Organic & Biomolecular Chemistry

Cite this: *Org. Biomol. Chem.*, 2012, **10**, 2011

www.rsc.org/obc

PAPER

Insights into a surprising reaction: The microwave-assisted direct esterification of phosphinic acids†

György Keglevich,*[a] Nóra Zsuzsa Kiss,[a] Zoltán Mucsi[a] and Tamás Körtvélyesi[b]

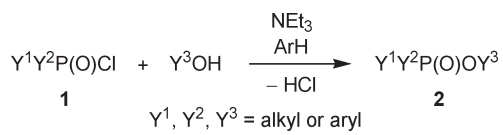
Received 23rd November 2011, Accepted 15th December 2011
DOI: 10.1039/c2ob06972e

It is well-known that phosphinic acids do not undergo direct esterifications with alcohols under thermal conditions. However, the esterifications take place under microwave (MW) irradiation due to the beneficial effect of MW. As a comparison, maximum 12–15% conversions were observed on traditional heating. It was proved experimentally that the MW-assisted esterifications are not reversible under the conditions applied that may be the consequence of the hydrophobic medium established by the long chain alcohol/phosphinic ester. Neither the thermodynamic, nor the kinetic data obtained by high level quantum chemical calculations justify the direct esterification of phosphinic acids under thermal conditions. The thermodynamic data show that there is no driving force for the reactions under discussion. As a consequence of the relatively high values of activation enthalpy (102–161 kJ mol^{-1}), these esterifications are controlled kinetically. Comparing the energetics of the esterification of phosphinic acids and the preparative results obtained under MW conditions, one can see the potential of the MW technique in the synthesis of phosphinates. During our study, a series of new cyclic phosphinates with lipophilic alkyl groups was synthesized.

1. Introduction

As phosphinic acids do not undergo direct esterification with hydroxy-compounds, phosphinates are usually prepared by the reaction of phosphinic chlorides with alcohols and phenols (Scheme 1).[1,2]

Although this method has drawbacks from the point of view of "green" chemistry and costs, it is widely applied in industry. The hydrochloric acid liberated is removed by a tertiary amine or alkali hydroxide. The phosphinic chlorides may be obtained from phosphoryl chloride ($POCl_3$) by two successive substitutions. It is also possible to make available the starting phosphinic chlorides from phosphinic acids by reaction with inorganic chlorides, such as thionyl chloride, phosphorus pentachloride or phosgene/triphosgene. In a one-pot accomplishment, the phosphinic chloride is prepared *"in situ"* from the corresponding acid by thionyl chloride and the intermediate so-formed reacts immediately with the alcohol present in the mixture.[3]



Scheme 1 General procedure for the synthesis of phosphinates.

It is also possible to synthesize phosphinates by the alkylation of phosphinic acids. In this case, either alkyl halides, or unsaturated reactants, such as olefins or acetylenes are used. Applying an alkyl halide, the phosphinic acid should first be converted to an alkali salt,[4,5] or the alkylation should be carried out under phase transfer catalytic conditions.[6] The addition of an acid to an unsaturated species may be carried out in the presence of catalysts.[7]

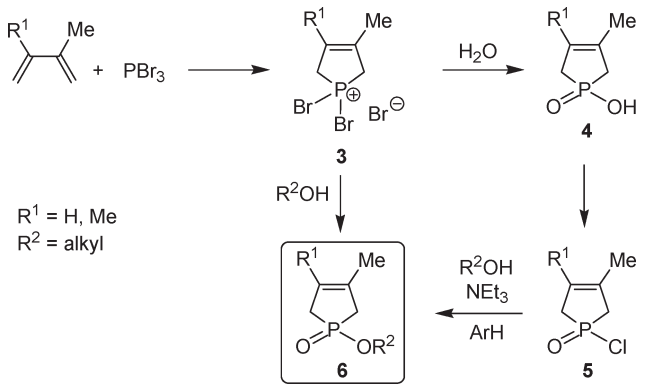
An additional possibility for the synthesis of phosphinates involves the use of coupling reagents, such as carbodiimides,[8–10] uronium,[11] and phosphonium derivatives.[11] The esterification of phosphinic acids is also possible by special methods applying orthoacetates,[12] chloroformates,[13] orthosilicates[14–16] and trialkyl phosphites.[17,18]

Direct esterification was only described for the dithio derivative of phenylphosphinic acid. In reaction with phenol, the corresponding phenylphosphinothioate was obtained.[19]

The phosphinic chloride → phosphinate conversion is also a good choice for the synthesis of cyclic P-esters. For example, 1-alkoxy-3-phospholene oxides (**6**) were synthesized from the 1-hydroxy-3-phospholene oxides **4**, *via* 1-chloro-3-phospholene oxides **5**. Phosphinic acids **4** were obtained by the hydrolysis of the McCormack cycloadducts **3** (Scheme 2).[20] The 1-alkoxy-3-

[a]*Department of Organic Chemistry and Technology, Budapest University of Technology and Economics, 1521 Budapest, Hungary. E-mail: gkeglevich@mail.bme.hu; Fax: +36 1 463 3648; Tel: +36 1 463 1111/5883*
[b]*Department of Physical Chemistry and Material Science, University of Szeged, H-6701 Szeged, Hungary*

†Electronic supplementary information (ESI) available. See DOI: 10.1039/c2ob06972e



Scheme 2 Possibilities for the synthesis of cyclic phosphinates.

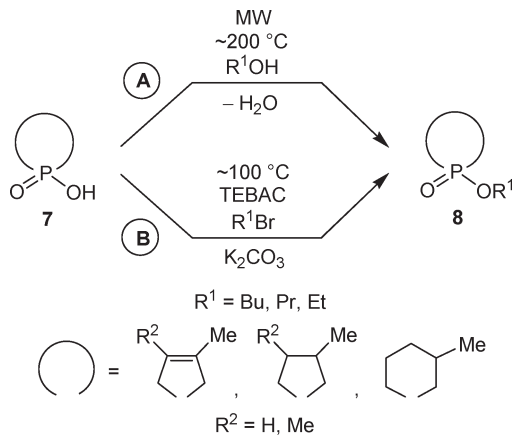
phospholene oxides (**6**) could also be obtained directly from the tribromophospholium salts (**3**) by alcoholysis.[21–23]

We were successful in utilizing the microwave (MW) technique in the synthesis of phosphinates either in direct esterification, or in phase transfer catalyzed alkylating esterification. On the one hand, a series of cyclic phosphinic acids (**7**), such as 1-hydroxy-3-phospholene oxides, 1-hydroxy-phospholane oxides and 1-hydroxy-1,2,3,4,5,6-hexahydrophosphinine oxides were subjected to direct esterification in reaction with alcohols under MW conditions at or above 180 °C. The corresponding phosphinates (**8**) were obtained in 45–60% preparative yields (Scheme 3/Route A).[24,25] The MW-assisted alkylating esterifications of cyclic phosphinic acids using alkyl halides provided a good alternative (Scheme 3/Route B).[25,26]

The MW-assisted esterifications were made possible by the beneficial effect of MW. The search for reactions that take place only under MW conditions is under focus these days.[27]

We have found that MW irradiation allowed transformations that otherwise were impossible under thermal conditions.[28] In other instances, MW irradiation resulted in an increase in the rate[28,29] and selectivity,[30,31] or served as a substitute for the catalyst.[32,33]

In this paper, we wish to describe our new findings on the MW-assisted direct esterifications of phosphinic acids. The possibility of reversibility has been studied and quantum chemical calculations were carried out to clarify the thermodynamic



Scheme 3 Esterification of cyclic phosphinic acids.

and kinetic background of the different type of esterifications. Beside the above objectives, the most suitable alcohols were selected for the direct esterification of phosphinic acids.

2. Results and discussion

2.1 The question of reversibility in the MW-assisted esterification of phosphinic acids with alcohols

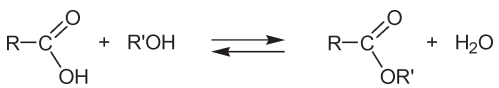
It is well-known that the direct esterification of carboxylic acids involves an equilibrium (Scheme 4).

However, the question arises, if the MW-assisted reaction of phosphinic acids with alcohols is reversible or not (Scheme 5)?

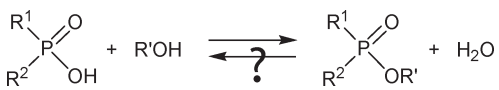
For this, the possibility of reversibility for the formation of phosphinates was investigated in detail. The reactions of 3-methyl- and 3,4-dimethyl-1-hydroxy-3-phospholene 1-oxides (**1** and **2**) with dodecanol or octanol served as the models (Scheme 6).

In the first set of experiments, 1-hydroxy-3,4-dimethyl-3-phospholene 1-oxide (**1**) was esterified with a 12-fold excess of dodecanol. The excess of alcohol served as the solvent. Applying dodecanol (with a boiling point of 260 °C), the reaction tolerated the use of an open vessel at a temperature of 230 °C and hence the water formed in the esterification could leave. The reaction was also carried out in a closed vessel. After 2 h irradiation, a quantitative conversion was achieved in both cases, no matter if the reaction vessel was closed or open (Table 1/Entries 1 and 2). In the latter case, the preparative yield of phosphinate **3a** was 95%. It was also observed that the conversion was quantitative even in the presence of five equivalents of water added to the reaction mixture prior to irradiation in a closed vessel (Table 1/Entry 3).

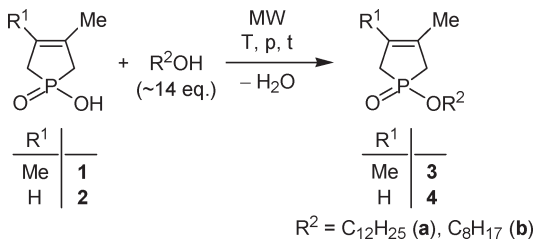
The reaction of 1-hydroxy-3-methyl-3-phospholene 1-oxide (**2**) with a 14-fold excess of octanol was studied as the other



Scheme 4 Direct esterification of carboxylic acid.



Scheme 5 The problem of reversibility for the esterification of phosphinic acids.



Scheme 6 MW-assisted direct esterification of 1-hydroxy-3-phospholene 1-oxides.

Table 1 MW-assisted esterification of 3-phospholene 1-oxides with higher carbon chain alcohols under different conditions

Entry	Starting materials	T (°C)	p (bar)	t (h)	H_2O added	Conversion[a] (%)	Yield (%)
1	**1** + $C_{12}H_{25}OH$	230	0[b]	2	—	100 (**3a**)	
2	**1** + $C_{12}H_{25}OH$	230	[c]	2	—	100 (**3a**)	~95
3	**1** + $C_{12}H_{25}OH$	230	0[b]	2	5 eq.	95 (**3a**)	
4	**2** + $C_8H_{17}OH$	185	[c]	2	—	43 (**4b**)	
5	**2** + $C_8H_{17}OH$	185	0.7[b]	2	—	44 (**4b**)	
6	**2** + $C_8H_{17}OH$	185	0.7[b]	4	—	77 (**4b**)	65
7	**2** + $C_8H_{17}OH$	220	1.2[b]	2	—	100 (**4b**)	71
8	**2** + $C_8H_{17}OH$	185	0.7[b]	2	5 eq.	50 (**4b**)	
9	**2** + $C_8H_{17}OH$	220	1.2[b]	2	5 eq.	95 (**4b**)	

[a] On the basis of relative ^{31}P NMR intensities. [b] Closed reaction vessel. [c] Open reaction vessel.

model. In this case, as the boiling point of the alcohol is 195 °C, a temperature of 185 °C was selected to be able to work in an open vessel. The esterification was not, however, too fast at 185 °C. A 2 h irradiation at 185 °C in an open vessel led to a conversion of 43% (Table 1/Entry 4). After an irradiation for 2 h and 4 h in a closed vessel, the conversion was 44% and 77%, respectively (Table 1/Entries 5 and 6). Elevating the temperature to 220 °C in a closed vessel, the formation of phosphinate **4b** was, however, quantitative after 2 h (Table 1/Entry 7). In this case, the preparative yield of ester **4b** was 71%. The addition of 5 eq. of water to the mixture prior to the irradiation had no impact on the course of the reaction, as similar conversions were observed, as in the absence of water (Table 1/Entry 8 *vs.* 5 and Entry 9 *vs.* 7).

It was proved in separate experiments that the quantity of the alcohols used can dissolve well the water formed.

One experiment was done, in which the esterification of phosphinic acid **2** was performed only in 5 equivalents of octanol. At 220 °C, the starting material was consumed after 3 h, but the yield of phosphinate **4b** was only 74% due to a small extent of decomposition.

It was also investigated if phosphinic esters **3a** and **4b** undergo hydrolysis under MW conditions. No reverse reaction occurred after heating at 185 °C for 2 h, as the starting materials (**3a** and **4b**) were recovered in ~96% yields.

It can be seen that the MW-assisted direct esterification of 1-hydroxy-3-phospholene oxides (**1** and **2**) is not influenced, whether the reactions are carried out in a closed or an open vessel. In other words it does not count if the water formed remains in the reaction mixture or is removed. Moreover, the addition of extra water to the reaction mixture did not prevent, and what is more, did not even influence the esterification. At the same time, no reversion took place, when the phosphinates (**3a** and **4b**) were attempted to be hydrolysed under similar conditions. These experiences suggest that the MW-assisted esterifications of the phosphinic acids (**1** and **2**) investigated are not reversible macroscopically under the conditions applied. MW irradiation favours only one direction that is the formation of phosphinate. A possible explanation may be that under the rather hydrophobic conditions established by the long alkyl chain alcohols/phosphinic esters, the equilibrium is on the side of the ester, and hence the reverse reaction is slower than the forward reaction.

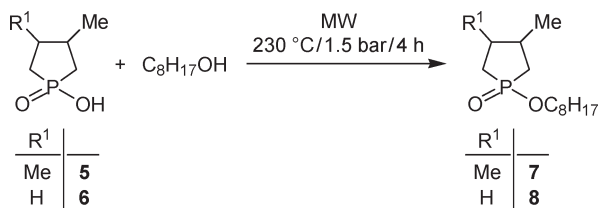
According to comparative thermal experiments, phosphinates **3a** and **4b** were formed only in low conversions that were not increased on a prolonged heating. Keeping hydroxy-phospholene oxide **1** and dodecanol in an oil bath at 220 °C for 2 h, the conversion to **3a** was 15%. The esterification of phosphinic acid **2** with octanol took place in a conversion of 12% at 185 °C after 2 h. It is recalled that the similar esterification of phosphinic acids **1** and **2** with butanol occurred in 11/13% conversions at 200 °C after a heating time of 2 h.[25] From these results one can conclude that although the effect of MW is clearly beneficial, the acceleration compared to the thermal variations is not many orders of magnitude. It is also important to note that traditional heating may lead only to low conversions even after prolonged reaction times.

Other 1-alkoxy-3-phospholene oxides, such as **3b** and **4a** were also prepared using a *ca*. 13-fold excess of the alcohols in closed vessels at 220 and 230 °C, respectively. The yields of phosphinates **3b** and **4a** were almost quantitative.

All of the phosphinates prepared (**3a,b**, **4a,b**) were characterised by ^{31}P, ^{13}C and ^{1}H NMR, as well as mass spectral data. Alkoxy-phospholene oxides **4a** and **4b** were described in the literature, but no spectral characterisation was provided.[34,35] Phosphinate **4b** was characterised only by a ^{31}P NMR chemical shift of 69.0.[35] That does not really match the δ_P of 74.6 ($CDCl_3$) we obtained on a pure sample identified also by ^{13}C and ^{1}H NMR, as well as mass spectral data.

Hydroxy-phospholane oxide **5** consisting of a 2 : 1 mixture of two isomers and hydroxy-phospholene oxide **6** were also subjected to MW-assisted esterification with octanol (Scheme 7).

Carrying out the reactions at 230 °C in closed vessels using a *ca.* 13-fold excess of octanol, the work-up resulted in phosphinates **7** and **8** in ca 72% yields. The octyloxy-phospholane oxides (**7** and **8**) consisted of diastereomers. Product **7** comprised three isomers, while phosphinate **8** was formed as a 50–50% mixture of two diastereomers. The new octyloxyphospholane oxides (**7** and **8**) were characterised by ^{31}P, ^{13}C and ^{1}H NMR, as well as by mass spectral data.



Scheme 7 MW-assisted direct esterification of 1-hydroxy-phospholane 1-oxides.

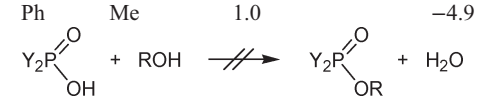
It is also seen that the choice of reactants in the direct esterification of phosphinic acids involves alcohols with longer alkyl chains, as in these cases, the pressure is not so high due to the higher boiling points of these alcohols.

2.2 Thermodynamic background of the direct esterification of phosphinic acids

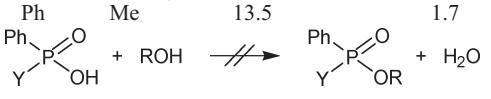
First, as a comparison, the free energy (ΔG^0) and enthalpy (ΔH^0) values were calculated for the esterification of carboxylic acids (acetic acid and benzoic acid) with simple alcohols including methanol, butanol and dodecylalcohol under traditional conditions. On the basis of the ΔH^0 values of −3.9–−5.0 kJ mol^{-1} obtained by B3LYP/6-31++G(d,p) calculations for 210 °C in the gas phase, it can be said that these esterifications are slightly favoured and lead to an equilibrium (Table 2/Entries 1–4). At the same time, the reaction of dimethylphosphinic acid with the same alcohols is not favoured at all, as suggested by the ΔG^0 values of 6.3–7.1 kJ mol^{-1} and ΔH^0 values of 0.03–1.0 kJ mol^{-1} (Table 2/Entries 5–7). The same is true, but the situation is somewhat more unfavourable for the direct esterification of diphenylphosphinic acid with methanol. The ΔG^0 of 13.5 kJ mol^{-1} and the ΔH^0 of 1.7 kJ mol^{-1} does not mean a driving force for the thermal esterification (Table 2/Entry 8). As can be seen, the reaction of phenyl-*H*-phosphinic acid with alcohols is not favoured either. This is shown by the ΔG^0 values of 7.3–8.4 kJ mol^{-1} and ΔG^0 values of 0.07–1.2 kJ mol^{-1} (Table 2/Entries 9–11). For the monoesterification of phenylphosphonic acid, the unreactivity is expressed by a ΔG^0 and ΔH^0 value of 8.0 kJ mol^{-1} and 2.4 kJ mol^{-1}, respectively (Table 2/Entry 12). Going to cyclic phosphinic acids, the reaction of 3-methyl-3-phospholene oxide with alcohols is characterised by ΔG^0 values of 12.8–15.6 kJ mol^{-1} and ΔH^0 values of 3.2–4.0 kJ mol^{-1} (Table 2/Entries 13–15).

Table 2 Free energy and enthalpy values calculated for the esterification of carboxylic acids, phosphinic acids and phosphonic acids by the B3LYP/6-31++G(d,p) method for 210 °C in the gas phase

Entry	Y	R	ΔG^0 (kJ mol^{-1})	ΔH^0 (kJ mol^{-1})
1	Me	Me	0.8	−5.0
2	Me	Bu	2.1	−3.9
3	Me	$C_{12}H_{25}$	2.3	−4.0
4	Ph	Me	1.0	−4.9



Entry	Y	R	ΔG^0 (kJ mol^{-1})	ΔH^0 (kJ mol^{-1})
5	Me	Me	6.3	1.0
6	Me	Bu	6.1	0.9
7	Me	$C_{12}H_{25}$	7.1	0.03
8	Ph	Me	13.5	1.7



Entry	Y	R	ΔG^0 (kJ mol^{-1})	ΔH^0 (kJ mol^{-1})
9	H	Me	7.3	1.2
10	H	Bu	8.4	0.3
11	H	$C_{12}H_{25}$	7.3	0.07
12	OH	Me	8.0[a]	2.4[a]

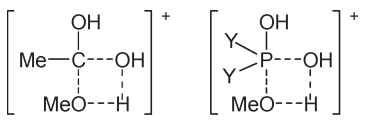
[a] For monoesterification

Entry	R	ΔG^0 (kJ mol^{-1})	ΔH^0 (kJ mol^{-1})
13	Me	14.1	4.0
14	Bu	12.8	3.3
15	$C_{12}H_{25}$	15.6	3.2

The thermodynamic data show that, in the cases studied, there is no driving force for the direct esterification of phosphinic acids. As shown by the ΔH^0 values, the reactions investigated are almost "thermoneutral". Judging from the values of ΔG^0, it is also seen that the direct esterifications of phosphinic acids should theoretically be reversible. The reason for the non-reversibility experienced may lie hidden in the hydrophobic medium established by the long alkyl chain of the alcohols used, as was discussed above. Hence, there is no contradiction between the theory and practice. It can be expected that mainly kinetic factors are responsible for the unreactivity under thermal conditions.

2.3 Kinetic background of the direct esterification of phosphinic acids

It was shown that the thermodynamics of the direct esterification is significantly different for carboxylic acids and phosphinic acids. We wished to study the kinetics of these two types of esterifications. For this, the energy content of the first transition state determining the formation of the carboxylic acid alcohol adduct or phosphinic acid alcohol adduct was calculated by the PM6 and the B3LYP/6-31++G(d,p) methods in the gas phase and in solvent using an alcohol. Interestingly, both for the esterification of carboxylic acids and phosphinic acids, the first transition state (TS) comes from the attack of the alcohol (*eg.* methanol) on the protonated C=O or P=O function of the esters, where the hydrogen atom of methanol is half-way between the oxygen atom of the alkoxy group and that of the hydroxy group (see structures **A** and **B**).



A **B**

PM6 calculations support the intermediacy of the adduct itself formed by the addition of methanol on the C=O or P=O function of the protonated acid. According to DFT calculations, these primary adducts are not stable and TSs **A** or **B** are formed directly. The TSs are similar as in radical H-atom shift reactions, where the activation energies are approximately the sum of the ring strain energy and the activation energy of the bimolecular H-shift reaction.[36,37] The formation of TSs **A** or **B** is followed by the elimination of water. This mechanism is in some respects novel and is the subject of a detailed study to be published under

Table 3 Activation energy and enthalpy values calculated for the esterification of carboxylic acids, phosphinic acids and phosphonic acids by the B3LYP/6-31++G(d,p) method at 210 °C in the gas phase

Entry	R	$\Delta G^{\#}$ (kJ mol^{-1})	$\Delta H^{\#}$ (kJ mol^{-1})
1	Me	158.4	75.0
2	Bu	139.2	49.2

Entry	Y	R	$\Delta G^{\#}$ (kJ mol^{-1})	$\Delta H^{\#}$ (kJ mol^{-1})
3	Me	Me	234.0	140.1
4	Me	Bu	212.1	130.8
5	Ph	Me	242.7	161.4
6	Ph	^{i}Pr	241.2	157.8

Entry	R	$\Delta G^{\#}$ (kJ mol^{-1})	$\Delta H^{\#}$ (kJ mol^{-1})
7	Me	202.3	114.6
8	Bu	184.0	101.7

a separate cover. The relative energies and enthalpies of activation ($\Delta G^{\#}$ and $\Delta H^{\#}$, respectively) obtained by the above mentioned methods for the first TS of the esterification of acetic acid, dimethyl- and diphenylphosphinic acid, as well as 1-hydroxy-3-methyl-phospholene 1-oxide with different alcohols are listed in Table 3. It can be seen that the esterification of carboxylic acids with alcohols goes with an enthalpy of activation of 75.0/49.2 kJ mol^{-1} according to DFT calculations (Table 3/Entries 1 and 2). At the same time, the $\Delta H^{\#}$ values for the esterification of phosphinic acids are much higher and are in the range of 130.8–161.4 kJ mol^{-1} (Table 3/Entries 3–6). For the esterification of 1-hydroxy-3-methyl-3-phospholene oxide the $\Delta H^{\#}$ is 114.6/101.7 kJ mol^{-1} (Table 3/Entries 7 and 8).

The activation entropies for the reactions $MeCO_2H$ + MeOH and $Me_2P(O)OH$ + MeOH are 91.2 and 69.5 J K^{-1} mol^{-1}, respectively. The difference of *ca.* 20 J K^{-1} mol^{-1} means that (on the basis of the Eyring equation $\kappa\Gamma\lambda\ kT/h\ (RT/p^{o})\exp(\Delta S^{\#}/R)$ [where κ is the transmission coefficient, γ is the quantum coefficient and λ includes the reaction degeneration; all the three were considered to be equally one] the preexponential factor is ten times smaller for the reaction $Me_2P(O)OH$ + MeOH, than for the esterification of acetic acid. The relative difference in the exponential part for the reactions of $MeCO_2H$ + MeOH and $Me_2P(O)OH$ + MeOH (where the activation enthalpy difference is 65.1 kJ mol^{-1}) is *ca.* 10^{-7}. This means that the rate constant for the $Me_2P(O)OH$ + MeOH reaction must be *ca.* 10^{-6}–10^{-7} times smaller at 483.16 K, than for the esterification of acetic acid.

The first TSs obtained by the above methods for the $MeCO_2H$ + MeOH, $Me_2P(O)OH$ + MeOH and $Ph_2P(O)OH$ + MeOH reactions are shown in Fig. 1–3, respectively. The aforementioned situation with the intermediate position of the hydrogen atom to be transferred can be seen well. The geometry of the TSs are very similar in the reactions studied. According to DFT calculations, the distance of MeO···H in ring TSs **A** and **B** (Y = Me) is 1.26 Å and 1.11 Å, respectively. Similarly, the H···OH distances are 1.23 Å (**A**) and 1.33 Å (**B**, Y = Me). For **A**, the HO···C and C···OMe distances are 1.53 Å and 1.49 Å, respectively, while for **B** (Y=Me), the HO···P and P···OMe distances are 1.85 Å and 1.84 Å, respectively. The bond angles around the central carbon (**A**) and phosphorus atom (**B**, Y=Me) are in the range of 88.5–114.8° and 70.3–155.2°, respectively.

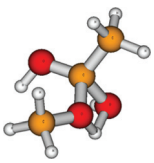


Fig. 1 TS for the acid catalyzed esterification of $MeCO_2H$ and MeOH calculated by the B3LYP/6-31++G(d,p) method in methanol. Selected geometries (bond distances, bond angles and torsion angles) are given in Å and deg. C–C 1.499, C–O(1)H 1.345, C–O(2)H 1.492, C–OMe 1.461, C–C–O(1)H 112.71, C–C–O(2)H 112.02, C–C–OMe 112.61, MeO–C–O(1)H 114.83, MeO–C–O(2)H 88.49, HO(1)–C–O(2)H 114.04.

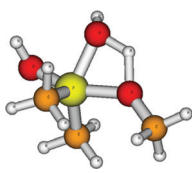


Fig. 2 TS for the acid catalyzed esterification of Me_2PO_2H and MeOH calculated by the B3LYP/6-31++G(d,p) method in the gas phase. Selected geometries (bond distances, bond angles and torsion angles) are given in Å and deg. P–C(1) 1.813, P–C(2) 1.815., P–O(1)H 1.843, P–O(2)H 1.656, P–OMe 1.843, C(1)–P–O(1)H 109.78, C(1)–P–O(2)H 101.58, C(1)–P–OMe 96.98, C(2)–P–O(1)H 128.76, C(2)–P–O(2)H 92.95, C(2)–P–OMe 91.88, MeO–P–O(1)H 70.26, MeO–P–O(2)H 155.15, HO(1)–P–O(2)H 87.87.

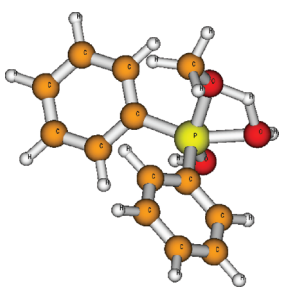


Fig. 3 TS for the acid catalyzed esterification of Ph_2PO_2H and MeOH calculated by the B3LYP/6-31++G(d,p) method. Selected geometries (bond distances, bond angles and torsion angles) are given in Å and deg. P–C(1) 1.842, P–C(2) 1.802, P–O(1)H 1.859, P–O(2)H 1.651, P–OMe 1.837, C(1)–P–O(1)H 152.90, C(1)–P–O(2)H 95.91, C(1)–P–OMe 92.48, C(2)–P–O(1)H 96.10, C(2)–P–O(2)H 111.12, C(2)–P–OMe 107.14, MeO–P–O(1)H 70.71, MeO–P–O(2)H 135.26, HO(1)–P–O(2)H 82.87.

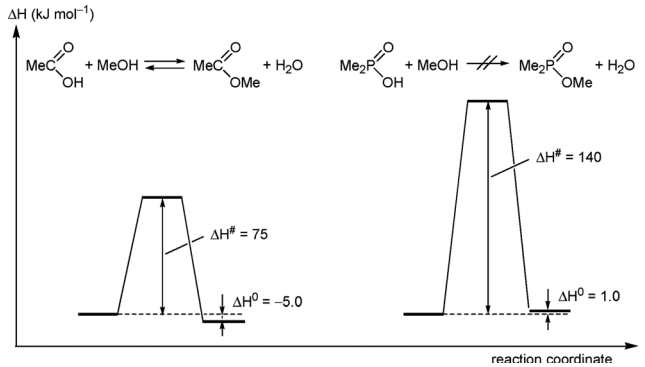


Fig. 4 Enthalpy profile for the esterification of acetic acid and dimethylphosphinic acid (see also Tables 2 and 3).

The high $\Delta H^{\#}$ values of 101.7–161.4 kJ mol^{-1} suggest that, in contrast to the esterification of carboxylic acids (where the $\Delta H^{\#}$ is 49.2–75.0 kJ mol^{-1}), the phosphinic acids cannot be expected to undergo direct esterification under thermal conditions. The fact that the esterification of phosphinic acids does take place under MW irradiation is the consequence of the beneficial effect of MW. Our experience confirms the high potential of the MW technique making, on this occasion, possible a thermally reluctant (practically impossible) reaction. The nature of this phenomenon is studied further. It is also clear that the MW-assisted esterification of phosphinic acids is kinetically controlled.

As a comparison, the enthalpy – reaction coordinate relationship is shown in Fig. 4 for the esterification of acetic acid and for the similar reaction of dimethylphosphinic acid. In both cases, methanol is the reagent.

2.4 Conclusions

New results on the novel MW-assisted direct esterification of phosphinic acids are described. Suitable model reactions comprising alcohols with longer alkyl chain and higher boiling point were explored that can be accomplished in quantitative yields. Comparative thermal experiments provided the phosphinates in only 10–15% conversions even after prolonged reaction times. DFT calculations suggested that the esterifications are almost "thermoneutral" and go through a high activation barrier justifying the unreactivity of phosphinic acids in direct esterification under thermal conditions. The fact that the phosphinic acids still undergo esterification under MW conditions refers to the potential of the MW technique. On the basis of the free energy values calculated, the direct esterification of phosphinic acids should be reversible. The reason for the macroscopic non-reversibility observed in our experiments lies hidden in the hydrophobic conditions brought about by the long alkyl chain alcohol used as the solvent and the long chain phosphinic ester formed.

3. Experimental

3.1 General

The ^{31}P, ^{13}C, ^{1}H NMR spectra were taken on a Bruker DRX-500 spectrometer operating at 202.4, 125.7 and 500 MHz, respectively. The couplings are given in Hz. Mass spectrometry was performed on a ZAB-2SEQ instrument.

GC was carried out on an HP5890 series 2 GC-FID chromatograph, using a 15 m × 0.18 mm Restek, Rtx-5 column with a film layer of 0.20 μm. The temperature of the column was initially held at 40 °C for 1 min, followed by programming at 25 °C min^{-1} up to 300 °C, and a final period at 300 °C (isothermal) for 10 min. The temperature of the injector was 290 °C, and of the FID detector 300 °C. The carrier gas was H_2.

The esterifications were carried out in a CEM Discover microwave reactor equipped with a stirrer and a pressure controller using 60–160 W irradiation.

3.2 General procedure for the MW-assisted direct esterification of cyclic phosphinic acids by octanol and dodecanol

A mixture of 0.10 g of the phosphinic acid (0.68 mmol of **1**, 0.76 mmol of **2**, 0.68 mmol of **5**, or 0.75 mmol of **6**) and 1.8 mL (11.4 mmol) of octanol or 2.0 mL (8.9 mmol) of dodecanol was measured in a sealed tube and irradiated in the MW reactor equipped with a pressure controller at temperatures and for the times shown below. (The pressure developed was in the range of 1–2 bar.) Then the excess of alcohol was removed under reduced pressure, and the residue so obtained purified by flash column chromatography using silica gel and 3% methanol in chloroform as the eluant to afford phosphinates as oils in a purity of ~98% according to GC. The following products were thus prepared:

3.2.1 1-Dodecyloxy-3,4-dimethyl-3-phospholene 1-oxide (3a). 230 °C, 2 h; Yield: 95%; ^{31}P NMR ($CDCl_3$) δ 68.6; ^{13}C NMR ($CDCl_3$) δ 14.1 (CH_2CH_3), 16.5 (^3J = 15.9, C_3–CH_3), 22.7 (CH_2), 25.6 (CH_2), 29.21 (CH_2), 29.35 (CH_2), 29.52 (CH_2), 29.57 (CH_2), 29.64 (2×CH_2), 30.7 (^3J = 6.0, OCH_2CH_2), 31.9 (CH_2), 35.7 (^1J = 90.8, C_2), 64.9 (^2J = 6.7, OCH_2), 127.5 (^2J = 12.9, C_3); ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 6.9, 3H, CH_2CH_3), 1.23–1.38 (m, 18H, CH_2), 1.65–1.73 (m, 2H, CH_2), 1.73 (s, 6H, C_3–CH_3), 2.37–2.50 (m, 4H, PCH_2), 3.99–4.03 (m, 2H, OCH_2); $[M + H]^+_{found}$ = 315.2453, $C_{18}H_{36}O_2P$ requires 315.2453.

3.2.2 1-Octyloxy-3,4-dimethyl-3-phospholene 1-oxide (3b). 230 °C, 2 h; Yield: 73%; ^{31}P NMR ($CDCl_3$) δ 69.2; ^{13}C NMR ($CDCl_3$) δ 14.0 (CH_2CH_3), 16.5 (^3J = 15.8, C_3–CH_3), 22.5 (CH_2), 25.5 (CH_2), 29.1 (2×CH_2), 30.6 (^3J = 6.0, OCH_2CH_2), 31.7 (CH_2), 35.7 (^1J = 90.8, C_2), 64.8 (^2J = 6.7, OCH_2), 127.4 (^2J = 12.8, C_3); ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J = 7.0, 3H, CH_2CH_3), 1.25–1.35 (m, 10H, CH_2), 1.64–1.68 (m, 2H, CH_2), 1.71 (s, 6H, C_3–CH_3), 2.36–2.49 (m, 4H, PCH_2), 3.97–4.02 (m, 2H, OCH_2); $[M + H]^+_{found}$ = 259.1829, $C_{14}H_{28}O_2P$ requires 259.1827.

3.2.3 1-Dodecyloxy-3-methyl-3-phospholene 1-oxide (4a). 230 °C, 2 h; Yield: 95%; ^{31}P NMR ($CDCl_3$) δ 74.8; ^{13}C NMR ($CDCl_3$) δ 14.0 (CH_2CH_3), 20.7 (^3J = 12.9, C_3–CH_3), 22.6 (CH_2), 25.5 (CH_2), 29.11 (CH_2), 29.26 (CH_2), 29.42 (CH_2), 29.47 (CH_2), 29.54 (2×CH_2), 30.5 (^3J = 6.0, OCH_2CH_2), 30.7 (^1J = 88.3, C_2*), 31.8 (CH_2), 33.4 (^1J = 92.2, C_5*), 64.9 (^2J = 6.7, OCH_2), 120.3 (^2J = 10.8, C_4), 136.2 (^2J = 16.8, C_3), *may be reversed; ^{1}H NMR ($CDCl_3$) δ 0.86 (t, J = 7.0, 3H, CH_2CH_3), 1.22–1.31 (m, 18H, CH_2), 1.61–1.72 (m, 2H, CH_2), 1.78 (s, 3H, C_3–CH_3), 2.24–2.51 (m, 4H, PCH_2), 3.96–4.05 (m, 2H, OCH_2), 5.51 (d, J = 35.8, 1H, CH); $[M + H]^+_{found}$ = 301.2298, $C_{17}H_{34}O_2P$ requires 301.2296.

3.2.4 1-Octyloxy-3-methyl-3-phospholene 1-oxide (4b). 220 °C, 2 h; Yield: 71%; ^{31}P NMR ($CDCl_3$) δ 74.6; ^{13}C NMR ($CDCl_3$) δ 14.0 (CH_2CH_3), 20.7 (^3J = 13.0, C_3–CH_3), 22.6 (CH_2), 25.5 (CH_2), 29.1 (2×CH_2), 30.6 (^3J = 5.8, OCH_2CH_2), 30.7 (^1J = 87.9, C_2*), 31.7 (CH_2), 33.4 (^1J = 90.7, C_5*), 64.9 (^2J = 6.7, OCH_2), 120.3 (^2J = 10.8, C_4), 136.2 (^2J = 16.9, C_3), *may be reversed; ^{1}H NMR ($CDCl_3$) δ 0.85 (t, J = 6.9, 3H, CH_2CH_3), 1.25–1.36 (m, 10H, CH_2), 1.61–1.70 (m, 2H, CH_2), 1.77 (s, 3H, C_3–CH_3), 2.31–2.46 (m, 4H, PCH_2), 3.96–4.03 (m, 2H, OCH_2), 5.50 (d, J = 35.9, 1H, CH); $[M + H]^+_{found}$ = 245.1671, $C_{13}H_{26}O_2P$ requires 245.1670.

3.2.5 1-Octyloxy-3,4-dimethyl-3-phospholane 1-oxide (7). 230 °C, 4 h; Yield: 70%; ^{31}P NMR ($CDCl_3$) δ 72.4 (60%), 78.3 (20%) and 79.0 (20%); $[M + H]^+_{found}$ = 261.1985, $C_{14}H_{30}O_2P$ requires 261.1983.

For the major isomer (**A**): ^{13}C NMR ($CDCl_3$) δ 14.0 (CH_2CH_3), 18.8 (^3J = 15.7, C_3–CH_3[a]), 19.0 (^3J = 14.7, C_4–CH_3[a]), 22.5 (CH_2CH_3), 25.5 (CH_2), 29.1 (2×CH_2), 30.6 (^3J = 6.0, OCH_2CH_2), 31.7 (CH_2), 34.3 (^1J = 88.5, C_2[b]), 34.6 (^1J = 88.1, C_5[b]), 38.59 (^2J = 10.8, C_3[b]), 38.62 (^2J = 10.8, C_4[c]), 64.52 (^2J = 6.7, OCH_2); ^{1}H NMR ($CDCl_3$) δ 0.84 (t, J = 6.7, CH_2CH_3), 1.03–1.06 (m, C_3–CH_3 and C_4–CH_3), 3.88–4.00 (m, 2H, OCH_2).

For the minor isomers (**B-1** and **B-2**): ^{13}C NMR ($CDCl_3$) δ 14.0 (CH_2CH_3), 15.7 (^3J = 9.2) and 16.0 (^3J = 9.3) C_3–CH_3, 22.5 (CH_2CH_3), 25.5 (CH_2), 29.1 (2×CH_2), 30.5 (^3J = 6.2) and 30.6 (^3J = 6.0) OCH_2CH_2, 31.7 (CH_2), 31.8 (^1J = 87.5) and 32.0 (^1J = 87.5) C_2, 34.7 (^2J = 12.1) and 34.8 (^2J = 12.4) C_3, 64.46 (^2J = 6.5) and 64.68 (^2J = 6.8) OCH_2; ^{1}H NMR ($CDCl_3$) δ 0.84 (t, J = 6.7, CH_2CH_3), 0.93 (d, J = 6.7) and 0.99 (d, J = 6.7) C_3–CH_3, 3.88–4.00 (m, 2H, OCH_2).

3.2.6 1-Octyloxy-3-methyl-3-phospholane 1-oxide (8). 230 °C, 4 h; Yield: 74%; ^{31}P NMR ($CDCl_3$) δ 79.61 (50%) and 79.66 (50%); ^{13}C NMR ($CDCl_3$) δ 14.2 (CH_2CH_3), 21.4 (^3J = 14.7) and 21.5 (^3J = 12.3) C_3–CH_3, 22.7 (CH_2CH_3), 25.5 (^1J = 87.9) and 26.2 (^1J = 87.4) C_5, 25.7 (CH_2), 29.3 (2×CH_2), 30.8 (^3J = 6.0, OCH_2CH_2), 31.4 (^2J = 9.7) and 31.6 (^2J = 9.8) C_4*, 31.9 (CH_2), 32.0 (^2J = 13.0) and 32.2 (^2J = 13.0) C_3*, 33.0 (^1J = 89.6) and 33.3 (^1J = 89.2) C_2, 64.8 (^2J = 6.5, OCH_2), *may be reversed; ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J = 7.0, 3H, CH_2CH_3), 1.07–1.12 (m, 3H, C_3–CH_3), 1.20–1.40 (m, 12H, CH_2), 1.61–1.80 (m 2H, CH_2), 1.87–2.10 (m, 5H, CH_2, CH), 3.93–4.00 (m, 2H, OCH_2); $[M + H]^+_{found}$ = 247.1828, $C_{13}H_{28}O_2P$ requires 247.1827.

3.2.7 Comparative thermal experiments. The comparative thermal experiments were performed in a similar way, as the MW experiments (see 3.2) placing the bombs in oil bathes heated to the appropriate temperature. The residue obtained after evaporation and flash column chromatography (as above) was analysed by ^{31}P NMR spectrometry. The conversion of **1** to **3a** was 15% after a heating at 220 °C for 2 h, while the conversion of **2** to **4b** was 12% after a treatment of 185 °C for 2 h.

3.2.8 Attempted hydrolysis of phosphinic esters 3a and 4b under MW conditions. A mixture of 0.10 g of the phosphinic esters (0.32 mmol of **3a**, or 0.41 mmol of **4b**) and 2.5 mL of water was measured in a sealed tube and irradiated (as above, see 3.2). Then the mixture was extracted by 3 × 8 mL of dichloromethane, the combined extracts were dried (Na_2SO_4) and evaporated to regenerate phosphinates **3a** and **4b** in 95% and 98%, respectively (δ_P for **3a**: 68.6 and δ_P for **4b**: 75.0 ($CDCl_3$)).

Thermal experiments led to the same results.

3.3 Quantum chemical calculations

All computations were carried out using the Gaussian03 program package (G03).[38] The thermodynamic parameters were calculated by the B3LYP/6-31++G(d,p) method in gas phase, followed by frequency calculations at the same level of theory. Thermodynamic functions U, H and G were computed at 483.13 K, using the quantum chemical rather than the conventional, thermodynamic reference state.

The transition states were calculated by semi-empirical quantum chemical method PM6[39] in gas phase and with implicit solvation method COSMO.[40] In gas phase, the reactants and products had only positive force constants, in the transition state only one negative force constant was found. The structures were used as initial structure in the density functional calculations B3LYP/6-31++G(d,p) in gas phase and in solution.[38] In the solvation PCM method was applied with Pauling radii. Dielectric constants 32.6 with RSOLV = 2.53 (methanol), 19.9 with RSOLV = 3.12 (isopropanol) were used.[41]

The vibrational contribution to the partition functions (activation enthalpies and activation free energies) were calculated by harmonic oscillator model. The scale factor of the zero point vibrational energy was considered to be one.

Acknowledgements

The above project was supported by the Hungarian Scientific and Research Fund (OTKA K83118). This work is connected to the scientific program of the "Development of quality-oriented and harmonized R+D+I strategy and functional model at BME" project. This project is supported by the New Széchenyi Plan (Project ID: TÁMOP-4.2.1/B-09/1/KMR-2010-0002). TK is indebted for the support from TÁMOP-4.2.1/B-09/1/KONV-2010-0005.

References

1 R. S. Edmundson, In *Comprehensive Organic Chemistry*, ed. D. Barton, D. Ollis and I. O. Sutherland, Pergamon, Oxford, 1979; Vol. 2, Ch. 10.5, p.1291.
2 L. D. Quin, *A guide to organophosphorus chemistry*, Wiley, New York, 2000.
3 M. J. P. Harger and S. Westlake, *Tetrahedron*, 1982, **38**, 1511–1515.
4 K. A. Andrianov and I. K. Kuznetsova, *Izv. Akad. Nauk SSSR, Otdel. Khim. Nauk*, 1961, 1454–1456.
5 N. N. Godovikov, N. A. Kardanov, T. A. Chepaikina and M. I. Kabachnik, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1981, 2824–2828.
6 Z. E. Golubski, *Synthesis*, 1980, 632–634.
7 M. Tanaka and R. Hua, *JP 11180990 A*, 1999, 5 pp
8 D. S. Karanewsky and M. C. Badia, *Tetrahedron Lett.*, 1986, **27**, 1751–1754.
9 N. S. Sampson and P. A. Bartlett, *J. Org. Chem.*, 1988, **53**, 4500–4503.
10 S. Chen and J. K. Coward, *J. Org. Chem.*, 1998, **63**, 502–509.
11 A. Winqvist and R. Strömberg, *Eur. J. Org. Chem.*, 2008, 1705–1714.
12 T. Yoshino, S. Imori and H. Togo, *Tetrahedron*, 2006, **62**, 1309–1317.

13 K. Afarinkia and H-W. Yu, *Tetrahedron Lett.*, 2003, **44**, 781–783.
14 K. Bravo-Altamirano, Z. Huang and J-L. Montchamp, *Tetrahedron*, 2005, **61**, 6315–6329.
15 S. Depréle and J.-L. Montchamp, *J. Organomet. Chem.*, 2002, **643–644**, 154–163.
16 Y. R. Dumond, R. L. Baker and J-L. Montchamp, *Org. Lett.*, 2000, **2**, 3341–3344.
17 I. V. Berezovskaya, L. A. Eliseeva, E. V. Kuznetsov, E. Kh. Mukhametzyanova and I. M. Shermergorn, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1968, 1369–1371.
18 A. Markowska, J. Olejnik and J. Michalski, *Chem. Ber.*, 1975, **108**, 2589–2592.
19 T. R. Hopkins and P. W. Vogel, *J. Am. Chem. Soc.*, 1956, **78**, 4447–4450.
20 L. D. Quin, *The heterocyclic chemistry of phosphorus: system based on the phosphorus–carbon bond* Wiley, New York, 1981.
21 K. Hunger, U. Hasserodt and F. Korte, *Tetrahedron*, 1964, **20**, 1593–1604.
22 G. Keglevich, J. Brlik, F. Janke and L. Tőke, *Heteroat. Chem.*, 1990, **1**, 419–424.
23 G. Keglevich, L. Tőke, A. Kovács, G. Tóth and K. Újszászy, *Heteroat. Chem.*, 1993, **4**, 61–72.
24 N. Z. Kiss, K. Ludányi, L. Drahos and G. Keglevich, *Synth. Commun.*, 2009, **39**, 2392–2404.
25 G. Keglevich, E. Bálint, N. Z. Kiss, E. Jablonkai, L. Hegedűs, A. Grün and I. Greiner, *Curr. Org. Chem.*, 2011, **15**, 1802–1810.
26 E. Bálint, E. Jablonkai, M. Bálint and G. Keglevich, *Heteroat. Chem.*, 2010, **21**, 211–214.
27 K. Kranjc and M. Kočevar, *Curr. Org. Chem.*, 2010, **14**, 1050–1074.
28 G. Keglevich, E. Dudás, M. Sipos, D. Lengyel and K. Ludányi, *Synthesis*, 2006, 1365–1369.
29 G. Keglevich and E. Dudás, *Synth. Commun.*, 2007, **37**, 3191–3199.
30 G. Keglevich, E. Bálint, É. Karsai, A. Grün, M. Bálint and I. Greiner, *Tetrahedron Lett.*, 2008, **49**, 5039–5042.
31 G. Keglevich, E. Bálint, É. Karsai, J. Varga, A. Grün, M. Bálint and I. Greiner, *Lett. Org. Chem.*, 2009, **6**, 535–539.
32 G. Keglevich, T. Novák, L. Vida and I. Greiner, *Green Chem.*, 2006, **8**, 1073–1075.
33 G. Keglevich, K. Majrik, L. Vida and I. Greiner, *Lett. Org. Chem.*, 2008, **5**, 224–228.
34 U.-H. Felcht, BE631416, 1963; U.-H. Felcht, *Chem. Abstr.*, 1964, **61**, 688
35 V. I. Paramonova, M. P. Zykov, V. P. Dushina, B. A. Arbuzov, A. O. Vizel' and L. I. Shchukina, *Bull. Acad. Sci. USSR, Div. Chem. Sci. (Engl. Transl.)*, 1988, **37**, 1560–1564.
36 B. Viskolcz, G. Lendvay, T. Körtvélyesi and L. Seres, *J. Am. Chem. Soc.*, 1995, **118**, 3008–3012.
37 T. Körtvélyesi and L. Seres, *React. Kinet. Catal. Lett.*, 1996, **18**, 27–31.
38 M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, 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, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez and J. A. Pople, *Gaussian 03, Revision E.01*, Gaussian, Inc., Wallingford CT, 2004
39 J. J. P. Stewart, *J. Mol. Model.*, 2007, **13**, 1173–1213.
40 A. Klamt and G. Schüümann, *J. Chem. Soc., Perkin Trans. 2*, 1993, 799–805.
41 http://gabedit.sourcearchive.com/documentation/2.2.7/MopacRem_8c-sourchttp://gabedit.sourcearchive.com/documentation/2.2.7/MopacRem_8c-source.htmle.html.

