS AND DISCUSSION

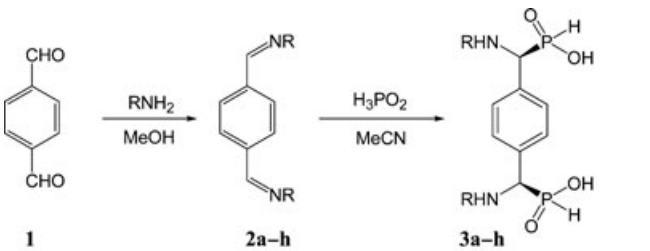
Schiff bases **2a–h** were prepared following the published procedure [6] by the condensation of corresponding amines with terephthalic aldehyde **1** in methanol at room temperature. Corresponding imines were obtained in quantitative yields.

The preparation of terephthalic bis-aminophosphonous acids **3a–h** has been performed adopting the general procedure reported by Baylis et al. [11]. Reactions were carried out in boiling acetonitrile for 5 h, and subsequently mixtures were left overnight to stir at room temperature (Scheme 1).

The novel phosphonous acids were obtained in moderate yields varying from 40%–90%, which was more then expected, since several authors [2–5] suggested much lower conversion rates for additions to two azomethine groups.

In general, two individual diastereoisomeric forms might be expected for the title compounds: a meso form and a racemic mixture. However, it was proven in papers [2–10] that the addition of dialkyl or diaryl phosphites to *N*-alkyl terephthalic Schiff bases led to the exclusive formation of one diastereoisomeric form. Our previous study [6–9] revealed that this diastereoisomer was the meso form. On the other hand, the addition of dialkyl or diaryl phosphites to *N*-aryl terephthalic Schiff bases led exclusively either to the formation of the meso form or to both diastereomeric forms, which depended on the nature of the aryl substituent [8,9]. Our findings are consistent with reports by Barycki et al. [5]: these authors observed the exclusive formation of one diastereoisomeric form for the addition of hypophosphorous acid to *N*-benzyl terephthalic Schiff base.

After analyzing all eight aminophosphonous acids **3a–h**, we realized that the addition reaction is not diastereospecific for all cases. The exclusive formation of one diastereoisomer was observed for the following cases: *N*-benzyl (**3a**), *N*-tert-butyl (**3c**), *N*-benzhydryl (**3d**), and *N*-*p*-methoxyphenyl (**3e**). But pairs of diastereoisomers were formed for cases: *N*-*m*-methoxyphenyl (**3f**), *N*-*p*-methylphenyl (**3g**), and *N*-*m*-methylphenyl (**3h**), in effect, which was rather expected as addition of dialkyl phosphites to the Schiff bases **2f–h** led to both diastereomeric forms [8]. In the case of the *N*-furfuryl-substituted product (**3b**), both diastereomers were formed in a 1:1 ratio (Table 1)



a: R = CH_2Ph, **b**: R = CH_2Fur, **c**: R = $C(CH_3)_3$, **d**: R = $CHPh_2$
e: R = *p*-$MeOC_6H_4$, **f**: R = *m*-$MeOC_6H_4$, **g**: R = *p*-MeC_6H_4,
h: R = *m*-MeC_6H_4,

SCHEME 1

TABLE 1 Diastereomeric Composition of Products

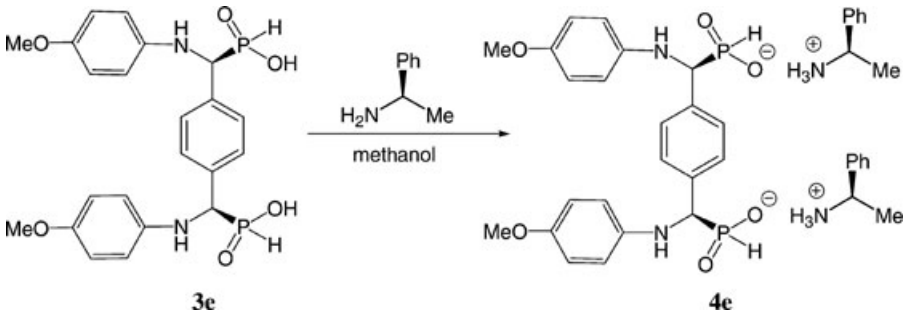
Acid	*R*	*Number of Diastereoisomers*	*Diastereomeric Ratio*
3a	CH_2Ph	1	–
3b	CH_2Fur	2	1:1
3c	$C(CH_3)_3$	1	–
3d	$CHPh_2$	1	–
3e	*p*-$MeOC_6H_4$	1	–
3f	*p*-MeC_6H_4	2	5:2
3g	*m*-$MeOC_6H_4$	2	2:1
3h	*m*-MeC_6H_4	2	3:1

To determine the configuration of the aminophosphonous acids **3a** and **3c–e**, which occurred as pure but hitherto unknown diastereomeric forms, we prepared the chiral salts of acid **3e** with (*S*)-α-methylbenzylamine by simply mixing both components in methanol (Scheme 2).

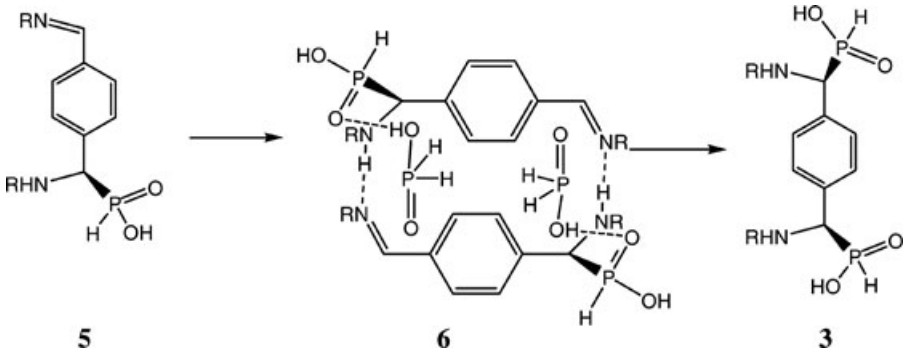
We expected one set of ^1H NMR and $^{31}P\{^1H\}$ NMR signals for the meso form, whereas the racemic mixture should give rise to two signal sets. Since NMR spectra of this salt exhibited one set of signals only, the exclusive formation of the meso form in the reaction of hypophosphorous acid with terephthalic Schiff bases is deduced unequivocally.

In our previous reports [6,8], the hypothetical reasons were proposed for the highly stereoselective addition of dialkyl phosphites to achiral terephthalic Schiff bases. This model may be also well adapted to the case of the similar addition of hypophosphorous acid. According to this hypothesis, the reaction is controlled kinetically. The key step is the formation of an active complex **6**, consisting of two molecules of iminoester **5**, and two molecules of phosphite linked to each other with hydrogen bonds (Scheme 3), which forces the attack of the hypophosphorous acid molecule from one strictly defined side.

Therefore, when the possibility for the formation of such a dimer is lower, the formation of both diastereoisomeric forms is expected. In the case of addition of dialkyl phosphites to the *N*-furfuryl terephthalic Schiff base, the diaminophosphonic derivative was formed in 100% diastereospecifity, whereas the addition of hypophosphorous acid to this Schiff base



SCHEME 2



SCHEME 3

led to the formation of both diastereoisomers in a 1:1 ratio.

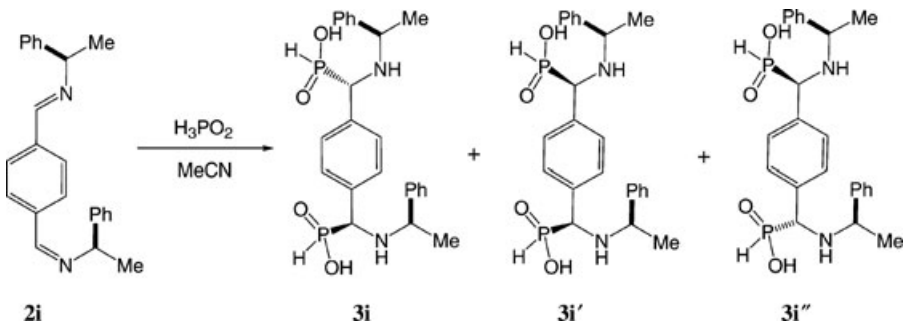
Since previous studies [12] showed that the addition of hypophosphorous acid to chiral (*R*)-*N*-α-methylbenzyl Schiff bases is diastereoselective to 100% [12], we performed analogous addition to the bifunctional *N*-(*R*)-α-methylbenzyl Schiff base **2i** derived from terephthalic aldehyde.

Using those Schiff bases, we expected to obtain exclusively the (*S*, *S*) diastereoisomer **3i**, but in practice a mixture of all three possible diastereoisomers of 1,4-phenylene-bis-(*N*-(*R*)-α-methyl-benzylaminomethanephosphonous) acid exhibited a 4:1:1 ratio for **3i**, **3i′**, and **3i″** and a total yield of 97% (Scheme 4).

These findings demonstrate that the influence of the chiral substituent attached to nitrogen is competing with the phenomenon discussed above, determining the stereochemistry for additions of hypophosphorous acid to terephthalic Schiff bases. Intriguing stereochemical problems will encourage forthcoming studies.

EXPERIMENTAL

All solvents were routinely distilled prior to use. Hypophosphorous acid 50% (Aldrich, Poznań, Poland) was dehydrated following the published procedure [10]. Amines and terephthalic aldehyde (Aldrich) were used as received. Schiff bases **2a–i** were



SCHEME 4

prepared following the previously published procedure [6,8]. NMR spectra were recorded on a Varian Gemini 200 BB apparatus operating at 200 MHz (^{1}H NMR) with internal TMS standard and 81 MHz (^{31}P{^{1}H} NMR) with external 85% H_3PO_4 standard.

Elemental analyses were made in the Center for Molecular and Macromolecular Science of the Polish Academy of Science in Łódź.

*1,4-Phenylene-bis-aminomethanephosphonous Acids (**3a–i**). General Procedure*

Terephthalic aldehyde (10 mmol, 1.34 g) was dissolved in 30 mL of methanol, and the appropriate amine (20 mmol) was added. The mixture was stirred overnight at room temperature, then it was evaporated, redissolved in dichloromethane, dried over $MgSO_4$, filtered, and evaporated. The residue, which was the pure Schiff base, was dissolved in 40 mL of acetonitrile, and hypophosphorous acid (20 mmol, 1.32 g) was added. The mixture was refluxed for 5 h and then stirred overnight at room temperature. The precipitated solid was collected by filtration, washed with cold water then cold methanol to give almost pure acids **3a–i**. Compounds **3d** and **3h–i** were additionally purified by dissolving in aqueous NaOH solution and precipitating by acidification.

*1,4-Phenylene-bis-(N-benzylaminomethanephosphonous) Acid (**3a**).* $Y = 89\%$ (3.95 g); mp 235–238°C (lit. [5] 243–246°C). ^{1}H NMR (NaOD/D_2O, 200 MHz): δ 7.12 (s, C_6H_4, 4H); 7.04 (m, C_6H_5, 10H); 6.67 (d, $^1J_{PH} = 522.0$ Hz, PH, 2H); 3.52 (d, $^2J_{PH} = -17.4$ Hz, PCH, 2H); 3.50 and 3.31 (2d, $^2J_{HH} = -13.2$ Hz, CH_2Ph, 4H). ^{31}P {^{1}H} NMR (NaOD/D_2O, 81 MHz): δ 28.31. Anal. Calcd for $C_{22}H_{26}N_2O_4P_2$: C, 59.46; H, 5.90; N, 6.30. Found: C, 59.19; H, 5.66; N, 6.11.

*1,4-Phenylene-bis-(N-furfurylaminomethanephosphonous) Acid (**3b**).* $Y = 58\%$ (1.40 g); mp: 240–243°C. ^{1}H NMR (NaOD/D_2O, 200 MHz): δ 7.50 (d, $J = 1.4$ Hz, CH^5_{fur}, 2H); 7.45 (s, C_6H_4, 4H); 6.45 (d, $J = 3.0$ Hz, CH^3_{fur}, 2H); 6.39 (m, CH^4_{fur}, 2H); 7.05 (d, $^1J_{PH} = 549.0$ Hz, PH, 2H); 3.55 (d, $^2J_{PH} = -15.5$ Hz, PCH, 2H); 3.60 and 3.44 (2d, $^2J_{HH} = -14.5$ Hz, CH_2Ph, 4H). ^{31}P {^{1}H} NMR (NaOD/D_2O, 81 MHz): δ 28.19 and 28.09. Anal. Calcd for $C_{18}H_{22}N_2O_6P_2$: C, 50.95; H, 5.23; N, 6.60. Found: C, 50.66; H, 5.05; N, 6.63.

*1,4-Phenylene-bis-(N-tert-butylaminomethanephosphonous) Acid (**3c**).* $Y = 57\%$ (2.14 g); mp: 259–260°C. ^{1}H NMR (NaOD/D_2O, 200 MHz): δ 7.31 (s, C_6H_4, 4H); 6.75 (d, $^1J_{PH} = 520.9$ Hz, PH, 2H); 3.84 (d, $^2J_{PH} = -18.0$ Hz, PCH, 2H); 0.92 (s, $(CH_3)_3$, 18H). ^{31}P {^{1}H} NMR (NaOD/D_2O, 81 MHz): δ 29.66. Anal. Calcd for $C_{16}H_{30}N_2O_4P_2$: C, 51.06; H, 8.03; N, 7.44. Found: C, 50.86; H, 7.93; N, 7.23.

*1,4-Phenylene-bis-(N-benzhdrylaminomethanephosphonous) Acid (**3d**).* $Y = 20\%$ (1.19 g); mp: 242–245°C. ^{1}H NMR (DMSO, 200 MHz): δ 8.21 (s, C_6H_4, 4H); 7.35 (m, C_6H_5, 20H); 6.74 (d, $^1J_{PH} = 524.0$ Hz, PH, 2H); 5.71 (s, $CHPh_2$, 2H); 5.02 (d, $^2J_{PH} = -17.8$ Hz, PCH, 2H). ^{31}P {^{1}H} NMR (DMSO, 81 MHz): δ 23.35. Anal. Calcd for $C_{34}H_{34}N_2O_4P_2$: C, 68.45; H, 5.74; N, 4.70. Found: C, 68.21; H, 5.72; N, 4.77.

*1,4-Phenylene-bis-(N-p-methoxyphenylaminomethanephosphonous) Acid (**3e**).* $Y = 77\%$ (3.67 g); mp: 183–186°C. ^{1}H NMR (DMSO, 200 MHz): δ 7.27 (s, C_6H_4, 4H); 6.58 (m, p-C_6H_4, 8H); 6.87 (d, $^1J_{PH} = 526.5$ Hz, PH, 2H); 4.42 (d, $^2J_{PH} = -17.0$ Hz, PCH, 2H); 3.46 (s, CH_3, 6H). ^{31}P {^{1}H} NMR (DMSO, 81 MHz): δ 24.82. Anal. Calcd for $C_{22}H_{26}N_2O_6P_2$: C, 55.47; H, 5.50; N, 5.88. Found: C, 55.17; H, 5.40; N, 5.72.

*1,4-Phenylene-bis-(N-p-methylphenylaminomethanephosphonous) Acid (**3f**).* $Y = 54\%$ (2.40 g); mp: 138–140°C. ^{1}H NMR (DMSO, 200 MHz): δ 7.31 (s, C_6H_4, 4H); 6.75 (m, p-C_6H_4, 4H); 6.53 (m, p-C_6H_4, 4H); 6.87 (d, $^1J_{PH} = 526.5$ Hz, PH, 2H); 4.52 (d, $^2J_{PH} = -17.3$ Hz, PCH, 2H); 2.07 (s, CH_3, 6H). ^{31}P {^{1}H} NMR (DMSO, 81 MHz): δ 25.07 and 24.91, (5:2). Anal. Calcd for $C_{22}H_{26}N_2O_4P_2$: C, 59.46; H, 5.90; N, 6.30. Found: C, 59.05; H, 5.97; N, 6.09.

*1,4-Phenylene-bis-(N-m-methoxyphenylaminomethanephosphonous) Acid (**3g**).* $Y = 98\%$ (4.67 g); mp: 236–239°C. ^{1}H NMR (DMSO, 200 MHz): δ7.37 (s, C_6H_4, 4H); 6.80 (m, m-C_6H_4, 2H); 6.28 (m, m-C_6H_4, 4H); 6.17 (m, m-C_6H_4, 2H); 7.00 (d, $^1J_{PH} = 543.2$ Hz, PH, 2H); 4.75 (d, $^2J_{PH} = -16.9$ Hz, PCH, 2H); 3.57 (s, CH_3, 6H). ^{31}P {^{1}H} NMR (DMSO, 81 MHz): δ 24.60 and 24.35, (2:1). Anal. Calcd for $C_{22}H_{26}N_2O_6P_2$: C, 55.47; H, 5.50; N, 5.88. Found: C, 55.30; H, 5.39; N, 5.70.

*1,4-Phenylene-bis-(N-m-methylphenylaminomethanephosphonous) Acid (**3h**).* $Y = 49\%$ (2.20 g); mp: 124–126°C. ^{1}H NMR (DMSO, 200 MHz): δ 7.39 (s, C_6H_4, 4H); 6.85 (dd, $J = 7.6$ and 7.2 Hz, m-C_6H_4, 2H); 6.56 (s, m-C_6H_4, 2H); 6.49 (d, $J = 7.6$, m-C_6H_4, 2H); 6.35 (d, $J = 7.2$, m-C_6H_4, 2H); 7.01 (2d, $^1J_{PH} = 545.0$ Hz, PH, 2H); 6.83 (2d, $^1J_{PH} = 536.0$ Hz, PH, 2H); 4.78 (d, $^2J_{PH} = -17.6$ Hz, PCH, 2H); 2.08 (s, CH_3, 6H). ^{31}P {^{1}H} NMR (DMSO, 81 MHz): δ 24.93 and 24.55 (3:1). Anal. Calcd for $C_{22}H_{26}N_2O_4P_2$: C,

59.46; H, 5.90; N, 6.30. Found: C, 59.76; H, 6.08; N, 5.95.

*1,4-Phenylene-bis-(N-(R)-α-methylbenzylamino-methanephosphonous) Acid (**3i**).* $Y = 97\%$ (4.58 g); mp: 238–241°C. ^{1}H NMR (NaOD/D_2O, 200 MHz): δ 7.02 (s, C_6H_4, 4H); 6.90 (m, C_6H_5, 10H); 6.76 (d, $^1J_{PH} = 521.7$ Hz, PH, 2H); 3.71 (d, $^2J_{PH} = -15.9$ Hz, PCH, 2H); 3.51 (q, $^3J_{HH} = 6.3$ Hz, $CH_3\underline{CH}$, 4H); 1.11 (d, $^3J_{HH} = 6.3$ Hz, $\underline{CH_3}CH$, 4H). ^{31}P $\{^1H\}$ NMR (NaOD/D_2O, 81 MHz): δ 28.61; 28.07; 27.10 (4:1:1). Anal. Calcd for $C_{24}H_{30}N_2O_4P_2$: C, 61.01; H, 6.40; N, 5.93. Found: C, 60.98; H, 6.23; N, 6.28.

*1,4-Phenylene-bis-(N-p-methoxyphenylamino-methanephosphonous) Acid Bis-(S)-α-methylbenzyl-ammonium Salt (**4e**)*

The acid **3e** (1 mmol, 0.48 g) was dissolved in 5 mL of methanol-d^4, (*R*)-α-methylbenzylamine (2 mmol, 0.24 g) was added, and the mixture was stirred at room temperature for 24 h. Then, an appropriate sample was taken for NMR measurements.

^{1}H NMR (CD_3OD, 200 MHz): δ 7.45 (m, C_6H_5, 10H); 7.39 (s, C_6H_4, 4H); 6.65 and 6.54 (AA′XX′ system, $J = 9.0$ Hz, *p*-C_6H_4, 4H); 6.87 (d, $^1J_{PH} = 518.3$ Hz, PH, 2H); 4.35 (d, $^2J_{PH} = -17.8$ Hz, PCH, 2H); 3,74 (q, $^3J_{HH} = 6.5$ Hz, $CH_3\underline{CH}$, 4H); 3.67 (s, CH_3, 6H); 1.60 (d, $^3J_{HH} = 6.3$ Hz, $\underline{CH_3}CH$, 4H). ^{31}P $\{^1H\}$ NMR (CD_3OD, 81 MHz): δ 24.68.

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