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Rationalization of the Stereochemistry of an Addition of Dialkyl Phosphites to Certain Chiral Aldimines: The Experimental and Theoretical Approach

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ABSTRACT: *The absolute configuration of an α-P stereogenic center in two diastereomeric O,O-dialkyl α-aminophosphonates (**3**), arising from an induced 1,3-asymmetric phosphite addition to the C=N bond of furfural-derived Schiff bases (**1**), was established from single product ^{1}H NMR data. Such spectra were interpreted with anisotropic shielding in relation to the AM1 and MNDO/d structures of **3**; the former ones turned out to be closer to the obtained experimental results (^{1}H NMR spectra of **3**, crystallographic database study). Since favored 3-21G geometries of starting imines **1** were modeled as well, it was inferred that a stereochemical outcome of this reaction is governed by Cram selectivity.* © 2002 Wiley Periodicals, Inc. Heteroatom Chem 13:120–125, 2002; Published online in Wiley Interscience (www.interscience.wiley.com). DOI 10.1002/hc.10005

INTRODUCTION

α-Aminophosphonic acids and their esters have been of interest to chemists since the late 1940s, when aminomethanephosphonic acid was obtained as a phosphorus analog of glycine [1]. Extensive investigations over the last thirty years have shown that they are of particular importance in biological, medicinal, and agricultural research [2]. Among numerous methods for the preparation of such kinds of compounds, the most convenient route is the addition of a dialkyl (or diaryl) phosphite to the azomethine bond of a Schiff base [3]. Using this methodology, we recently obtained some phenylene-bisaminomethanephosphonates, and an unusual stereochemical outcome of these reactions was pointed out. It was demonstrated that such bisaddition to phenylene-bisimines is highly stereoselective though some exceptions were also noted [4]. In order to explain the mechanism of these reactions, we restudied our previous investigations on a single addition of phosphites to chiral Schiff bases [5–7], considering this as a model process.

The reaction of *N*-furfurylidene α-methylbenzylamines (**1**, R = H, CH_2OH) with dialkyl phosphites (**2**, R′ = Et, CH_2Ph) resulted in diastereomeric pairs of dialkyl (2-furyl)-*N*-methylbenzylaminophosphonates (**3**) (Scheme 1). Both products were separated by column chromatography and obtained as viscous liquids [5–9]. The stereochemistry of the process was initially interpreted [5,6] with the consideration that the predominant isomer **3a** was formed in addition to an azomethine C=N bond of a prochiral aldimine **1**, which followed the general Cram model

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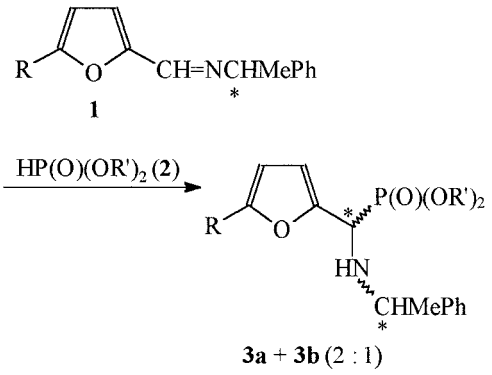


SCHEME 1

of stereoselectivity [10]. Simultaneously, an attempt to explain the ^{1}H NMR spectra of single esters **3A** and **3B** (R = CH_2OH, R′ = CH_2Ph) derived from the chiral imine (*R*)-**1** was made. Accordingly, the Newman-type projections along single bonds in probable conformations of both products (**3**) were considered [6,7]. Dreiding's models were used for a geometrical representation of molecular objects in question. An analogous NMR study was used by Latypov et al. [11] in the case of arylmethoxyacetamides. An analysis of our case gave results confirming an initially proposed spatial aspect of the reaction mechanism. Therefore, we postulate that the chiral center in an α-P position of the predominant diastereomer of the **3a** type (e.g., **3A**) is in the *R* configuration [5–7].

In this work, some new structural results based on theoretical calculations (ab initio and semiempirical) are presented, which reveal new facts and give us a new view of the stereochemistry of the reaction.

RESULTS AND DISCUSSION

Unambiguous assignment of an absolute configuration of the α-P stereogenic center in isomers **3** (R = H [8] or CH_2OH [5–7,9]) was necessary for a definitive explanation of the title process stereochemistry. Since the X-ray structure analysis could not be performed, the only method of configuration determination (i.e., omitting a derivatization technique) was computer modeling of the reliable geometry for both isomers under study. In the next step, attempts were made to match obtained geometric models with the spectroscopic images of the products, especially their ^{1}H NMR properties (Table 1). Recently, we employed an analogous, NMR-based joint approach with two different diastereomeric systems [12,13].

Such a three-step modeling strategy was used for the two esters **3A** and **3B**. Both exhibit considerable conformational freedom arising from internal rotations and an additional pyramidal nitrogen inversion. Therefore, an approach of the "random MMX search/MM+ geometry refinement/AM1 (or MNDO/d) energy minimization" type was used in a molecular modeling of their chemical structure (Experimental). Calculated geometries of the **I** and **II** type (see Fig. 1 for the AM1 structures, $\mathbf{I}_{AM1}$ and $\mathbf{II}_{AM1}$) seem to be useful 3D models of conformations corresponding to global potential-energy minima for the *SR* and *RR* molecules of **3** (R = CH_2OH), respectively.

An AM1 quantum-chemical semiempirical method, widely applied in the absence of intramolecular hydrogen bonding, is only approximate for molecules with tetravalent phosphorus(V) atom(s), as d-functions are neglected in such SCF-MO calculations. It concerns especially the dπ—pπ back bonding in the phosphoryl P=O group the geometry of which is usually rather poorly represented theoretically without an inclusion of d-orbitals. Fortunately, the P(:O)$(OR')_2$ grouping, although structurally very important as the "clamp" for the three fragments of system **3**, is identically reflected for both stereoisomers in this approach (systematic error). On the other hand, the recently available MNDO/d method [14] provides facilities for calculations that include the d-orbitals. However, for **3**, such an improvement of the tool (with respect to the original MNDO method) concerns only the P atoms. So, we expected that the MNDO/d technique (less accurate, in general) afforded the much more reliable geometry, but around these atoms solely.

The resulting energy-minimized structures **I** and **II**, calculated for molecules of **3A** and **3B** with

TABLE 1 Representative ^{1}H NMR Data (200 MHz, $CDCl_3$) for Diastereomeric Pairs **3** (R = H [8] or CH_2OH [5–7, 9], R′ = CH_2Ph), δ_H (ppm)

R	*Product*	H*C4 fur*	H*C3 fur*	*C*H_2*Ph*	*C*H_2*Ph*	*C*H_2*OH*	HC_α*P*	*C*H*MePh*	*CH*Me*Ph*
H	Major	6.31	6.31	5.2–5.0	5.0–4.7	–	4.24	3.86	1.26
H	Minor	6.36	6.24	5.3–5.0	5.0–4.7	–	3.95	3.65	1.26
CH_2OH	Major (**3A**)	6.15	6.15	5.2–5.0	5.0–4.8	4.46	4.19	3.86	1.25
CH_2OH	Minor (**3B**)	6.23	6.16	5.3–5.0	4.7–4.5	4.54	3.90	3.67	1.26

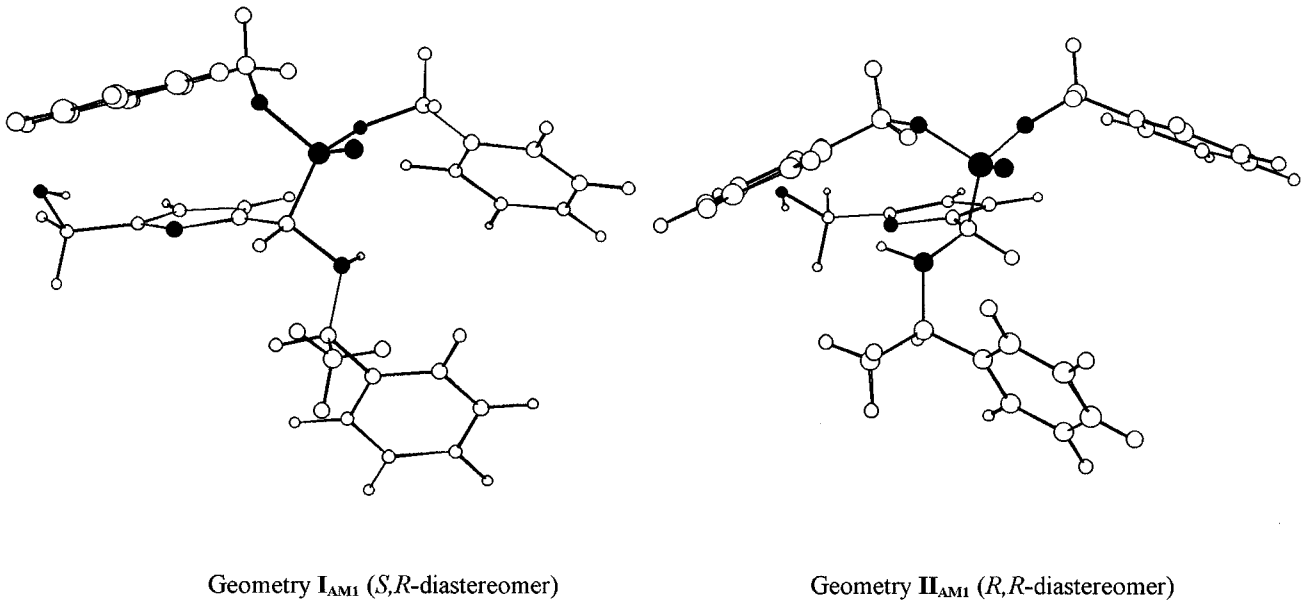


FIGURE 1 The AM1 geometries of global potential minima established for diastereomers **3A** and **3B** (heteroatoms are shown in black).

the AM1 (molecular models $\mathbf{I}_{AM1}$ and $\mathbf{II}_{AM1}$) or MNDO/d ($\mathbf{I}_{MNDO}$ and $\mathbf{II}_{MNDO}$) Hamiltonian, were investigated extensively. The possibility of their explanation/differentiation, using Boltzmann-averaged ^{1}H solution NMR data measured for esters **3** (especially a strongly differentiated spectrum of the minor isomer **3B**) and vice versa, was a principal criterion for an accuracy of computed structures. Selected geometrical data of obtained models are presented in Table 2; the large differences in the C—P bond lengths and some of the C—P—O—C torsion angles found using both techniques are noteworthy. Thus, the former parameters calculated with the MNDO/d method (l C—P = 1.900 Å) are slightly closer to the average literature data (1.819(23) Å; the Cambridge Structural Database System search, 1998 [17]). However, for the last two bonds involving the P atom, i.e., l P=O and l P—O, the AM1 results are much better (1.457 and 1.611 Å (isomers **3**) vs. 1.459(19) and 1.562(17) Å (the X-ray data search [17]), respectively). The second available criterion for testing the reliability of calculated molecular structures, i.e., their accurate "representation" of the distribution of experimental products, was also considered. This ratio was roughly estimated from total-energy values, E_{tot}, calculated for global minimum-energy forms of both

TABLE 2 Selected Geometrical Data of Models (*S,R*)-**3A** and (*R,R*)-**3B** Obtained by AM1 [15] and MNDO/d [16] Calculations, Bond Lengths l(Å) and Angles ∠ (deg)

Con gur ation	*SR (structure* **I***)*		*RR (structure* **II***)*	
Method	*AM1*	*MNDO/d*	*AM1*	*MNDO/d*
l P=O_p	1.4569	1.4891	1.4573	1.4883
l P–O_l	1.6110	1.6527	1.6110	1.6554
l P–O_r	1.6107	1.6560	1.6103	1.6528
l C–P	*1.6844*	*1.8993*	*1.6870*	*1.9013*
∠ C–P–O_l	105.1	99.8	106.3	105.7
∠ C–P–O_r	105.7	106.2	104.5	99.6
∠ C–P–O_p	119.6	115.4	119.9	115.9
∠ O_l–P–O_r	100.3	102.1	100.9	102.1
∠ O_l–P–O_p	110.8	115.4	112.1	116.0
∠ O_r–P–O_p	113.3	115.9	111.3	115.5
∠ C–P–O_l–C_l	*127.4*	*175.1*	109.4	118.3
∠ C–P–O_r–C_r	−132.6	−116.5	*−137.2*	*−172.5*

Numbers in italic represent the large differences.

stereomers. In view of the approximate character of applied methods and considering only the lowest energy conformations, this criterion was assumed to be of less value.

The $\mathbf{I}_{AM1}$ geometry obtained for an energetically favored conformation of the isomer (*S*,*R*)-**3** (R = CH_2OH), $E_{tot} = -572673.93$ kJ mol^{-1}, allowed us to suppose the existence of only a weak anisotropic shielding of the methyl CH*Me*Ph group. It may suggest that this effect is due to the π-electron aromatic system of one of two benzyl groups (named throughout this work with the Bn_r symbol, see group at the right-hand side of Fig. 1). In contrast, a consideration of the higher energetic isomer (*R*,*R*)-**3** of structure $\mathbf{II}_{AM1}$, $E_{tot} = -572672.23$ kJ mol^{-1}, shows an existence of such interactions for all three phenyl rings. Thus, the magnetic-anisotropy cone of the phenyl CHMe*Ph* group most likely causes the chemical nonequivalence of methylene CH_2Ph groups (i.e., shielding the Bn_r group) and β-protons of a furan ring by shielding the *H*C3$_{fur}$ proton. The strong upfield shift of the *H*CαP proton signal is also observed. On the other hand, an aromatic system of the left benzyl group (Bn_ℓ) deshields the methylene protons of the CH_2OH group and shields the methyl protons of the CH*Me*Ph fragment, respectively. Moreover, the Bn_r group shields the methine C*H*MePh proton.

On the contrary, the $\mathbf{I}_{MNDO}$ geometry (not shown) of the preferred conformation of (*S*,*R*)-**3** (R = CH_2OH), $E_{tot} = -574888.77$ kJ mol^{-1}, allowed for a suggestion of a weak shielding of the methylene protons of the CH_2OH group because of the Bn_ℓ substituent. Moreover, a consideration of the corresponding structure $\mathbf{II}_{MNDO}$ [computed for the second slightly disfavored isomer (*R*,*R*)-**3**, $E_{tot} = -574886.87$ kJ mol^{-1}] only suggests shielding of the *H*C3$_{fur}$ proton (correctly) and methylene protons of the CH_2OH unit (wrongly) by Bn_ℓ and Bn_r groups, respectively. In view of these mutually inconsistent MNDO/d results, which are not compatible with the observed chemical shift trends, it is evident that AM1 geometries are certainly the much better 3D molecular models of real objects **3** in solution. It can be believed that some "twisting" found for phosphorus fragments in their MNDO/d structures (C—P—O—C angles, Table 2) results mainly from an overestimation of such kind of C—P distance by this method (*vide supra*). Obviously, the single-bond rotation causes an important change in the orientation of OCH_2Ph groups with respect to the rest of molecules **3**, and so their different shielding. Thus, the inclusion of d-orbitals was not useful in our calculations.

Actually, effects of all through-space interactions discussed above at the AM1 level for a structure $\mathbf{II}_{AM1}$ are observed well on the ^{1}H NMR spectrum of the isomer **3B**. The β*H*C$_{fur}$ and CH_2Ph protons resonate in two separate regions; the CH_2OH protons are deshielded, while the *H*Cα*P* and C*H*MePh protons are shielded. In contrast, the spectrum of the isomer **3A** is much less differentiated; phenyl protons and methyl CH*Me*Ph groups of both isomers gave signals at practically the same δ_H value, as expected (Table 1). Thus, an anisotropy of the π_{arom} bonds, which operates in a structure $\mathbf{II}_{AM1}$ of the *RR* configuration, explains very well the differentiated ^{1}H NMR spectrum of minor product **3B**. The analogous NMR results which were found very recently for the second diastereomeric pair **3** (R = H) [8] argue that our finding is general in character. Moreover, a distribution of an electric charge at both β-protons of the furan ring, calculated by the AM1 method for molecules **3A** and **3B**, is also more differentiated for the *RR* object (0.172 and 0.166) than for the *SR* one (0.170 and 0.167) in line with the above results; the values given in parentheses are partial point charges calculated for hydrogens *H*C3$_{fur}$ and *H*C4$_{fur}$, respectively (Experimental).

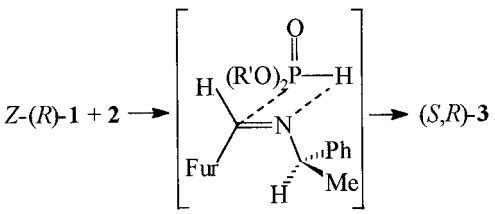
All results of the above-presented "molecular modeling (mainly AM1)/NMR spectra interpretation" protocol [12,13] allowed us to state, with a high degree of confidence, that the diastereomers **3A** and **3B** are represented by structures of type $\mathbf{I}_{AM1}$ (*SR* configuration) and $\mathbf{II}_{AM1}$ (*RR* configuration), respectively. Moreover, contrary to our preliminary doubts on the reliability of such energy calculations, the total-energy differences (computed for AM1 and MNDO/d geometric models of the global energy minima of each object; $\Delta E_{tot} = 1.70$ and 1.90 kJ mol^{-1}, respectively) agree rather well with the experimental ratio **3A**:**3B** ~ 2:1. (For the simple A ⇌ B isomeric equilibrium at 298.15°C, ΔG° values of 1.54 and 2.10 kJ mol^{-1} were found for isomer ratios of 65/35 and 70/30, respectively [18].) Obviously, the discussed minimum-energy forms of **3** are not the only ones populated. However, the closely related conformations are most likely favored.

As both stereoisomers **3** occur in enough similar amounts, it can be suggested that their formation is governed by fine structural effects. Yuan and Cui, studying the influence of catalyst and solvent on a stereochemical outcome of the title reaction, also found that the direction of an asymmetric induction during this process is presumably determined by the conformational requirements of the aldimine-catalyst complex formed [3a]. In consequence, a profound monitoring of addition of phosphite **2** to the C=N bond of an imine **1** is not highly reliable by the AM1 or MNDO/d semiempirical method. Nevertheless, the study of this reaction pathway at an ab initio level of theory using adequate basis sets was

impossible, because of the magnitude of reactants involved.

Thus, the formation of about 66% of *O,O*-dibenzyl (*S*)-[2-(5-Rfuryl)]-(*R*)-*N*-α-methyl-benzyl-aminophosphonate (**3**) (R = H or CH_2OH) starting from the corresponding imine (*R*)-**1** indicates that the main attack of the $HP(O)(OCH_2Ph)_2$ molecule occurs in full accord with the Cram rule [10]. This statement seems to be slightly unexpected, especially in the light of our preliminary assignment of the *RR* configuration to the product **3A** (*vide supra*). However, such a conclusion results from the present more precise view at a mechanism of the discussed process, which is based on reliable models of thermodynamically preferred forms of the starting Schiff bases. These fully relaxed structures of imines **1**, geometrical isomers and/or rotamers, were obtained in ab initio 3-21G calculations. It has been shown that their *Z* forms with a phenyl group and an electrophilic center of the C=N bond mutually *transoid* are predominating [19]; details of these computational experiments will be presented in the near future. Thus, the most probable qualitative image of the transition state occurred in the title process is pictured in Scheme 2; the *Z*-(*R*) substrate only being considered. Consequently, the attack of a phosphite molecule from the least sterically hindered side of a preferred form of imines (*R*)-**1** and/or (*S*)-**1** leads to adducts (*S,R*)-**3** and/or (*R,S*)-**3**, respectively.

The stereochemical findings of this work are in full accordance with the preference for mechanism of a structurally similar Strecker-like synthesis of furfural derivatives, using chiral alkylammonium hypophosphites. A spatial outcome of this reaction was univocally established by a single-crystal X-ray study [20]. However, in this case, where addition of hypophosphorous acid $H_2P(:O)OH$ to an initially formed aldimine (*R*)-**1** (R = H) probably occurs, the process is totally diastereoselective, yielding a (*S*)-(2-furyl)-(*R*)-*N*-α-methyl-benzylaminomethane adduct as a sole product. An extremely high stereoselectivity in such a synthesis of other α-aminophosphonous acids was described by Hamilton et al. [2b].



SCHEME 2

CONCLUSION

It has been established herein, by the solution ^1H NMR spectra assignment performed in conjunction with vacuum molecular modeling, that a stereochemical outcome of the title reaction is governed by the Cram selectivity. Thus, an addition of dialkyl phosphite is realized mainly from the least sterically hindered side of the thermodynamically most preferable form of the starting imine **1**. Such a finding is in full accordance with a mechanism of the Strecker-type synthesis of structurally related furan-derived systems.

EXPERIMENTAL

Molecular Modeling

The wide seeking for minima of conformational energy hypersurfaces of both **3A** and **3B** was carried out initially, with an external coordinate Monte Carlo (MC) technique in a molecular mechanics [21] searching protocol. A randomization procedure of the Saunders-type [22] was used within the PCMODEL [23] (version 3.2, MMX force field). Such calculations on isolated molecules in vacuo were performed for closely structurally related α-aminosulfites with $S(:O)(OR')_2$ moieties, as an applied software does not have implemented parameters for the $-P(:O)(OR')_2$ function. Typically, 8,000–10,000 MC steps were used within a 21 kJ mol^{-1} energy window; a bulk value of dielectric constant being applied, $\varepsilon = 1.50$ [24]. The generated conformational families of the *SR* and *RR* configuration were applied next as starting points in the modeling geometry of studied phosphonates **3**, after replacing S with P atoms. Accordingly, the MM+ force field of the HyperChem package [15] was used and structures obtained were examined thoroughly. Resulting models of global potential minima were selected in the light of ^1H NMR results and fully optimized by the AM1 (HyperChem, RMS gradient < 0.005 kJ $mol^{-1}Å^{-1}$) and MNDO/d methods (MOPAC 2000, version 1.21 [16]). The net charges were found from the Mulliken distribution of an electron density. All calculations, including the RHF/3-21G//3-21G ab initio computations (HyperChem, RMS gradient < 0.05 kJ $mol^{-1}Å^{-1}$) for a wide variety of aldimine **1** (R = H) forms, were performed on an Intel® 700 MHz Pentium® III PC machine.

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