Received: 26 April 2016 | Revised: 1 July 2016

DOI: 10.1002/hc.21324

RESEARCH ARTICLE

WILEY Heteroatom Chemistry

Synthesis of α-aminophosphonates from α-hydroxyphosphonates; a theoretical study

Nóra Zsuzsa Kiss | Zita Rádai | Zoltán Mucsi | György Keglevich

Department of Organic Chemistry and Technology, Budapest University of Technology and Economics, Budapest, Hungary

Correspondence
György Keglevich, Department of Organic Chemistry and Technology, Budapest University of Technology and Economics, Budapest, Hungary.
Email: gkeglevich@mail.bme.hu

Abstract

Two types of reactions, namely the Pudovik reaction of benzaldehyde and acetophenone with diethyl phosphite as well as the substitution of the α-hydroxyphosphonates so-formed by primary amines to afford α-aminophosphonates, were evaluated by quantum chemical calculations at the B3LYP/6-31G(d,p) level. An unexpected neighboring group effect was found to enhance the substitution. A series of new α-aminophosphonates was synthesized by the microwave-assisted substitution of α-hydroxyphosphonates by alkylamines.

1 | INTRODUCTION

α-Hydroxyphosphonates and α-aminophosphonates represent prominent classes of biologically active substrates within organophosphorus compounds. α-Hydroxyphosphonates may exhibit antibacterial,[1] antiviral,[2,3] anticancer,[4] and enzyme inhibitor[5–9] properties, and may also have pesticidal[10] effect.

α-Aminophosphonic acid derivatives have received much interest due to their wide range of bioactivity.[11,12] Beside the antibiotic, antihypertensive and osteoarthritic effects, and the positive effect on heart failure, α-aminophosphonic acids may be antitumor,[13] enzyme inhibitor[14–18] and antiviral[19,20] agents.

The basic method for the synthesis of α-hydroxyphosphonates is the Pudovik reaction involving direct phosphonylation of carbonyl compounds by the addition of dialkyl phosphites.[21–25] Base- or acid-catalyzed variations were also described.[24,26,27] The solvent-free accomplishment using alumina,[28,29] magnesia,[30] or other solids (mainly salts)[31,32] was a big step further, but the reaction times remained variable between 10 min and 3 days. Microwave irradiation was also a useful tool in the synthesis of α-hydroxyphosphonates.[33,34] A number of solid-phase/solvent-free variations applying piperazine,[35] $MgCl_2$/Et_3N,[36] $Ba(OH)_2$,[37] Na_2CO_3,[38] K_3PO_4,[39] Na-modified fluorapatite,[40] silica-supported tungstic acid,[41] and ^nBuLi[42] as the catalyst have been developed.

The best protocol for the synthesis of α-aminophosphonates is the Kabachnik–Fields reaction.[43–47] Green chemical accomplishments[48,49] including solvent- and catalyst-free microwave-assisted variations,[50,51] and the use of ionic liquids[52] have also been described.

2 | RESULTS AND DISCUSSION

2.1 | A theoretical study

A versatile, two-step synthetic procedure was developed by us for the preparation of variously substituted aminophosphonates (**3**) from simple, commercially available starting materials, such as benzaldehyde and diethyl phosphite under MW conditions. The α-hydroxyphosphonate (**2a**) obtained in the first step[34] was converted to α-aminophosphonates (**3a**) by reaction with primary amines.[53] We wished to investigate both steps by quantum chemical calculations at the DFT level. It was also our aim to study the effect of the methyl substituent on the reaction center. Hence, we computed the energetics of the acetophenone (**1b**) → **2b** → **3b** transformation using methylamine in the second step. It can be expected that starting from benzaldehyde (**1a**, R^1=H) or acetophenone (**1b**, R^1=Me) makes a significant difference (Scheme 1). Several reaction mechanisms were considered, excluding or involving an extra base. Computations were carried out using G09 program at the B3LYP/6-31G(d,p) level of theory. In order to mimic the neat reaction media, the

Contract grant sponsor: Hungarian Research Development and Innovation Fund. Contract grant number: K 119202.

implicit solvent model was represented by an average value of dipolar aprotic ether type solvents as a good compromise.

2.1.1 | Step 1: attack of diethyl phosphite on the C=O group of the carbonyl compounds 1a and 1b

The results obtained by the B3LYP/6-31G(d,p)//PCM method are shown in Scheme 2, Table 1 and Figs 1–3. α-Hydroxyphosphonate may be formed by the reaction of aromatic carbonyl compound **1** and diethyl phosphite without or with a base using forcing reaction conditions. The P-reagent is inactive in its thermodynamically stable pentavalent form, but the tervalent tautomer formed in an endothermic reaction is suitable for nucleophilic addition.

Without a base, the reaction may proceed *via* two routes. The one-step mechanism (*ROUTE A*) involves a single, not too high energy transition state (**TS1**) towards the product (**2**). The enthalpy gap is somewhat higher for **TS1b** (101.4 kJ mol^{-1}) than for **TS1a** (85.9 kJ mol^{-1}), however, this difference cannot justify a significant difference in the reactivity. Hydroxyphosphonate **2a** is formed in an exothermic way (−17.2 kJ mol^{-1}), while the formation of product **2b** is practically thermoneutral (−0.4 kJ mol^{-1}) meaning that there is no driving force in respect of the **1b** → **2b** transformation.

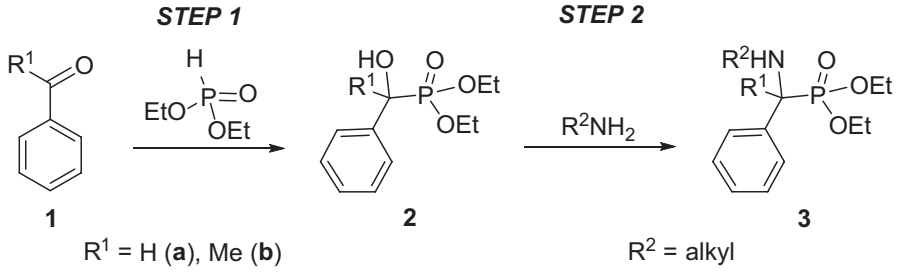
In *ROUTE B*, an epoxyphosphonate intermediate (**4**) was identified on the potential energy surface, near to the preceding **TS2**. This structure comprises a three-membered C–O–P ring, involving the P atom in a pentavalent form. For the two cases, these intermediates (**4a** and **4b**) represent a somewhat higher enthalpy level (94.0 and 109.3 kJ mol^{-1}), as compared with the corresponding TSs of *ROUTE A* (85.9 and 101.4 kJ mol^{-1}); consequently, it is not favored. Moreover, in the transformation **1a** → **4a**, the entropy (−64.1 kJ mol^{-1}), decreased significantly and unbeneficial due to the strained three-membered ring in intermediate **4a**, as compared to the entropy (−43.8 kJ mol^{-1}) belonging to the final stage the **1a** → **2a** conversion within *ROUTE A*. It is noteworthy that for the Me-substituted model, there is no significant difference between the entropy of **2b** and **4b**, presumably due to the already overcrowded α-carbon atom in **2b** and **4b**. The following, ring-opening process via **TS3** reveals enthalpy values of 101.4 and 116.6 kJ mol^{-1} for the two cases.

In *ROUTE C*, the added TEA base is not able to deprotonate the starting diethyl phosphite (DEP), due to the very endothermic deprotonation equilibrium between $(EtO)_2P(O)H$ and TEA $\{(EtO)_2P(O)H+Et_3N \rightarrow [(EtO)_2PO]^- + Et_3HN^+;$ $\Delta H = 128.5$ kJ mol^{-1}, $\Delta G = 132.3$ kJ mol$^{-1}\}$. However, TEA can promote the proton transfer in the TS by weakening the PO–H bond, and decreasing the enthalpy level of the corresponding TS (**TS4**). As compared with the base-free case (**TS1**), the decreases are 85.9 → 68.8 kJ mol^{-1} and 101.4 → 82.2 kJ mol^{-1}. Eventually, the TEA may increase the reaction rate by lowering the activation barrier with *ca.* 18 kJ mol^{-1}. At the final stage, TEA forms a strong H-bonding with the hydroxy group of hydroxyphosphonate **2** (**2**+TEA), resulting in a more exothermic reaction.

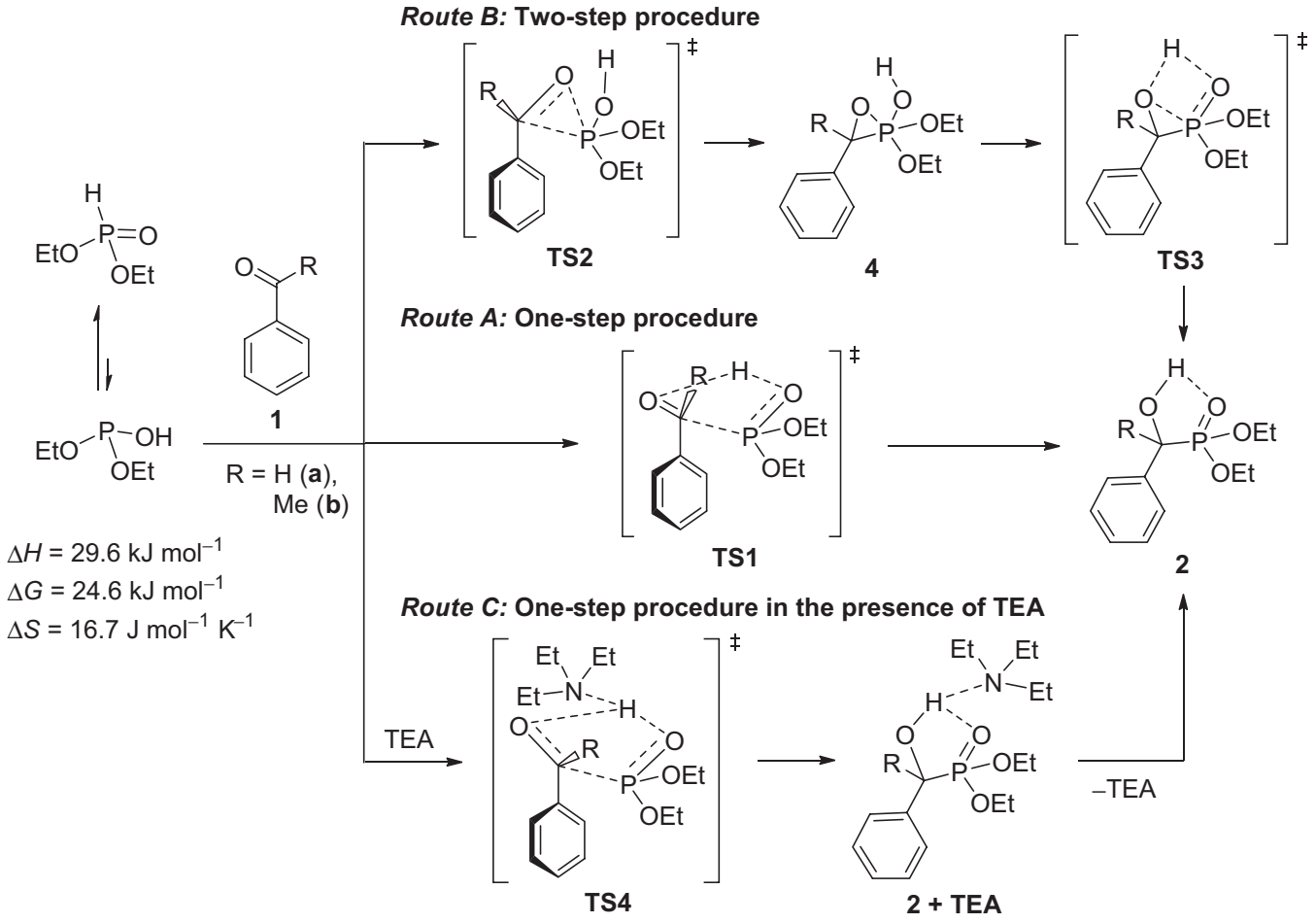
2.1.2 | Step 2: nucleophilic substitution of α-hydroxyphosphonate 2 by methylamine

The nucleophilic attack of methylamine (MA) chosen as the reagent on the central carbon atom of hydroxyphosphonate **2** was also studied by calculations. The results obtained for this transformation are shown in Scheme 3, Table 2 and Fig. 4. The proposed reaction mechanism comprises several elementary steps. In the first stage, methylamine attacks the carbon atom bearing the hydroxy group; meanwhile, the OH group migrates to the neighboring phosphorus atom forming a pentavalent pentacoordinated intermediate (**5**) via **TS5**. This beneficial neighboring effect of the P atom assisting the leaving of the OH group decreases significantly the enthalpy gap of the reaction. After a low enthalpy pseudorotation, species **5** is transformed to isomer **6**, that finally undergoes water elimination through **TS6**, providing the α-aminophosphonate (**7**).

According to the computed enthalpy values, in the case of **2b** (R=Me), the enthalpy of **TS5** is by 20 kJ mol^{-1} higher, than that for the TS of **2a** (R=H) meaning a more than 500 times smaller reaction rate constant. Consequently, the Me group in position α is expected to slow down the rate of the substitution significantly. Moreover, the small enthalpy benefit (−1.6 kJ mol^{-1}) leads to an equilibrium preventing a complete conversion. The enthalpy difference for intermediates **5** and **6**, as well as for **TS6** is 13.0 kJ mol^{-1}, 20.0 kJ mol^{-1} and 11.3 kJ mol^{-1}, respectively.



SCHEME 1 The reaction path showing the synthesis and nucleophilic substitution reaction of α-hydroxyphosphonates



SCHEME 2 The three proposed reaction mechanisms (*ROUTE A–C*) for the formation of α-hydroxyphosphonates **2**

TABLE 1 Calculated enthalpy (ΔH° or $\Delta H^{\ddagger}$; kJ mol^{-1}), Gibbs free energy (ΔG° or $\Delta G^{\ddagger}$; kJ mol^{-1}), and entropy (ΔS° or $\Delta S^{\ddagger}$; J K^{-1} mol^{-1}) values for the three reaction mechanisms (*ROUTE A–C*), computed at the B3LYP/6-31G(d,p)//PCM(THF) level of theory

	R=H (a)			**R=Me** (b)		
	ΔH° or $\Delta H^{\ddagger}$ (kJ mol^{-1})	**ΔG° or $\Delta G^{\ddagger}$ (kJ mol^{-1})**	**ΔS° or $\Delta S^{\ddagger}$ (J K^{-1} mol^{-1})**	**ΔH° or $\Delta H^{\ddagger}$ (kJ mol^{-1})**	**ΔG° or $\Delta G^{\ddagger}$ (kJ mol^{-1})**	**ΔS° or $\Delta S^{\ddagger}$ (J K^{-1} mol^{-1})**
ROUTE A (one-step procedure)						
TS1	85.9	100.3	−48.4	101.4	126.6	−84.5
2	−17.2	−4.1	−43.8	−0.4	24.8	−84.7
ROUTE B (two-step procedure)						
TS2	100.2	121.0	−69.8	122.7	150.4	−92.6
4	94.0	113.1	−64.1	109.3	135.7	−88.6
TS3	101.4	115.5	−47.3	116.6	139.3	−76.2
2	−17.2	−4.1	−43.8	−0.4	24.8	−84.7
ROUTE C (with TEA)						
TS4	68.8	105.1	−121.7	82.2	113.3	−104.6
2	−45.7	−15.6	−101.2	−23.0	5.5	−95.6

Moreover, the very small exothermicity of the overall reaction profile for the transformation of **2b** to **7b** provides only a marginal driving force for the reaction, and suggests an equilibrium state. To reach higher conversions, one needs to force the reaction by, e.g., MW irradiation at a higher temperature.

2.2 | Synthesis of α-aminophosphonates from α-hydroxyphosphonates under MW-assisted conditions – experimental results

The α-hydroxyphosphonates (**2a**, **8**, **10**, and **12**) prepared earlier[34] by us were converted to the

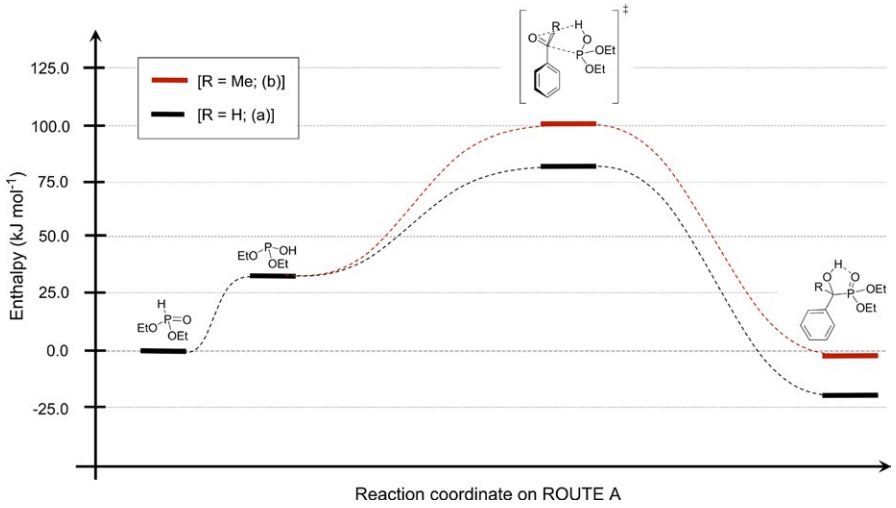


FIGURE 1 *ROUTE A* for the formation of hydroxyphosphonates **2** starting from benzaldehyde **1a** (R=H, black) and acetophenone **1b** (R=Me, red), computed at the B3LYP/6-31G(d,p)//PCM(THF) level of theory

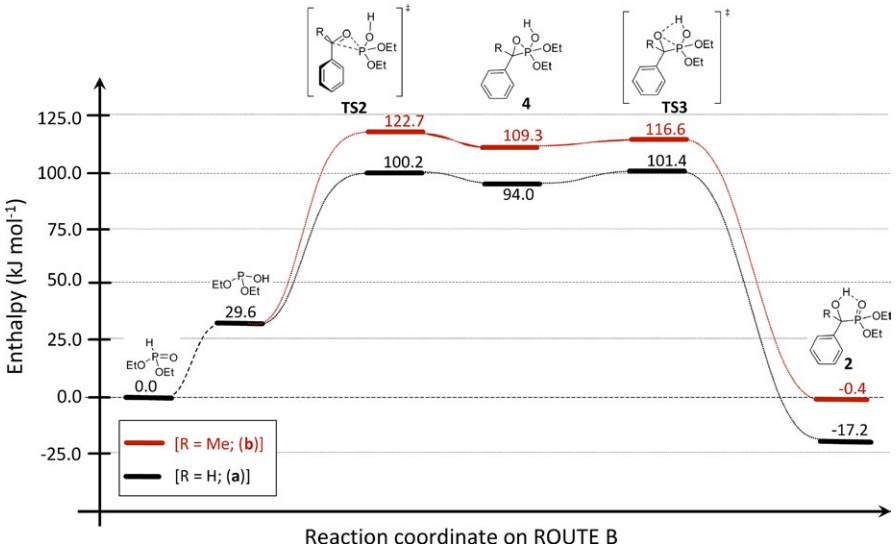


FIGURE 2 *ROUTE B* for the formation of hydroxyphosphonates **2** starting from benzaldehyde **1a** (R=H, black) and acetophenone **1b** (R=Me, red), computed at the B3LYP/6-31G(d,p)//PCM(THF) level of theory

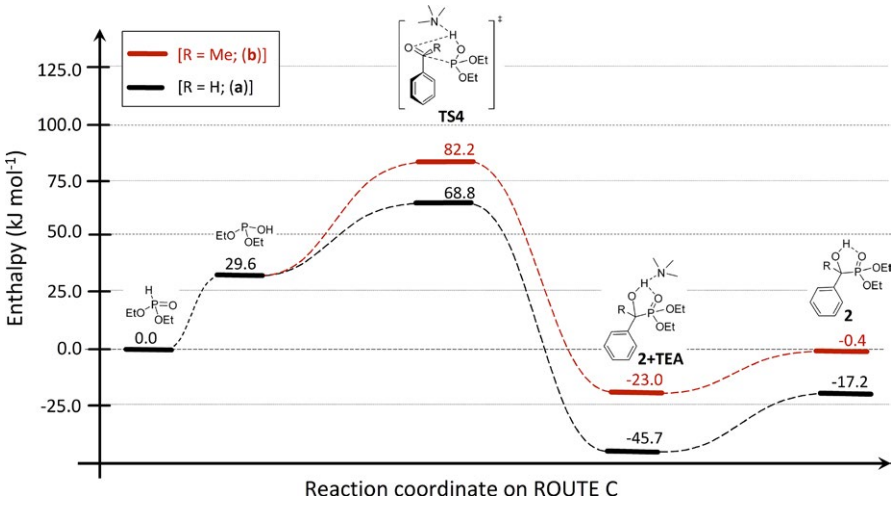
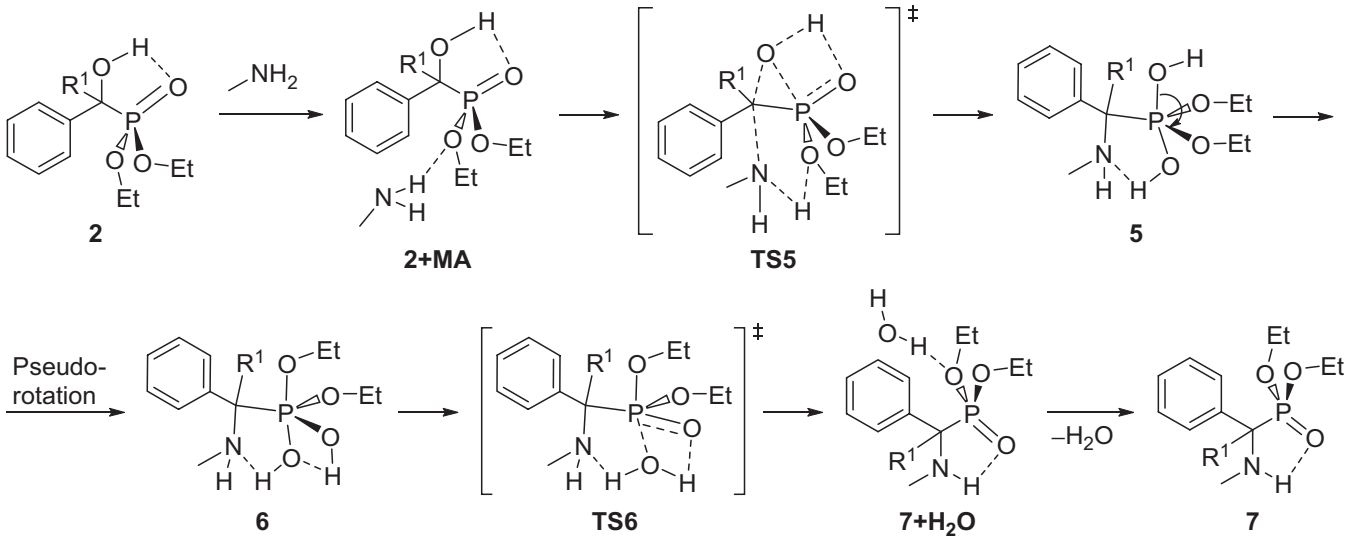


FIGURE 3 *ROUTE C* for the formation of hydroxyphosphonates **2** starting from benzaldehyde **1a** (R=H, black) and acetophenone **1b** (R=Me, red), computed at the B3LYP/6-31G(d,p)//PCM(THF) level of theory

corresponding α-aminophosphonates (**3a**, **9**, **11**, and **13**) by reaction with alkylamines (*n*-propylamine, *n*-butylamine, and *c*-hexylamine) under MW and solvent-free conditions at 100°C (Scheme 4). Experimental details can be found in Table 3. It can be seen that the reaction time was 10–30 min, while the yields after purification by column chromatography fell in the range of 50–79%. On the basis of our preliminary[53] and present calculations, it is not surprising



SCHEME 3 Proposed reaction mechanism for the nucleophilic substitution on hydroxyphosphonate **2** by methylamine

TABLE 2 Calculated enthalpy (ΔH° or ΔH‡; kJ mol^{-1}), Gibbs free energy (ΔG° or ΔG‡; kJ mol^{-1}), and entropy (ΔS° or ΔS‡; J K^{-1} mol^{-1}) values for the hydroxyphosphonate → aminophosphonate transformation computed at B3LYP/6-31G(d,p)//PCM(THF) level of theory

	R=H (a)			**R=Me** (b)		
	ΔH° or ΔH‡ (kJ mol^{-1})	**ΔG° or ΔG‡ (kJ mol^{-1})**	**ΔS° or ΔS‡ (J K^{-1} mol^{-1})**	**ΔH° or ΔH‡ (kJ mol^{-1})**	**ΔG° or ΔG‡ (kJ mol^{-1})**	**ΔS° or ΔS‡ (J K^{-1} mol^{-1})**
TS5	167.6	175.4	−26.2	187.8	192.1	−14.4
5	80.3	84.2	−13.1	93.3	98.7	−18.1
6	85.8	90.7	−16.4	105.8	106.8	−3.4
TS6	138.1	146.8	−29.2	149.4	156.8	−24.8
7 + H_2O	−23.4	−27.6	14.1	−10.9	−15.6	15.8
7	−10.9	−32.8	73.5	−1.6	−24.5	76.8

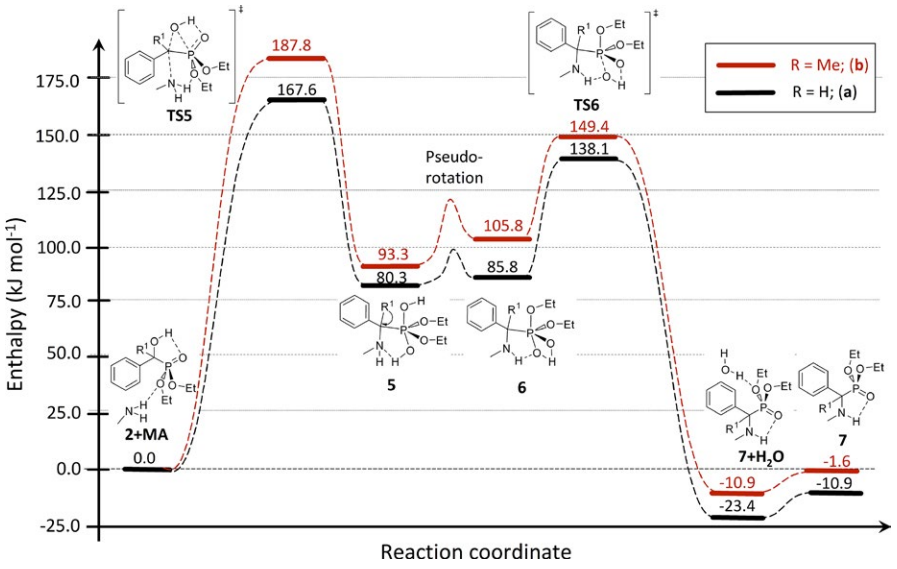
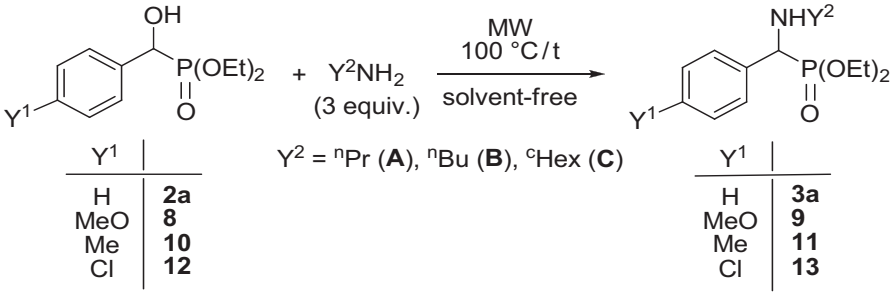


FIGURE 4 Comparison of the enthalpy profiles for the formation of aminophosphonates **7** by the nucleophilic substitution of hydroxyphosphonates **2a** (R=H, black) and **2b** (R=Me, red) with methylamine computed at the B3LYP/6-31G(d,p)//PCM(THF) level of theory

that the nucleophilic substitutions took place rather easily. There was no detectable steric hindrance in the case of cyclohexylamine as the nucleophile. The unsubstituted α-hydroxy-benzylphosphonate (**2a**) was the most reactive species, and the related aminophosphonates **3aA–C** could be obtained in the best (78–86%) yields.



SCHEME 4 Nucleophilic substitution reaction of diethyl α-hydroxy-benzylphosphonates (**2a**, **4**, **6**, and **8**) by primary amines

TABLE 3 Experimental details for the preparation of α-aminophosphonates (**3a**, **5**, **7**, and **9**)

Starting HP	Amine	Time (min)	Product	Yield (%)
2a	$^{n}PrNH_2$	10	3aA	78[53]
2a	$^{n}BuNH_2$	15	3aB	86[53]
2a	$^{c}HexNH_2$	10	3aC	84[53]
8	$^{n}PrNH_2$	15	9A	72
8	$^{n}BuNH_2$	30	9B	66
8	$^{c}HexNH_2$	30	9C	70
10	$^{n}PrNH_2$	15	11A	58
10	$^{n}BuNH_2$	15	11B	79
10	$^{c}HexNH_2$	30	11C	73
12	$^{n}PrNH_2$	15	13A	60
12	$^{n}BuNH_2$	20	13B	50
12	$^{c}HexNH_2$	30	13C	54[a]

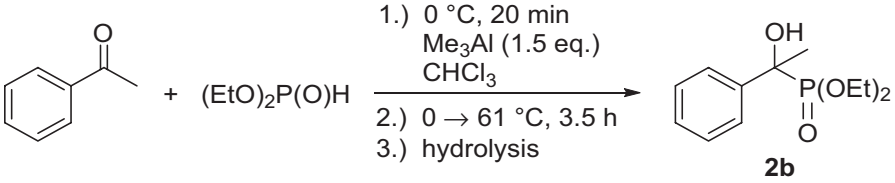
[a]In this instance, only two equivalents of the amine was used.

As acetophenone failed to undergo phosphonylation reaction with dialkyl phosphites even on MW irradiation at 110°C, the sterically more hindered α-methyl-α-hydroxyphosphonate (**2b**) was prepared by the reaction of acetophenone with diethyl phosphite activated by Me_3Al (Scheme 5). In the latter case, the target hydroxyphosphonate **2b** was obtained in a yield of 62%. It is recalled that the **1b** → **2b** transformation has a 15.5 kJ mol^{-1} higher enthalpy of activation value than the **1a** → **2a** conversion (Scheme 2/*ROUTE A*, Table 1). Moreover, in contrast to the exothermic **1a** → **2a** transformation, the **1b** → **2b** conversion is practically thermoneutral. These differences are in agreement with the difficulties, we faced in the synthesis.

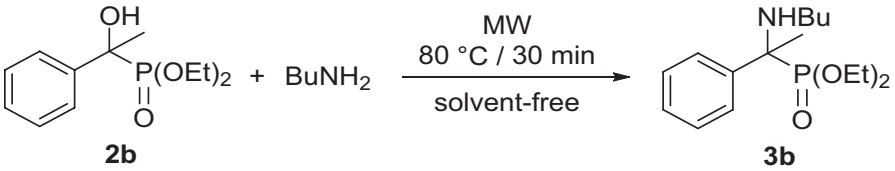
Then, diethyl α-hydroxy-α-methyl-benzylphosphonate (**2b**) was reacted with *n*-butylamine under MW-assisted and solvent-free conditions to prepare α-aminophosphonate **3b** (Scheme 6).

It was experienced that the **2b** → **3b** transformation was more sensitive to thermal effects in the presence of a primary amine than the **2a** → **3aB** conversion. To decrease the decomposition of the starting hydroxyphosphonate **2b**[54] and the product (**3b**), the substitution was performed at 80°C. Even at this temperature, aminophosphonate **3b** could be obtained only in a lower yield of 30% after purification by column chromatography. This experience is in accord with the results of the calculations discussed above (Scheme 3 and Table 2). The **2b** → **3b** substitution may have a *ca.* 20 kJ mol^{-1} higher enthalpy of activation as compared with the **2a** → **3aB** amination, and the **2b** → **3b** route is much less exothermic.

In summary, the mechanism and energetics of the Pudovik reaction of benzaldehyde and acetophenone with diethyl phosphite, and those of the substitution reaction of the resulting α-hydroxyphosphonates with methylamine were evaluated by quantum chemical calculations that underlined the critical role of the α-methyl group. The sterically congested acetophenone–diethyl phosphite adduct could only be prepared via a metal organic activation. The substitution of both kinds of α-hydroxyphosphonates with primary amines could be performed under MW irradiation. The amination was enhanced by a neighboring group effect of the P=O moiety. The less hindered α-aminophosphonates were obtained in yields of 50–86%, while the α-methyl derivative in only 30%. The theory and practice were in good agreement.



SCHEME 5 Preparation of more hindered α-hydroxyphosphonate **2b**



SCHEME 6 Nucleophilic substitution of the sterically heavily hindered α-hydroxyphosphonate **2b** by *n*-butylamine

3 | EXPERIMENTAL

The ^{31}P, ^{13}C, and ^{1}H NMR spectra were taken on a Bruker Avance-300 instrument operating at 121.5, 75.5, and 300 MHz, respectively. The exact mass measurements were performed using a Q-TOF Premier mass spectrometer in positive electrospray mode.

*Diethyl α-hydroxy-α-methyl-benzylphosphonate (***2b***).* To a mixture of 5.0 mmol (0.37 mL) diethyl phosphite and 6.5 mmol Me_3Al (3.3 mL in a 2 M solution in heptane) in 20 mL of chloroform was added 4.2 mmol (0.5 mL) of acetophenone dropwise at 0°C and the contents of the flask were stirred for 20 min. Then, the reaction mixture was heated at reflux for 3.5 h. After cooling down, the reaction mixture was carefully hydrolyzed with 35 mL of water at 0°C. The organic phase was separated, and dried over Na_2SO_4. After evaporation of the solvent, the crude product so obtained was purified by flash column chromatography on silica gel using hexane–ethyl acetate 7: 3 as the eluting solvent to afford **2b** in a yield of 62% (0.67 g).

Yield: 62%; ^{31}P NMR ($CDCl_3$) δ: 24.1; δ_{lit}[53]: 24.5; ^{13}C NMR ($CDCl_3$) δ: 16.2 ($^3J = 5.0$) and 16.3 ($^3J = 5.0$) (OCH_2CH_3), 25.8 ($^2J = 3.9$, CH_3), 63.2 ($^2J = 7.8$) and 63.3 ($^2J = 7.6$) (OCH_2), 73.4 ($^1J = 159.0$, PCO), 125.8 ($^4J = 4.4$, $C_{3'}$)*, 127.3 ($^3J = 2.9$, $C_{2'}$)*, 127.9 ($^5J = 2.5$, $C_{4'}$), 141.0 ($C_{1'}$), *may be reversed; ^{1}H NMR ($CDCl_3$) δ: 1.19 (t, $J = 7.1$, 3H, OCH_2CH_3), 1.27 (t, $J = 7.1$, 3H, OCH_2CH_3), 1.82 (d, $J = 15.4$, 3H CH_3CPh), 2.91 (d, $J = 6.4$, 1H, OH), 3.76–4.28 (m, 4H, $2 \times OCH_2$), 7.25–7.62 (m, 5H, Ar); $[M+H]^+_{found} = 259.1090$, $C_{12}H_{20}O_4P$ requires 259.1094.

3.1 | General procedure for the preparation of α-aminophosphonates (3a, 9, 11, 13)

A mixture of 0.40 mmol of α-hydroxyphosphonate (**2a**: 0.10 g, **8**: 0.11 g, **10**: 0.11 g, or **12**: 0.11 g) and 1.2 mmol of amine [propylamine (0.10 mL), butylamine (0.12 mL) or cyclohexylamine (0.14 mL)] in a sealed tube was irradiated in a CEM microwave reactor equipped with a pressure controller at the temperatures and for the times shown in Table 3. The volatile components were removed under reduced pressure. The residue obtained was purified by flash column chromatography using silica gel and 3% MeOH in $CHCl_3$ as the eluent to afford α-aminophosphonates **3a**, **9**, **11**, and **13** as oils in purities of > 98%. For details, see Table 3. Spectral data of aminophosphonates **3aA–C** were described in the preliminary study.[53]

Diethyl α-Propylamino-4-methoxybenzylphosphonate (**9A**).[55] Yield: 72%; ^{31}P NMR ($CDCl_3$) δ: 24.1; ^{13}C NMR ($CDCl_3$) δ: 11.8 ($CH_2CH_2CH_3$), 16.5 ($^3J = 10.7$) and 16.6 ($^3J = 10.7$) (OCH_2CH_3), 23.1 ($CH_2CH_2CH_3$), 49.9 ($^3J = 16.5$, NCH_2), 55.4 ($ArOCH_3$), 60.5 ($^1J = 154.3$, PCN), 62.9 ($^2J = 7.0$) and 63.0 ($^2J = 7.1$) (OCH_2), 114.0 ($^4J = 2.4$, $C_{3'}$)*, 128.2 ($^5J = 4.3$, $C_{4'}$), 129.7 ($^3J = 6.3$, $C_{2'}$)*, 159.4 ($^2J = 3.0$, $C_{1'}$), *may be reversed; ^{1}H NMR ($CDCl_3$) δ: 0.87 (t, $J = 7.4$, 3H, $CH_2CH_2CH_3$), 1.16 (t, $J = 7.1$, 3H, OCH_2CH_3), 1.28 (t, $J = 7.1$, 3H, OCH_2CH_3), 1.40–1.54 (m, 2H, CH_2), 1.80 (bs, 1H, NH), 2.35–2.54 (m, 2H, NCH_2), 3.81 (s, 3H, OCH_3), 3.82–4.15 (m, total intensity 5H, PCH, $2 \times OCH_2$), 6.85–6.92 and 7.30–7.37 (m, 4H, Ar); $[M+H]^+_{found} = 316.1672$, $C_{15}H_{27}NO_4P$ requires 316.1672.

Diethyl α-Butylamino-4-methoxybenzylphosphonate (**9B**). Yield: 66%; ^{31}P NMR ($CDCl_3$) δ: 24.1 δ_{lit}[56]: 20.2; ^{13}C NMR ($CDCl_3$) δ: 13.9 ($CH_2CH_2CH_3$), 16.26 ($^3J = 10.6$) and 16.34 ($^3J = 10.6$) (OCH_2CH_3), 20.2 ($CH_2CH_2CH_3$), 31.9 ($CH_2CH_2CH_3$), 47.5 ($^3J = 16.5$, NCH_2), 55.1 ($ArOCH_3$), 60.3 ($^1J = 154.2$, PCN), 62.6 ($^2J = 7.1$) and 62.8 ($^2J = 7.1$) (OCH_2), 113.7 ($^4J = 2.3$, $C_{3'}$)*, 127.9 ($^5J = 4.3$, $C_{4'}$), 129.5 ($^3J = 6.3$, $C_{2'}$)*, 159.1 ($^2J = 3.1$, $C_{1'}$), *may be reversed; ^{1}H NMR ($CDCl_3$) δ: 0.86 (t, $J = 7.2$, 3H, $CH_2CH_2CH_3$), 1.16 (t, $J = 7.1$, 3H, OCH_2CH_3), 1.28 (t, $J = 7.1$, 3H, OCH_2CH_3), 1.34–1.49 (m, 6H, CH_2), 1.70 (bs, 1H, NH), 2.35–2.58 (m, 2H, NCH_2), 3.81 (s, 3H, OCH_3) and 3.84–3.89 (m, 1H, PCH) partially overlapped, total intensity 4H, 3.90–4.14 (m, 4H, $2 \times OCH_2$), 6.84–6.97 and 7.25–7.41 (m, 4H, Ar); $[M+H]^+_{found} = 330.1836$, $C_{16}H_{29}NO_4P$ requires 330.1834.

Diethyl α-Cyclohexylamino-4-methoxybenzylphosphonate (**9C**). Yield: 70%; ^{31}P NMR ($CDCl_3$) δ: 24.6; ^{13}C NMR ($CDCl_3$) δ: 16.3 ($^3J = 15.2$) and 16.4 ($^3J = 15.1$) (OCH_2CH_3), 24.4 (CH_2), 24.9 (CH_2), 26.0 (CH_2), 31.9 (CH_2), 34.4 (CH_2), 53.3 ($^3J = 15.5$, NCH), 55.2 ($ArOCH_3$) 56.8 ($^1J = 154.8$, PCN), 62.5 ($^2J = 6.9$) and 63.0 ($^2J = 7.0$) (OCH_2), 113.7 ($^4J = 2.2$, $C_{3'}$)*, 128.6 ($^2J = 3.2$, $C_{1'}$), 129.4 ($^3J = 6.4$, $C_{2'}$)*, 159.1 ($^5J = 3.0$, $C_{4'}$), *may be reversed; ^{1}H NMR ($CDCl_3$) δ: 0.93–1.36 (m, 4H, CH_2) partially overlapped by 1.13 (t, $J = 6.9$, 3H, OCH_2CH_3), 1.29 (t, $J = 6.9$, 3H, OCH_2CH_3), 1.44–1.76 (m, 6H, CH_2), 1.89 (bs, 1H, NH), 2.25–2.41 (m, 1H, NHCH), 3.68–3.87 (m, 1H, PCH) overlapped by 3.81 (s, 3H, $ArOCH_3$), 3.87–4.23 (m, 4H, $2 \times OCH_2$), 6.84–6.94 and 7.24–7.37 (m, 4H, Ar); $[M+H]^+_{found} = 356.1991$, $C_{18}H_{31}NO_4P$ requires 356.1991.

Diethyl α-Propylamino-4-methylbenzylphosphonate (**11A**). Yield: 58%; ^{31}P NMR ($CDCl_3$) δ: 24.0; ^{13}C NMR ($CDCl_3$) δ: 11.6 ($CH_2CH_2CH_3$), 16.3 ($^3J = 11.8$) and 16.4 ($^3J = 11.8$) (OCH_2CH_3), 21.1 ($ArCH_3$), 22.9 ($CH_2CH_2CH_3$), 49.8 ($^3J = 16.6$, NCH_2), 60.7 ($^1J = 153.3$, PCN), 62.6 ($^2J = 6.9$) and 62.8 ($^2J = 7.1$) (OCH_2), 128.3 ($^3J = 6.2$, $C_{2'}$)*, 129.0 ($^4J = 2.5$, $C_{3'}$)*, 133.0 ($^2J = 4.2$, $C_{1'}$), 137.3 ($^5J = 3.4$, $C_{4'}$),*may be reversed; ^{1}H NMR ($CDCl_3$) δ: 0.86 (t, $J = 7.4$, 3H, $CH_2CH_2CH_3$), 1.16 (t, $J = 7.0$, 3H, OCH_2CH_3), 1.28 (t, $J = 7.0$, 3H, OCH_2CH_3), 1.37–1.55 (m, 2H, CH_2), 1.7 (bs, 1H, NH), 2.34 (s, 3H, $ArCH_3$), 2.24–2.56 (m, 2H, NCH_2), 3.76–3.91 (m, 1H, PCH), 3.92–4.18 (m, 4H, $2 \times OCH_2$), 7.05–7.40 (m, 4H, Ar); $[M+H]^+_{found} = 300.1734$, $C_{15}H_{27}NO_3P$ requires 300.1729.

Diethyl α-Butylamino-4-methylbenzylphosphonate (**11B**). Yield: 79%; ^{31}P NMR ($CDCl_3$) δ: 24.0; ^{13}C NMR ($CDCl_3$) δ: 13.9 ($CH_2CH_2CH_3$), 16.3 (^3J = 11.6) and 16.4 (^3J = 11.6) (OCH_2CH_3), 20.3 ($CH_2CH_2CH_3$), 21.1 ($ArCH_3$), 31.9 ($CH_2CH_2CH_3$), 47.7 (^3J = 16.7, NCH_2), 60.8 (^1J = 153.2, PCN), 62.7 (^2J = 7.0) and 62.8 (^2J = 7.1) (OCH_2), 128.3 (^4J = 6.2, $C_{3'}$)*, 129.0 (^3J = 2.5, $C_{2'}$)*, 133.0 (^2J = 4.2, $C_{1'}$), 137.3 (^5J = 3.4, $C_{4'}$), *may be reversed; ^{1}H NMR ($CDCl_3$) δ: 0.86 (t, J = 7.0, 3H, $CH_2CH_2CH_3$), 1.16 (t, J = 7.0, 3H, OCH_2CH_3), 1.28 (t, J = 7.1, 3H, OCH_2CH_3) and 1.21–1.35 (m, CH_2) partially overlapped, total intensity 5H, 1.36–1.51 (m, 2H, CH_2), 1.64 (bs, 1H, NH), 2.34 (s, 3H, $ArCH_3$) 2.37–2.58 (m, 2H, NCH_2), 3.79–3.90 (m, 1H, PCH), 3.91–4.15 (m, 4H, 2 × OCH_2), 7.10–7.37 (m, 4H, Ar); $[M+H]^+_{found}$ = 314.1885, $C_{16}H_{29}NO_3P$ requires 314.1885.

Diethyl α-Cyclohexylamino-4-methylbenzylphosphonate (**11C**). Yield: 73%; ^{31}P NMR ($CDCl_3$) δ: 24.5; ^{13}C NMR ($CDCl_3$) δ: 16.3 (^3J = 16.8) and 16.4 (^3J = 16.9) (OCH_2CH_3), 21.1 ($ArCH_3$), 24.4 (CH_2), 24.9 (CH_2), 26.1 (CH_2), 32.0 (CH_2), 34.4 (CH_2), 53.3 (^3J = 15.7, NCH), 57.2 (^1J = 154.0, PCN), 62.5 (^2J = 6.9) and 63.0 (^2J = 6.9) (OCH_2), 128.2 (^4J = 6.3, $C_{3'}$)*, 129.0 (^3J = 2.4, $C_{2'}$)*, 133.6 (^5J = 2.9, $C_{4'}$), 137.2 (^2J = 3.3, $C_{1'}$),*may be reversed; ^{1}H NMR ($CDCl_3$) δ: 0.98–1.22 (m, 4H, CH_2) overlapped by 1.13 (t, J = 7.0, 3H, OCH_2CH_3), total intensity 7H, 1.29 (t, J = 7.1, 3H, OCH_2CH_3), 1.45–1.77 (m, 6H, CH_2), 1.64 (bs, 1H, NH), 2.34 (bs, 4H, $ArCH_3$, NHCH), 3.70–3.86 (m, 1H, PCH), 3.87–4.22 (m, 4H, 2 × OCH_2), 7.10–7.19 and 7.21–7.33 (m, 4H, Ar); $[M+H]^+_{found}$ = 340.2047, $C_{18}H_{31}NO_3P$ requires 340.2042.

Diethyl α-Propylamino-4-chlorobenzylphosphonate (**13A**). Yield: 60%; ^{31}P NMR ($CDCl_3$) δ: 23.9; ^{13}C NMR ($CDCl_3$) δ: 11.6 ($CH_2CH_2CH_3$), 16.3 (^3J = 8.9) and 16.4 (^3J = 8.9) (OCH_2CH_3), 22.9 ($CH_2CH_2CH_3$), 49.9 (^3J = 16.5, NCH_2), 60.5 (^1J = 152.7, PCN), 62.8 (^2J = 6.9) and 62.9 (^2J = 7.1) (OCH_2), 128.5 (^4J = 2.6, $C_{3'}$)*, 129.8 (^3J = 6.1, $C_{2'}$)*, 133.4 ($C_{4'}$), 134.9 (^2J = 4.8, $C_{1'}$), *may be reversed; ^{1}H NMR ($CDCl_3$) δ: 0.87 (t, J = 7.3, 3H, $CH_2CH_2CH_3$), 1.18 (t, J = 6.9, 3H, OCH_2CH_3), 1.28 (t, J = 6.9, 3H, OCH_2CH_3), 1.38–1.52 (m, 2H, CH_2CH_3), 1.63 (bs, 1H, NH), 2.34–2.49 (m, 2H, NCH_2), 3.85–4.16 (m, total intensity 5H, PCH, 2 × OCH_2), 7.23–7.42 (m, 4H, Ar); $[M+H]^+_{found}$ = 320.1184, $C_{14}H_{24}NO_3PCl$ requires 320.1182.

Diethyl α-Butylamino-4-chlorobenzylphosphonate (**13B**). Yield: 50%; ^{31}P NMR ($CDCl_3$) δ: 23.1; ^{13}C NMR ($CDCl_3$) δ: 13.9 ($CH_2CH_2CH_3$), 16.4 (^3J = 8.7) and 16.5 (^3J = 8.7) (OCH_2CH_3), 20.3 ($CH_2CH_2CH_3$), 31.9 ($CH_2CH_2CH_3$), 47.8 (^3J = 16.5, NCH_2), 60.7 (^1J = 152.5, PCN), 62.9 (^2J = 7.0) and 63.0 (^2J = 7.1) (OCH_2), 128.6 (^4J = 2.7, $C_{3'}$)*, 129.8 (^3J = 6.1, $C_{2'}$)*, 133.5 (^2J = 4.0, $C_{1'}$), 135.0 (^5J = 4.8, $C_{4'}$), *may be reversed; ^{1}H NMR ($CDCl_3$) δ: 0.86 (t, J = 7.3, 3H, $CH_2CH_2CH_3$), 1.18 (t, J = 7.1, 3H, OCH_2CH_3), 1.28 (t, J = 6.9, 3H, OCH_2CH_3), 1.35–1.49 (m, 2H, CH_2CH_3), 1.64 (bs, 1H, NH), 2.35–2.54 (m, 2H, NCH_2), 3.83–4.15 (m, total intensity 5H, PCH, 2 × OCH_2), 7.26–7.42 (m, 4H, Ar); $[M+H]^+_{found}$ = 334.1344, $C_{15}H_{26}NO_3PCl$ requires 334.1333.

Diethyl α-Cyclohexylamino-4-chlorobenzylphosphonate (**13C**). Yield: 54%; ^{31}P NMR ($CDCl_3$) δ: 23.7; ^{13}C NMR ($CDCl_3$) δ: 16.3 (^3J = 14.0) and 16.4 (^3J = 13.9) (OCH_2CH_3), 24.4 (CH_2), 24.9 (CH_2), 26.0 (CH_2), 32.0 (CH_2), 34.4 (CH_2), 53.6 (^3J = 15.4, NCH), 57.1 (^1J = 153.2, PCN), 62.7 (^2J = 7.0) and 63.2 (^2J = 7.1) (OCH_2), 128.5 (^4J = 2.5, $C_{3'}$)*, 129.7 (^3J = 6.2, $C_{2'}$)*, 133.3 (^2J = 3.9, $C_{1'}$), 135.5 (^5J = 3.4, $C_{4'}$), *may be reversed; ^{1}H NMR ($CDCl_3$) δ: 0.96–1.19 (m, 4H, CH_2) partially overlapped by 1.16 (t, J = 7.1, 3H, OCH_2CH_3), 1.29 (t, J = 7.1, 3H, OCH_2CH_3), 2.25–2.33 (m, 1H, NHCH), 3.80–3.89 (m, 1H, PCH), 3.93–4.17 (m, 4H, 2 × OCH_2), 7.29–7.37 (m, 4H, Ar); $[M+H]^+_{found}$ = 360.1502, $C_{17}H_{28}NO_3PCl$ requires 360.1490.

The α-methyl analogue (**3b**) was prepared similarly as compound **3aB**.

*Diethyl α-Butylamino-α-methyl-benzylphosphonate (**3b**).* Yield: 30%; ^{31}P NMR ($CDCl_3$) δ: 26.8, δ_{lit}[54]: 27.3; ^{13}C NMR ($CDCl_3$) δ: 13.9 ($CH_2CH_2CH_3$), 16.25 (^3J = 6.1) and 16.33 (^3J = 6.1) (OCH_2CH_3), 20.4 ($CH_2CH_2CH_3$), 20.6 (^2J = 2.0, CCH_3), 32.8 ($CH_2CH_2CH_2$), 41.2 (^3J = 13.9, NCH_2), 59.9 (^1J = 152.4, PCN), 62.8 (^2J = 7.3) and 63.0 (^2J = 7.3) (OCH_2), 127.0 (^5J = 3.1, $C_{4'}$), 127.9 and 128.0 ($C_{2'}$ and $C_{3'}$), 139.5 (^2J = 2.6, $C_{1'}$); ^{1}H NMR ($CDCl_3$) δ: 0.88 (t, J = 7.3, 3H, $CH_2CH_2CH_3$), 1.14 (t, J = 7.0, 3H, OCH_2CH_3), 1.23 (t, J = 7.1, 3H, OCH_2CH_3), 1.28–1.38 (m, 2H, NCH_2CH_2) and 1.39–1.51 (m, 2H, NCH_2), 1.69 (bs, 1H, NH) and 1.76 (d, J = 16.4, 3H, CCH_3) partially overlapped, total intensity 4H, 3.76–3.87 (m, 1H, NCHP) and 3.88–4.06 (m, 4H, 2 × OCH_2) partially overlapped, total intensity 5H, 7.30–7.39 and 7.50–7.58 (m, 5H, Ar), $[M+H]^+_{found}$ = 314.1883, $C_{16}H_{29}NO_3P$ requires 314.1885.

3.2 | Computational methods

All computations were carried out using the Gaussian09 program package (G09).[57] Geometry optimizations and subsequent frequency analyses were carried out at B3LYP/6-31G(d,p) level of theory[58] in order to properly confirm all structures as residing at minima (NImag = 0) or the saddle point (NImag = 1) on their potential energy hypersurfaces (PESs). The method and basis sets were chosen for their reliability in the characterization of phosphorous compounds in agreement with earlier publications. To model the experimental media, the integral equation formalism-polarizable continuum medium (IEF-PCM) method[59] was applied as an implicit solvent model, choosing the parameters of tetrahydrofuran as a good compromise. According to our estimation, the error of this solvent model was around 1–2 kJ mol^{-1}.

ACKNOWLEDGMENTS

The support from the Hungarian Research Development and Innovation Fund (K 119202) is acknowledged. Zita Rádai is grateful for the fellowship provided by Chinoin–Sanofi Pharmaceuticals.

REFERENCES

[1] H. Fleisch, *Endocr. Rev.* **1998**, *19*, 80.
[2] J. Neyts, E. De Clercq, *Antimicrob. Agents Chemother.* **1997**, *41*, 2754.
[3] R. Snoeck, A. Holy, C. Dewolf-Peeters, J. Van Den Ord, E. De Clercq, G. Andrei, *Antimicrob. Agents Chemother.* **2002**, *46*, 3356.
[4] M. V. Lee, E. M. Fong, F. R. Singer, R. S. Guenett, *Cancer Res.* **2001**, *61*, 2602.
[5] D. V. Patel, K. Rielly-Gauvin, D. E. Ryono, *Tetrahedron Lett.* **1990**, *31*, 5591.
[6] D. V. Patel, K. Rielly-Gauvin, D. E. Ryono, C. A. Free, W. L. Rogers, S. A. Smith, J. M. DeForrest, R. S. Oehl, E. W. Petrillo Jr, *J. Med. Chem.* **1995**, *38*, 4557.
[7] B. Stowasser, K. H. Budt, L. Jian-Qi, A. Peyman, D. Ruppert, *Tetrahedron Lett.* **1992**, *33*, 6625.
[8] M. Tao, R. Bihovsky, G. J. Wells, J. P. Mallamo, *J. Med. Chem.* **1998**, *41*, 3912.
[9] J. F. Dellaria Jr, R. G. Maki, H. H. Stein, J. Cohen, D. Whittern, K. Marsh, D. J. Hoffman, J. J. Plattner, T. J. Perun, *J. Med. Chem.* **1990**, *33*, 534.
[10] P. Kafarski, B. Lejczak, *J. Mol. Catal. B: Enzym.* **2004**, *29*, 99.
[11] V. P. Kukhar, H. R. Hudson (eds.), Aminophosphonic and Aminophosphinic Acids: Chemistry and Biological Activity, Wiley, Chichester, UK **2000**.
[12] S. C. Fields, *Tetrahedron* **1999**, *55*, 12237.
[13] P. Kafarski, B. Lejczak, *Curr. Med. Chem. Anticancer Agents* **2001**, *1*, 301.
[14] J. Bird, R. C. De Mello, G. P. Harper, D. J. Hunter, E. H. Karran, R. E. Markwell, A. J. Miles-Williams, S. S. Rahman, R. W. Ward, *J. Med. Chem.* **1994**, *37*, 158.
[15] W. S. Liu, C. J. Rogers, A. J. Fisher, M. D. Toney, *Biochemistry* **2002**, *41*, 12320.
[16] A. Mucha, P. Kafarski, L. Berlicki, *J. Med. Chem.* **2011**, *54*, 5955.
[17] M. Sienczyk, J. Oleksyszyn, *Curr. Med. Chem.* **2009**, *16*, 1673.
[18] J. Grembecka, A. Mucha, T. Cierpicki, P. Kafarski, *J. Med. Chem.* **2003**, *46*, 2641.
[19] N. Long, X. J. Cai, B. A. Song, S. Yang, Z. Chen, P. S. Bhadury, D. Y. Hu, L. H. Jin, W. Xue, *J. Agric. Food Chem.* **2008**, *56*, 5242.
[20] D. Y. Hu, Q. Q. Wan, S. Yang, B. A. Song, P. S. Bhadury, L. H. Jin, K. Yan, F. Liu, Z. Chen, W. Xue, *J. Agric. Food Chem.* **2008**, *56*, 998.
[21] J. A. Ma, *Chem. Soc. Rev.* **2006**, *35*, 630.
[22] I. L. Odinets, E. V. Matveeva, *Curr. Org. Chem.* **2010**, *14*, 1171.
[23] P. Merino, E. Marques-Lopez, R. P. Herrera, *Adv. Synth. Catal.* **2008**, *350*, 1195.
[24] A. N. Pudovik, I. V. Konovalova, *Synthesis* **1979**, *1979*, 81.
[25] M. S. Kharasch, R. A. Mosher, I. S. Bengelsdorf, *J. Org. Chem.* **1000**, *1960*, 25.
[26] M. A. Ruveda, S. A. de Licastro, *Tetrahedron* **1972**, *28*, 6012.
[27] H. Timmler, J. Kurz, *Chem. Ber.* **1971**, *104*, 3740.
[28] F. Texierboullet, A. Foucard, *Synthesis* **1982**, *1982*, 916.
[29] H. R. Hudson, R. O. Yusuf, R. W. Matthews. *Phosphorus Sulfur Silicon* **2008**, *183*, 1527.
[30] A. R. Sardarian, B. Kaboudin, *Synth. Commun.* **1997**, *27*, 543.
[31] F. Texierboullet, A. Foucard, *Tetrahedron Lett.* **1980**, *21*, 2161.
[32] A. Smahi, A. Solhy, R. Tahir, S. Sebti, J. A. Mayoral, J. I. Garc′ıa, J. M. Fraile, M. Zahouily, *Catal. Commun.* **2008**, *9*, 2503.
[33] B. Kaboudin, R. Nazari, *J. Chem. Res.* **2002**, *2002*, 291.
[34] G. Keglevich, V. R. Tóth, L. Drahos, *Heteroatom Chem.* **2011**, *22*, 15.
[35] K. S. Kumar, C. B. Reddy, M. V. N. Reddy, C. R. Rani, C. S. Reddy, *Org. Commun.* **2012**, *5*, 50.
[36] T. Mahmood, K. Samad, T. Zahra, B. Ahmadreza, *Chin. J. Chem.* **2012**, *30*, 827.
[37] P. N. Kamalakar, P. N. Jitendra, S. P. Vijay, V. B. Sidhanath, *Chem. Biol. Interface* **2012**, *2*, 314.
[38] D.-L. Kong, R.-D. Liu, G.-Z. Li, P.-W. Zhang, M.-S. Wu, *Asian J. Chem.* **2014**, *26*, 1246.
[39] M. A. Kulkarni, U. P. Lad, U. V. Desai, S. D. Mitragotri, P. P. Wadgaonkar, *Compt. Rend. Chim.* **2013**, *16*, 148.
[40] H. R. Ramananarivo, A. Solhy, J. Sebti, A. Smahi, M. Zahouily, J. Clark, S. Sebti, *ACS Sustain. Chem. Eng.* **2013**, *1*, 403.
[41] S. Santhisudha, P. Sreelakshmi, S. H. Jayaprakash, B. V. Kumar, C. S. Reddy. *Phosphorus Sulfur Silicon* **2015**, *190*, 1479.
[42] C. Liu, Y. Zhang, Q. Qian, D. Yuan, Y. Yao, *Org. Lett.* **2014**, *16*, 6172.
[43] M. I. Kabachnik, T. Y. Medved. *Dokl. Akad. Nauk SSSR* **1952**, *689*; Chem Abstr 1953, 47, 2724b.
[44] E. K. Fields, *J. Am. Chem. Soc.* **1952**, *74*, 1528.
[45] R. A. Cherkasov, V. I. Galkin, *Russ. Chem. Rev.* **1998**, *67*, 857.
[46] N. S. Zefirov, E. D. Matveeva, *ARKIVOC* **2008**, *1*, 1.
[47] G. Keglevich, E. Bálint, *Molecules* **2012**, *17*, 12821.
[48] B. C. Ranu, A. Hajra, *Green Chem.* **2002**, *4*, 551.
[49] M. M. Kabachnik, E. V. Zobnina, I. P. Beletskaya, *Synlett* **2005**, *2005*, 1393.
[50] S. Lee, J. K. Lee, C. E. Song, D.-C. Kim, *Bull. Korean Chem. Soc.* **2002**, *23*, 667.
[51] G. Keglevich, A. Szekrényi, *Lett. Org. Chem.* **2008**, *5*, 616.
[52] J. S. Yadav, B. V. S. Reddy, P. Sreedhar, *Green Chem.* **2002**, *4*, 436.
[53] N. Z. Kiss, A. Kaszás, L. Drahos, Z. Mucsi, G. Keglevich, *Tetrahedron Lett.* **2012**, *53*, 207.
[54] R. Gancarz, I. Gancarz, U. Walkowiak. *Phosphorus Sulfur Silicon* **1995**, *104*, 45.
[55] S. Hashem, E. Sakineh, M. D. Mohammad, *Tetrahedron* **2013**, *69*, 4708.
[56] H.-S. Mona, *Tetrahedron* **2008**, *64*, 5459.
[57] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, X. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery Jr, J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, D. J. Fox, Gaussian 09, Gaussian Inc., Wallingford, CT **2009**.
[58] A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648.
[59] J. Tomasi, B. Mennucci, R. Cammi, *Chem. Rev.* **2005**, *105*, 2999.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.