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The Semiempirical Study on the Addition of the Chiral Ammonium Hypophosphite to an Aldehyde

Jarosław Lewkowski

Department of Organic Chemistry, University of Łódź, Narutowicza 68, 90-136 Łódź, Poland

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ABSTRACT: *The PM3 and AM1 semiempirical computations were performed in order to explain the stereochemistry of the addition of the chiral α-methylbenzylammonium hypophosphite to an aldehyde, which is stereoselective to 100%. Both mechanisms: one considering the intermediate formation of α-hydroxy phosphonous acids followed by the nucleophilic substitution with a chiral amine and the second considering the formation of a Schiff base followed by the addition of hypophosphorous acid to an azomethine bond were taken.* Heteroatom Chem 15:162–168, 2004; DOI 10.1002/hc.10230

INTRODUCTION

In 1995, Hamilton et al. [1] found out that the reaction of an aldehyde with (*R*)-α-methylbenzylammonium hypophosphite led exclusively to the RS-isomers of *N*-(*R*)-α-methylbenzylaminophosphonous acids. They studied several aliphatic and aromatic aldehydes and we extended studies on furfural [2] finding out the same. So, it was postulated that the reaction of any aldehyde with chiral alkylammonium hypophosphites led exclusively to one diastereoisomer, so it is stereoselective to 100%. It seemed interesting to study this reaction in order to find the reason of such a high diastereoselectivity.

The first step to reveal the stereochemistry was to understand the mechanism of this addition. There are two possible mechanisms of this reaction, the first postulates formation of the Schiff base, followed by addition of hypophosphorous acid (Scheme 1, Path B) and the second takes into account the nucleophilic addition of hypophosphorous acid to an aldehyde and subsequent substitution of a hydroxyl group with the alkylamino one (Scheme 1, Path A).

For the Strecker synthesis, which is rather similar to the discussed one, Jerry March [3] postulated that both pathways of the mechanism are equally possible. Therefore, one could postulate that it is the same in the case of the discussed reaction.

In my previous paper [4], I have suggested that the discussed reaction followed the mechanism according to the Path A and there were two arguments for it. First concerned the stereoselectivity of the reaction and I supposed that in the case of the mechanism according to the Path A, the formation of a hydroxyphosphonous acid should have been controlled by the presence of the chiral amine, and that, in my opinion, (*R*)-α-methylbenzylamine was too simple to have any influence on the attack. After all, the stereoselectivity was exactly the same when the Schiff bases were synthesized first, isolated, and then reacted with hypophosphorous acid. This suggestion seemed not so obvious after carefully studying the computation results.

I wish to report here semiempirical theoretical studies on the addition of hypophosphorous acid to chiral *N*-(*R*)-α-methylbenzylimines of various

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Correspondence to: Jarosław Lewkowski; e-mail: jlewkow@uni.lodz.pl.

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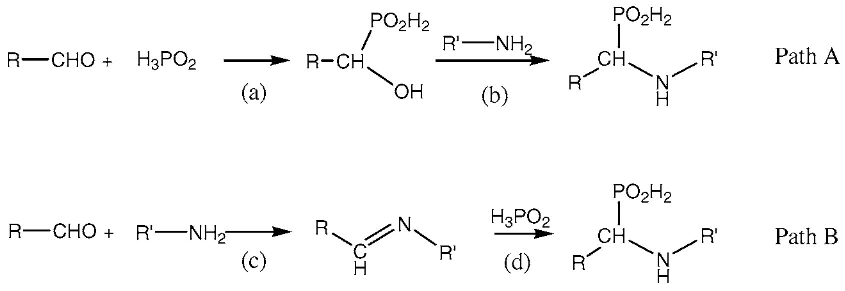


SCHEME 1 R = any alkyl or aryl; R′ = $CH(CH_3)Ph$.

aldehydes, which were previously studied experimentally [1,2] considering the mechanism of this reaction as well as its stereoselectivity.

EXPERIMENTAL

Methods of Computation

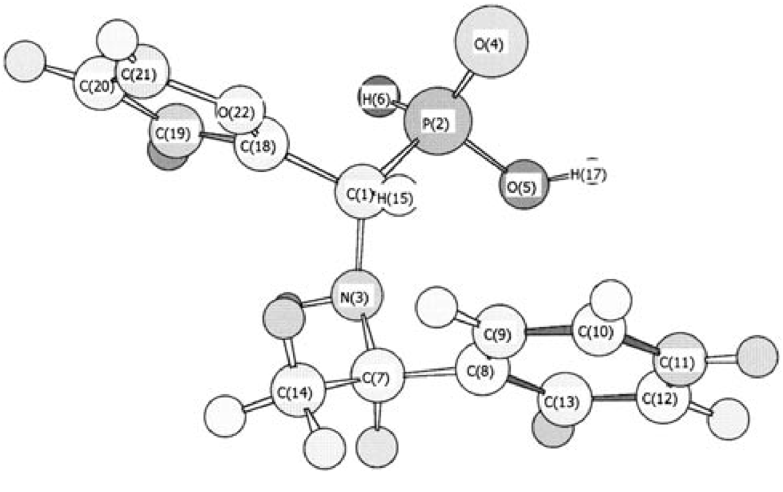
All computations were performed on a PC with a Celeron® 1 GHz processor and 128 MB RAM. Minima of all experimentally obtained RS diastereoisomers **4a–f** as well as all hypothetical RR diastereoisomers **4′a–f**, initial aldehydes **1a–f**, α-hydroxyphosphonous acids **2a–f**, Schiff bases **3a–f**, (*R*)-α-methylbenzylamine, hypophosphorous acid and water were searched by the use of Molecular Dynamics protocol in a 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 and PM3 methods, their geometries minimized and their total energies were computed. Semiempirical RHF PM3 and AM1 computations were performed by the use of the GAMESS [5,6] for ChemOffice 7.0 pack [7]. The tight convergence criteria have been used.

Heats of reaction were calculated following the Eq. (I) [8]:

$$\Delta E_R = \Sigma E_{tot}[\text{products}] - \Sigma E_{tot}[\text{substrates}] \qquad (I)$$

RESULTS AND DISCUSSION

Calculations have been performed using the AM1 and PM3 semiempirical method. In order to verify which method is more suitable, values of bond lengths and bond angles of (2-furyl)-(*R*)-α-methylbenzylamino-(*S*)-methanephosphonous acid obtained from the AM1 and PM3 computations were compared with values obtained by the X-ray measurements. They are summarized in Table 1 and Scheme 2. Generally, bond lengths fit more or less well except the P—O{H} bond length, which differs about 0.15 Å and the C—P bond about 0.18 Å.



SCHEME 2

TABLE 1 Bond Lengths and Bond Angles of (2-Furyl)-(*R*)-α-methylbenzylamino-(*S*)-methanephosphonous Acid **4e**

AM1		*PM3*		*Experimental [2]*	
Bond lengths (Å)					
C(1)–P(2)	1.694	C(1)–P(2)	1.929	C(1)–P(2)	1.861
C(1)–N(3)	1.457	C(1)–N(3)	1.480	C(1)–N(3)	1.493
C(1)–C(18)	1.480	C(1)–C(18)	1.479	C(1)–C(18)	1.483
C(1)–H(15)	1.142	C(1)–H(15)	1.114	C(1)–H(15)	0.960
P(2)–O(4)	1.457	P(2)–O(4)	1.462	P(2)–O(4)	1.466
P(2)–O(5)	1.602	P(2)–O(5)	1.692	P(2)–O(5)	1.487
P(2)–H(6)	1.282	P(2)–H(6)	1.243	P(2)–H(6)	1.125
N(3)–C(7)	1.467	N(3)–C(7)	1.501	N(3)–C(7)	1.485
O(5)–H(17)	0.956	O(5)–H(17)	0.946	O(5)–H(17)	0.850
C(7)–C(8)	1.509	C(7)–C(8)	1.511	C(7)–C(8)	1.511
C(7)–C(14)	1.529	C(7)–C(14)	1.523	C(7)–C(14)	1.531
C(8)–C(9)	1.398	C(8)–C(9)	1.393	C(8)–C(9)	1.380
C(8)–C(13)	1.401	C(8)–C(13)	1.398	C(8)–C(13)	1.387
C(9)–C(10)	1.395	C(9)–C(10)	1.392	C(9)–C(10)	1.375
C(10)–C(11)	1.394	C(10)–C(11)	1.389	C(10)–C(11)	1.367
C(11)–C(12)	1.395	C(11)–C(12)	1.391	C(11)–C(12)	1.363
C(12)–C(13)	1.394	C(12)–C(13)	1.391	C(12)–C(13)	1.385
C(18)–C(19)	1.388	C(18)–C(19)	1.380	C(18)–C(19)	1.335
C(18)–O(22)	1.405	C(18)–O(22)	1.390	C(18)–O(22)	1.372
C(19)–C(20)	1.444	C(19)–C(20)	1.439	C(19)–C(20)	1.429
C(20)–C(21)	1.381	C(20)–C(21)	1.371	C(20)–C(21)	1.323
C(21)–O(22)	1.390	C(21)–O(22)	1.376	C(21)–O(22)	1.365
Bond angles (°)					
P(2)–C(1)–N(3)	108.916	P(2)–C(1)–N(3)	103.641	P(2)–C(1)–N(3)	112.3
P(2)–C(1)–C(18)	110.885	P(2)–C(1)–C(18)	111.430	P(2)–C(1)–C(18)	108.9
P(2)–C(1)–H(15)	107.134	P(2)–C(1)–H(15)	107.729	P(2)–C(1)–H(15)	108.6
N(3)–C(1)–C(18)	114.300	N(3)–C(1)–C(18)	117.307	N(3)–C(1)–C(18)	110.4
N(3)–C(1)–H(15)	109.024	N(3)–C(1)–H(15)	108.470	N(3)–C(1)–H(15)	107.9
H(15)–C(1)–C(18)	106.305	H(15)–C(1)–C(18)	107.868	H(15)–C(1)–C(18)	108.8
C(1)–P(2)–O(4)	114.057	C(1)–P(2)–O(4)	114.151	C(1)–P(2)–O(4)	106.77
C(1)–P(2)–O(5)	113.170	C(1)–P(2)–O(5)	103.572	C(1)–P(2)–O(5)	109.23
C(1)–P(2)–H(6)	102.938	C(1)–P(2)–H(6)	101.815	C(1)–P(2)–H(6)	90.2
O(4)–P(2)–O(5)	104.641	O(4)–P(2)–O(5)	110.907	O(4)–P(2)–O(5)	119.9
O(4)–P(2)–H(6)	119.038	O(4)–P(2)–H(6)	122.630	O(4)–P(2)–H(6)	109.8
O(5)–P(2)–H(6)	102.724	O(5)–P(2)–H(6)	101.499	O(5)–P(2)–H(6)	116.4
C(1)–N(3)–C(7)	115.704	C(1)–N(3)–C(7)	118.571	C(1)–N(3)–C(7)	116.3
C(1)–N(3)–H(16)	110.028	C(1)–N(3)–H(16)	110.836	C(1)–N(3)–H(16)	121.4
C(7)–N(3)–H(16)	107.237	C(7)–N(3)–H(16)	108.414	C(7)–N(3)–H(16)	122.3
P(2)–O(5)–H(17)	115.095	P(2)–O(5)–H(17)	117.450	P(2)–O(5)–H(17)	109.2
N(3)–C(7)–C(8)	112.327	N(3)–C(7)–C(8)	108.970	N(3)–C(7)–C(8)	112.0
N(3)–C(7)–C(14)	114.826	N(3)–C(7)–C(14)	115.195	N(3)–C(7)–C(14)	107.8
C(8)–C(7)–C(14)	111.332	C(8)–C(7)–C(14)	113.144	C(8)–C(7)–C(14)	112.4
C(7)–C(8)–C(9)	122.163	C(7)–C(8)–C(9)	122.488	C(7)–C(8)–C(9)	120.2
C(7)–C(8)–C(13)	118.527	C(7)–C(8)–C(13)	118.309	C(7)–C(8)–C(13)	121.8
C(9)–C(8)–C(13)	119.306	C(9)–C(8)–C(13)	119.197	C(9)–C(8)–C(13)	118.1
C(8)–C(9)–C(10)	120.248	C(8)–C(9)–C(10)	120.320	C(8)–C(9)–C(10)	121.0
C(9)–C(10)–C(11)	120.217	C(9)–C(10)–C(11)	120.224	C(9)–C(10)–C(11)	120.9
C(10)–C(11)–C(12)	119.778	C(10)–C(11)–C(12)	119.804	C(10)–C(11)–C(12)	118.6
C(11)–C(12)–C(13)	120.141	C(11)–C(12)–C(13)	120.075	C(11)–C(12)–C(13)	121.5
C(8)–C(13)–C(12)	120.306	C(8)–C(13)–C(12)	120.377	C(8)–C(13)–C(12)	119.8
C(1)–C(18)–C(19)	134.478	C(1)–C(18)–C(19)	130.424	C(1)–C(18)–C(19)	134.4
C(1)–C(18)–O(22)	115.816	C(1)–C(18)–O(22)	120.182	C(1)–C(18)–O(22)	115.9
C(19)–C(18)–O(22)	109.426	C(19)–C(18)–O(22)	109.370	C(19)–C(18)–O(22)	109.6
C(18)–C(19)–C(20)	106.895	C(18)–C(19)–C(20)	106.779	C(18)–C(19)–C(20)	107.5
C(19)–C(20)–C(21)	106.599	C(19)–C(20)–C(21)	106.358	C(19)–C(20)–C(21)	105.4
C(20)–C(21)–O(22)	110.413	C(20)–C(21)–O(22)	110.542	C(20)–C(21)–O(22)	111.8
C(18)–O(22)–C(21)	106.625	C(18)–O(22)–C(21)	106.936	C(18)–O(22)–C(21)	105.7

TABLE 2 Total Energies of Both Diastereoisomers of Acids **4a–f** Calculated by the AM1 or (PM3) Method

		Total Energy (E_{tot})		
Acid	*Substituent*	*RS Isomer*	*RR Isomer*	ΔE_{tot}
4a	R = *i*-Pr	−102.51073 (−95.65333)	−102.49857 (−95.64631)	7.63 (4.41)
4b	R = *i*-Bu	−108.23643 (−101.15812)	−108.20874 (−101.14897)	17.38 (5.74)
4c	R = Ph	−115.57527 (−107.54266)	−115.55246 (−107.53541)	14.20 (4.55)
4d	R = CH_2Ph	−121.30253 (−113.01136)	−121.28585 (−113.00172)	10.47 (6.05)
4e	R = 2-furyl	−116.88547 (−108.46868)	−116.86758 (−108.46251)	11.23 (3.87)
4f	R = *c*-C_6H_{11}	−118.67756 (−111.00067)	−118.65133 (−110.99486)	16.46 (3.65)

Total energies are given in hartrees (1 hartree = 627.5095 kcal/mol) [9].
ΔE_{tot} are given in kcal/mol.

Although the PM3 method gave slightly better results for several bond length and angle values, in the point of view of the geometry both methods are similarly adequate or inadequate. Considering this I performed the analysis of the problem using both the AM1 and the PM3 methods and compared them.

Computed energies of all aldehydes **1a–f**, α-hydroxyphosphonous acids **2a–f**, Schiff bases **3a–f**, (*R*)-α-methylbenzylamine, hypophosphorous acid, water and acids **4a–f** and **4′a–f** are collected in Tables 2–5.

Differences in total energies between diastereoisomers **4a–f** and **4′a–f** of acids are rather high and they vary from 7.6 to 16.5 kcal/mol computed by the AM1 method. It could explain the stereoselectivity of the reaction, as in the previously published paper [10] we have demonstrated that in the addition of dibenzyl phosphite to the azomethine bond of the Schiff base leading to RS and RR diastereoisomers in the 2:1 ratio, the difference in total energies ΔE_{tot} is 0.41 kcal/mol (1.72 kJ/mol). Generally, as it is quoted [11], the 999:1 ratio of diastereoisomers is reflected by the difference of their standard free enthalpy around 4 kcal/mol, so the difference of such an order may indicate to the exclusive formation of RS isomers.

TABLE 3 Total Energies of Both Isomers of Schiff Bases **3a–f** Calculated by the AM1 or (PM3) Method

		Total Energy (E_{tot})		
Schiff Base	*Substituent*	*E Isomer*	*Z Isomer*	ΔE_{tot} (*Z* − *E*)
3a	R = *i*-Pr	−72.65909 (−67.84124)	−72.66003 (−67.83956)	−0.59 (−1.05)
3b	R = *i*-Bu	−78.38351 (−73.33494)	−78.38512 (−73.33378)	−1.01 (+0.73)
3c	R = Ph	−85.72090 (−79.72423)	−85.72169 (−79.72328)	−0.50 (+0.60)
3d	R = CH_2Ph	−91.44781 (−85.21909)	−91.44863 (−85.21797)	−0.52 (+0.70)
3e	R = 2-furyl (cisoid)	−87.03089 (−80.64716)	−87.03064 (−80.64032)	+0.16 (+4.29)
	R = 2-furyl (transoid)	−87.03202 (−80.64851)	−87.03333 (−80.64807)	−0.82 (+0.28)
3f	R = *c*-C_6H_{11}	−88.82477 (−83.18421)	−88.82507 (−83.18463)	−0.19 (−0.26)

Total energies are given in hartrees (1 hartree = 627.5095 kcal/mol) [9].
ΔE_{tot} are given in kcal/mol.

TABLE 4 Total Energies of Aldehydes **1a–f** and α-Hydroxymethane Phosphonic Acids **2a–f** Calculated by the AM1 or (PM3) Method

Substituent	*Aldehyde*	*Total Energy* (E_{tot})	*Hydroxyacids*	*Total Energy* (E_{tot})
R = *i*-Pr	**1a**	−34.65916 (−32.76250)	**2a**	−64.50846 (−60.57558)
R = *i*-Bu	**1b**	−40.38559 (−38.25779)	**2b**	−70.22779 (−66.07029)
R = Ph	**1c**	−47.72171 (−44.64500)	**2c**	−77.57081 (−72.45564)
R = CH_2Ph	**1d**	−53.44770 (−50.14067)	**2d**	−83.28978 (−77.95179)
R = 2-furyl	**1e**	−49.03063 (−45.56773)	**2e**	−78.88080 (−73.38478)
R = *c*-C_6H_{11}	**1f**	−50.82389 (−48.10585)	**2f**	−80.67207 (−75.91570)

Total energies are given in hartrees (1 hartree = 627.5095 kcal/mol) [9].
ΔE_{tot} are given in kcal/mol.

TABLE 5 Total Energies of (R)-α-Methylbenzylamine, Water, and Hypophosphorous Acid Calculated by the AM1 or (PM3) Method

Compound	*Total Energy (E_{tot})*
(R)-α-Methylbenzylamine	−50.80801 (−47.02250)
Hypophosphorous acid	−29.80727 (−27.81531)
Water	−12.80931 (−11.93999)

Total energies are given in hartrees (1 hartree = 627.5095 kcal/mol) [9].
ΔE_{tot} are given in kcal/mol.

On the basis of Eq. (I), heats of all reaction paths were calculated for SR and RR diastereoisomers. They are summarized in Tables 6 and 7. According to the AM1 computations, the formation of SR acids **4a–f** via the path A from α-hydroxyphosphonous acids **2a–f** with (R)-α-methylbenzylamine is characterized by the negative value of the heat of reaction, while the formation of RR acids **4′a–f**—by positive values. In a case of the mechanism via the path B, i.e., the addition of hypophosphorous acid to the azomethine bond of chiral Schiff bases **3a–f**, both the formation of SR and RR is characterized by negative values of the heat of reaction, although the RR values are 8–17 kcal/mol higher than the SR ones (Scheme 3).

It would demonstrate that the exclusive formation of various N-(R)-α-methylbenzylamino-(S)-methanephosphonous acids follows the mechanism presented as the Path A, as the formation of the RR diastereoisomer **(4′a–f)** from hydroxy acids **2a–f** is thermodynamically forbidden.

However, when the Schiff bases**3a–f** were synthesized first, isolated, and then reacted with hypophosphorous acid, the difference in heats of reactions is high enough to make the formation of the RR isomers **(4′a–f)** impossible.

On the other hand, it is to consider the kinetic control of the reaction. The AM1 geometry optimization of Schiff bases (Table 3) helped to evaluate their most convenient configurations and conformations. Energetically most convenient configurations occurred to be Z in all of cases and Schiff bases turned out to be easily accessible from the *pro-S* side according to the Cram-Felkin-Ahn model [12], which was applied to the azomethine bond by Yamamoto [13] (Scheme 4). Thus, the addition of hypophosphorous acid to Schiff bases **3a–f** led exclusively to SR acids **4a–f** too and may be controlled thermodynamically and kinetically.

Computations using the PM3 method demonstrated that differences in total energies between diastereoisomers **4a–f** and **4′a–f** of acids varied from

TABLE 6 Energies of Reaction for Each Reaction Path Calculated With the AM1 Method

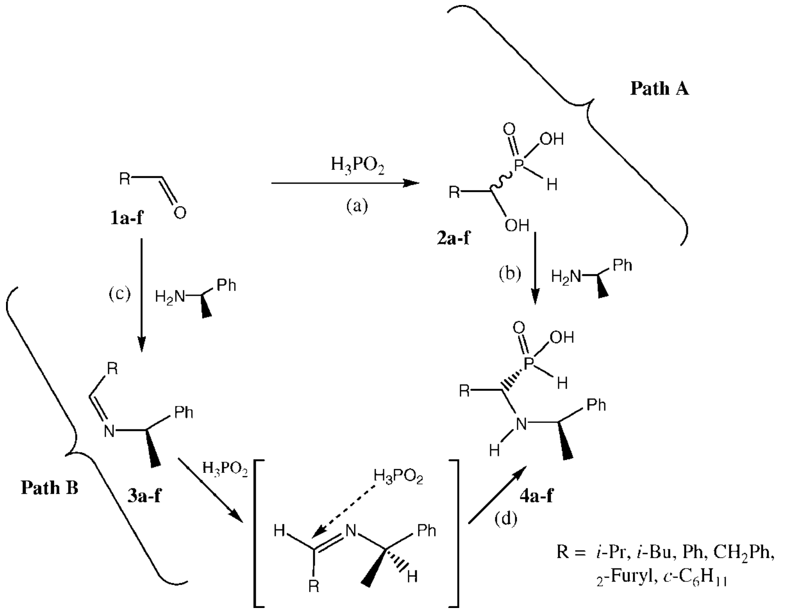
	Path A			*Path B*		
R	*Reaction (a)*	*Reaction (b) with RS*	*Reaction (b) with RR*	*Reaction (c)*	*Reaction (d) with RS*	*Reaction (d) with RR*
i-Pr	−26.37	−2.24	+5.39	−1.36	−27.25	−19.62
i-Bu	−21.99	−6.17	+11.21	−0.52	−27.64	−10.26
Ph	−26.25	−3.62	+10.58	−0.80	−29.06	−14.86
CH_2Ph	−21.84	−8.82	+1.65	−1.40	−29.26	−18.79
2-Furyl	−26.92	−3.75	+7.48	−2.51	−28.16	−16.93
c-C_6H_{11}	−25.67	−4.26	+12.20	−1.56	−28.38	−11.92

ΔE_{tot} are given in kcal/mol.

TABLE 7 Energies of Reaction for Each Reaction Path Calculated With the PM3 Method

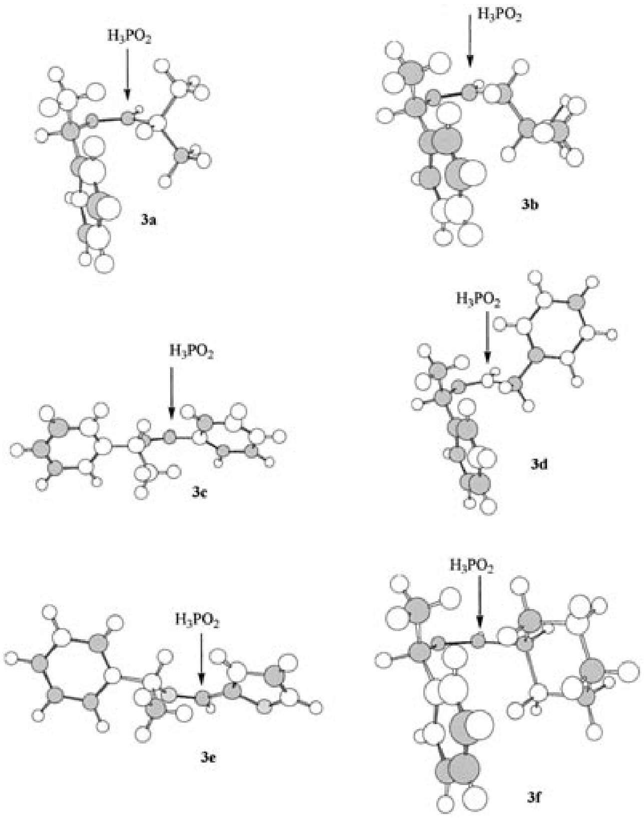
	Path A			*Path B*		
R	*Reaction (a)*	*Reaction (b) with RS*	*Reaction (b) with RR*	*Reaction (c)*	*Reaction (d) with RS*	*Reaction (d) with RR*
i-Pr	+1.40	−1.30	+3.11	+2.37	−2.27	+2.15
i-Bu	+1.76	−3.34	+2.40	+3.36	−4.94	+0.80
Ph	+2.93	−2.83	+1.72	+2.06	−1.96	+2.59
CH_2Ph	+2.63	+14.40	+20.45	+2.57	+14.46	+20.51
2-Furyl	−1.09	−0.87	+3.00	+1.09	−3.05	+0.82
c-C_6H_{11}	+1.70	+0.18	+3.83	+2.34	−0.46	+3.19

ΔE_{tot} are given in kcal/mol.



SCHEME 3

3.8 to 6.3 kcal/mol. The PM3 heats of all reaction paths for SR and RR diastereoisomers were also calculated based on the Eq. (I). According to them, the heats of reaction of hydroxy acids **2a–f** formation from aldehydes and hypophosphorous acid have positive values as well as the Schiff bases **3a–f** formation (Table 7). It would suggest that the formation of hydroxy acids **2a–f** from aldehydes and hypophosphorous acid as well as the formation of Schiff bases **3a–f** from aldehydes and (*R*)-α-methylbenzylamine are thermodynamically forbidden, which is not true. After all, the PM3 computations suggest that the formation of (benzyl)-*N*-(*R*)-α-methylbenzylamino-(*S*)-methanephosphonous acid **4d** is also forbidden. To conclude, it is to say that although the PM3 geometry (bond lengths and angles) predictions turned out to be slightly better than those of AM1, the analysis of energies performed using the AM1 method gave results much more consistent with the experiment.



SCHEME 4

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