A Study on the Direct Esterification of Monoalkylphosphates and Dialkylphosphates; The Conversion of the Latter Species to Trialkylphosphates by Alkylating Esterification

Péter Ábrányi-Balogh 1,2,*, Nikoletta Harsági 2, László Drahos 3 and György Keglevich 2,*

1 Medicinal Chemistry Research Group, Research Centre for Natural Sciences, 1117 Budapest, Hungary; abranyi-balogh.peter@ttk.hu
2 Department of Organic Chemistry and Technology, Budapest University of Technology and Economics, 1521 Budapest, Hungary; harsagi.nikoletta@vbk.bme.hu
3 MS Proteomics Research Group, Research Centre for Natural Sciences, 1117 Budapest, Hungary; drahos.laszlo@ttk.hu
* Correspondence: keglevich.gyorgy@vbk.bme.hu; Tel.: +36-1-463-1111 (ext. 5883)
† This article is dedicated to Professor Dr. László Nyulánszi (Budapest University of Technology and Economics) on the occasion of his 65th birthday.

Abstract: The microwave (MW)-assisted direct esterification of certain P-acids is a green method. Quantum chemical calculations revealed that the activation enthalpy ($\Delta H^\#$) for the exothermic monoalkylphosphate $\rightarrow$ dialkylphosphate transformation was on the average 156.6 kJ mol$^{-1}$, while $\Delta H^\#$ for the dialkylphosphate $\rightarrow$ trialkylphosphate conversion was somewhat higher, 171.2 kJ mol$^{-1}$, and the energetics of the elemental steps of this esterification was less favorable. The direct monoesterification may be performed on MW irradiation in the presence of a suitable ionic liquid additive. However, the second step, with the less favorable energetics as a whole, could not be promoted by MWs. Hence, dialkylphosphates had to be converted to triesters by another method that was alklylation. In this way, it was also possible to synthesize triesters with different alkyl groups. Eventually a green, P-chloride free MW-promoted two-step method was elaborated for the synthesis of phosphate triesters.

Keywords: P-ester acid; direct esterification; selectivity; alkylating esterification; energetics; mechanism; theoretical calculations; green method

1. Introduction

Microwave irradiation is a useful tool in promoting organic chemical reactions [1–7]. On the one hand, the transformations become faster with MW assistance; on the other hand, the conversions are more selective. Overall, the reactions can be accomplished in a more efficient way [8]. Another value is when MW irradiation substitutes catalysts [9–11] or allows the simplification of catalyst systems [12]. The greatest advantage of MWs is when reactions reluctant to conventional heating take place with irradiation [13].

An interesting discipline is the synthesis of P-esters, such as phosphinates, phosphonates and phosphates. The traditional way is to start from P-chlorides (phosphinic chloride, phosphonic dichloride and phosphorus oxychloride), and to react them with alcohols or phenols in the presence of a base [14,15]. However, these transformations require cost-meaning P-chlorides, and are not atomic efficient. We were successful in developing an MW-assisted, [bmim][PF$\_6$]-promoted method for the direct esterification of a series of phosphinic acids (Scheme 1A) [16]. Phosphonic acids could also be converted to monoalkylphosphonates in a similar way using [bmim][BF$\_4$] (Scheme 1B) [17]. The series is complete if the monoalkylphosphate $\rightarrow$ dialkylphosphate transformation is also considered (Scheme 1C) [18]. The MW-assisted direct esterification of P-acids is an important method,
as, in this way, the use of P-chlorides can be avoided. Hence, costs may be saved, and the formation of hydrochloric acid may be avoided.

![Scheme 1](image_url)

Scheme 1. MW-assisted esterification of different P-acids.

In this paper, we wished to evaluate the energetics of the \( \text{V} \to \text{VI} \) transformation, and that of the \( \text{VI} \to (\text{R}^2\text{O})_3\text{P(O)} \) conversion. Moreover, it was our purpose to elaborate the esterification of dialkylphosphates VI.

2. Results and Discussion

2.1. MW-Assisted Direct Esterification of Monoalkylphosphates

The monoalkylphosphates (1a-d) selected underwent esterification in reaction with the corresponding alcohol used in 15-fold quantity in the presence of 10% of [bmim][BF₄] as the catalyst at 175/200 °C under MW irradiation. Our preliminary results were useful to find the optimum conditions [18]. The dialkylphosphates (2a-d) were obtained selectively, in yields of 83–87% after chromatography (Table 1). The main role of the ionic liquid additive is to act as an MW absorber in the reaction mixture [17]. Our earlier experiences showed that in the absence of an ionic liquid additive, the efficiency of the esterifications was significantly lower, when compared to the case when 10% of the catalyst was applied. The difference may have amounted to 80% [17].

| Entry | R      | T (°C) | t (h) | Product Composition (%) * | Yield of 2 (%) |
|-------|--------|--------|-------|--------------------------|----------------|
| 1     | Bu (a) | 200    | 2     | 96                       | 83 [18]        |
| 2     | Pent (b) | 200    | 2     | 95                       | 84             |
| 3     | Pr (c) | 200    | 2.5   | 96                       | 87             |
| 4     | Et (d) | 175    | 4.5   | 95                       | 83             |

* On the basis of the relative \(^{31}\text{P} \) NMR integrals found in the spectrum of the crude mixture.

The dialkylphosphates (2) could not be converted to the triesters (3) in a similar fashion.
2.2. Theoretical Calculations on the Energetics and Mechanism of the Monoalkylphosphate → Dialkylphosphate → Trialkylphosphate Transformation

We analyzed the energetics of the direct esterification of phosphates (R = Et, Bu) with the corresponding alcohols (EtOH, BuOH) using DFT computations at the M062X/6–311+G (d,p) level of theory considering the solvent effect (SMD implicit solvent model) of the corresponding alcohol and 473 K as the temperature (Scheme 2, Table 2, Figure 1). Based on our previous model [17,19], we proposed a reaction complex containing three alcohol molecules and two phosphonic acid units, where one alcohol molecule acts as the reagent in the esterification. The other diester acid and ROH species in the reaction complex participated in the proton transfer chain supporting the establishment of the new P–O bond, and hence the formation of the diester acid, along with the departure of a water molecule.

Considering the difference in the energetics between the starting monoalkylphosphates and the final dialkylphosphates, the reaction may be regarded as slightly exothermic, supported by an enthalpy value of ΔH = −10.4 kJ mol⁻¹ for the ethyl, and ΔH = −16.3 kJ mol⁻¹ for the butyl substituted case. While the formation of the reaction complex (4) required a ca. 160 kJ mol⁻¹ Gibbs free energy (ΔG) investment for both cases (see Table S2) that was the consequence of the entropy increase during the complex formation, there was a significant enthalpy gain (ΔH = −151.6 kJ mol⁻¹ for the ethyl and −160.9 kJ mol⁻¹ for the butyl instance). As shown in TS1 (ΔH° = 94.7 kJ mol⁻¹ and 93.0 kJ mol⁻¹, respectively), the next step of the reaction was the attack of the alcohol on the phosphorus atom of the P=O moiety leading to intermediate 5. The following step was the elimination of a
water molecule via $\text{TS2} (\Delta H^\# = 158.8 \text{ kJ mol}^{-1} \text{ and } 154.3 \text{ kJ mol}^{-1}$, respectively) yielding product complex 6. The difference in the relative enthalpy ($\Delta \Delta H$) of 6 and 4 was 1.2 kJ mol$^{-1}$ and $-4.4$ kJ mol$^{-1}$ for the two cases. At the same time, the gain in $\Delta G$ was larger ($-22.6$ kJ mol$^{-1}$ and $-11.3$ kJ mol$^{-1}$, respectively). The disruption of complex 6 was driven by $\Delta H = -10.4$ kJ mol$^{-1}$ and $-16.3$ kJ mol$^{-1}$ (as well as by $\Delta G = -4.9$ kJ mol$^{-1}$ and $-7.8$ kJ mol$^{-1}$) for the ethyl and butyl substituted case, respectively. The whole sequence was just slightly exothermic requiring a high activation energy investment mainly due to the large entropy that needed to be overcome. This supports the need for harsh experimental conditions ensured by the MW irradiation at 200 °C.

![Figure 1. Enthalpy diagram for the monoalkylphosphate → dialkylphosphate → trialkylphosphate transformations obtained by DFT computations at the M062X/6–311+G (d,p) level of theory considering the solvent effect of the corresponding alcohol.](image)

Investigating the transformation of diethyl and dibutylphosphate to triethyl and tributylphosphate, we found that the total process was somewhat less exothermic ($\Delta H = -7.6$ kJ mol$^{-1}$ and $-13.7$ kJ mol$^{-1}$, respectively). The formation of the reaction complex was also less advantageous ($\Delta H = -143.3$ kJ mol$^{-1}$ and $-144.1$ kJ mol$^{-1}$) as compared to the monoalkyl → dialkyl transformation. Moreover, both following steps required a higher activation enthalpy (for $\text{TS1} \Delta H^\# = 98.2$ kJ mol$^{-1}$ and 108.1 kJ mol$^{-1}$, respectively, and for $\text{TS2}$, 173.7 kJ mol$^{-1}$ and 168.7 kJ mol$^{-1}$, respectively). Finally, the stabilization of $\text{TS2}$ to intermediate 6 was less advantageous, and significantly lower enthalpy gains ($\Delta H = -121.0$ kJ mol$^{-1}$ and $-107.8$ kJ mol$^{-1}$) could be observed, suggesting in total an endothermic $4 \rightarrow 6$ transformation ($\Delta \Delta H = 22.3$ kJ mol$^{-1}$ and 36.3 kJ mol$^{-1}$, respectively, and $\Delta \Delta G = 23.0$ kJ mol$^{-1}$ and 34.1 kJ mol$^{-1}$, respectively).

2.3. MW-Assisted Alkylation of Dialkylphosphates

We saw that the dialkylphosphates (2) resisted undergoing further esterification to the triesters (3) that is due to the high barrier of the activation enthalpy. Hence, the conversion of diesters 2 to trialkylphosphates 3 had to be carried out by another method, by alkylation esterification. This was realized by applying the corresponding alkyl halides (bromobutane, bromopentane, bromopropane and iodoethane) together with triethylamine as the base in toluene at 135 °C on MW irradiation. Again, our earlier results were useful in finding the optimum conditions [18]. The results are collected in Table 3. It can be seen that the trialkylphosphates were obtained in 84–86% yields after the chromatography.

We thought that the alkylation esterification may be also suitable for the preparation of trialkylphosphates with different alkyl groups. Dibutylphosphate 2a was reacted, as shown above, with a few haloalkanes. The results are shown in Table 4. One may suspect
that the difference of the two conversions covers the side-reactions. Indeed, LC–MS pointed out the presence of $\text{HOP(O)(OR)OBu}$, $\text{HOP(O)(OR)}_2$, $(\text{RO})_2\text{P(O)OBu}$ and $(\text{RO})_3\text{P(O)}$ by-products as well, during the reaction of diester 2a with haloalcanes. Their formation is not completely clear, and interconversions to the effect of the $\text{Et}_3\text{N}-\text{HBr}$ salt under MW irradiation are assumed.

### Table 3. Alkylating esterification of dialkylphosphates (2) under MW conditions.

| Entry | R        | X  | t (h) | Conversion (%) |
|-------|----------|----|-------|---------------|
| 1     | Bu (a)   | Br | 2.5   | 85 [18]       |
| 2     | Pent (b) | Br | 2.5   | 84            |
| 3     | Pr (c)   | Br | 3.5   | 86            |
| 4     | Et (d)   | I  | 5     | 84            |

### Table 4. Alkylating esterification of dibutylphosphate (2a) with alcohols under MW conditions.

| Entry | RX       | T (°C) | t (h) | Conversion (%) | Conversion to 7 (%) | Yield of 7 (%) |
|-------|----------|--------|-------|---------------|---------------------|----------------|
| 1     | EtI      | 135    | 3     | 92            | 71                  | 65 (7a)        |
| 2     | PrBr     | 135    | 3     | 94            | 71                  | 63 (7b)        |
| 3     | $^1\text{PrBr}$ | 150 | 3     | 100           | 67                  | 58 (7c)        |
| 4     | PentBr   | 135    | 2     | 98            | 98                  | 89 (7d)        |

Dipentylphosphate 2b was also subjected to alkylations. The experimental data are collected in Table 5. In this case, the proportion of the by-products was somewhat higher.

### Table 5. Alkylating esterification of dipentylphosphate (2b) with alcohols under MW conditions.

| Entry | RX       | T (°C) | t (h) | Conversion (%) | Conversion to 8 (%) | Yield of 8 (%) |
|-------|----------|--------|-------|---------------|---------------------|----------------|
| 1     | EtBr     | 135    | 4.5   | 83            | 67                  | 59 (8a)        |
| 2     | PrBr     | 150    | 3     | 89            | 51                  | 48 (8b)        |
| 3     | $^1\text{PrBr}$ | 150 | 3     | 45            | 27                  | 19 (8c)        |
| 4     | BuBr     | 150    | 3     | 91            | 49                  | 44 (8d)        |
The trialkylphosphates with different alkyl groups (7 and 8) synthesized by us were mostly new compounds. A few of them were described but were not fully characterized. We characterized all “mixed” derivatives by $^{31}$P, $^{13}$C and $^1$H NMR data, as well as HRMS.

3. Materials and Methods

3.1. General Information

The $^{31}$P, $^{13}$C and $^1$H NMR spectra were taken on a Bruker DRX-500 spectrometer operating at 202.4, 125.7 and 500 MHz, respectively. LC–MS measurements were performed with an Agilent 1200 liquid chromatography system coupled with a 6130 quadrupole mass spectrometer equipped with an ESI ion source (Agilent Technologies, Palo Alto, CA, USA). The MW-assisted esterifications were carried out in a CEM Discover microwave reactor equipped with a stirrer and a pressure controller using a 50–100 W irradiation.

The composition of the reaction mixtures was determined by the integration of the areas under the corresponding peaks of the starting material and product in the $^{31}$P NMR spectra. As the $^{31}$P NMR signals separated better in DMSO-D$_6$, this solvent was used during the analysis of the mixtures.

3.2. The Direct Esterification of Monoalkylphosphates (1a–d)

A mixture of 0.79 mmol monoalkylphosphate (1a: 0.12 g; 1b: 0.13 g; 1c: 0.11 g; 1d: 0.10 g) (prepared as described above), 11.9 mmol of alcohol (ethanol: 0.69 mL; propanol: 0.89 mL; butanol: 1.08 mL; pentanol: 1.30 mL) and 15 µL (0.079 mmol) of [bmim][BF$_4$] was irradiated in the MW reactor at 175–200 °C for 2–4.5 h (Table 1). The crude mixture obtained on evaporation was purified by chromatography using a silica-gel layer of 20 cm, and ethyl acetate as the eluent to furnish dialkylphosphates (2a–d) as colorless oils. For identification of the dialkylphosphates, see Table 6.

Table 6. Identification of dialkylphosphates (2a–d).

| Compound | $\delta^P$ (CDCl$_3$) | $\delta^P$ (CDCl$_3$) [18] | HRMS [M+Na]$^+$
|----------|----------------------|--------------------------|------------------|
| 2a       | 0.032                | 0.029                    | 233.0912         |
| 2b       | 0.15                 | 0.10                     | 239.1412 $^*$    |
| 2c       | 1.94                 | 2.0                      | 205.0606         |
| 2d       | 0.52                 | 0.55                     | 177.0293         |

$^*$ Identified as M+H.

3.3. The Alkylating Esterification of Dialkylphosphates (2a–2d)

A mixture of 1.4 mmol (2a: 0.30 g; 2b: 0.31 g; 2d: 0.22 g) dialkylphosphate, 1.8 mmol (EtBr: 0.14 mL, PrBr: 0.17 mL, iPrBr: 0.17 mL, BuBr: 0.20 mL, PentBr: 0.22 mL) of alkyl bromide and 0.22 mL (1.6 mmol) of triethylamine in 1 mL of toluene was stirred under MW conditions for 2–5 h at 135–150 °C (Tables 3–5). The crude mixtures obtained after filtration and evaporation were purified by column chromatography using a silica gel layer of 20 cm and ethyl acetate as the eluent to furnish trialkylphosphates (3a–d, 7a–d and 8a–d) as colorless oils. For the identification of the known trialkylphosphates, see Table 7.

Table 7. The identification of known trialkylphosphates (3a–d).

| Compound | $\delta^P$ (CDCl$_3$) | $\delta^P$ (CDCl$_3$) [18] | HRMS [M+Na]$^+$
|----------|----------------------|--------------------------|------------------|
| 3a       | −0.92                | −0.89                    | 267.1725 $^*$    |
| 3b       | −1.02                | −0.99                    | 331.2014         |
| 3c       | −0.89                | −0.88                    | 247.1075         |
| 3d       | −1.05                | −1.0                     | 205.0606         |

$^*$ Identified as M+H.
3.4. Characterization of New Trialkylphosphates (7a–d and 8a–d)

3.4.1. Dibutyl-ethylphosphate (7a)

$^{31}$P NMR (202.4 MHz, CDCl$_3$): $-0.79$, $\delta_P$ [20] (CDCl$_3$): 0.75; $^{13}$C NMR (125.7 MHz, CDCl$_3$): 13.5 (s, 2CH$_3$), 16.1 (d, $J = 6.7$, CH$_3$), 18.6 (s, 2CH$_2$), 32.2 (d, $J = 6.8$, 2CH$_2$), 63.5 (d, $J = 5.9$, OCH$_2$), 67.3 (d, $J = 6.0$, 2OCH$_2$); $^1$H NMR (500 MHz, CDCl$_3$): $0.95$ (t, $J = 7.4$, 6H, 2CH$_3$), 1.33–1.46 (m, 7H, 2CH$_2$), 1.63–1.72 (m, 4H, 2CH$_2$), 4.02–4.17 (m, 6H, 3OCH$_2$), $\delta_H$ [21] (CDCl$_3$): 0.91 (t, 6H, $J = 6.5$), 1.25 (t, 3H, $J = 5.8$), 1.35–1.88 (m, 8H), 3.80–4.30 (m, 6H). [M+Na]$^+$ found: 261.1227, [M+Na]$^+$ calculated: 261.1322.

3.4.2. Dibutyl-proplyphosphate (7b)

$^{31}$P NMR (202.4 MHz, CDCl$_3$): $-0.75$, $^{13}$C NMR (125.7 MHz, CDCl$_3$): 9.9 (s, CH$_3$), 13.4 (s, 2CH$_3$), 18.6 (s, 2CH$_2$), 23.6 (d, $J = 6.9$, CH$_2$), 32.2 (d, $J = 6.8$, 2CH$_2$), 67.2 (d, $J = 6.3$, 2OCH$_2$), 69.0 (d, $J = 6.0$, OCH$_3$); $^1$H NMR (500 MHz, CDCl$_3$): $0.94$ (dt, $J = 13.4$, $J = 7.4$, 9H, 3CH$_3$), 1.36–1.44 (m, 4H, 2CH$_2$), 1.62–1.71 (m, 6H, 3CH$_2$), 3.96–4.04 (m, 6H, 3OCH$_2$). [M+Na]$^+$ found: 275.1390, [M+Na]$^+$ calculated: 275.1388.

3.4.3. Dibutyl-isoproplyphosphate (7c)

$^{31}$P NMR (202.4 MHz, CDCl$_3$): $0.50$, $\delta_P$ [20] (CDCl$_3$): 0.60; $^{13}$C NMR (125.7 MHz, CDCl$_3$): 13.6 (s, 2CH$_3$), 18.7 (s, 2CH$_2$), 23.6 (d, $J = 5.0$, 2CH$_3$), 32.3 (d, $J = 7.0$, 2CH$_2$), 67.2 (d, $J = 6.2$, 2OCH$_2$), 72.3 (d, $J = 5.8$, OCH$_3$); $^1$H NMR (500 MHz, CDCl$_3$): $0.93$ (t, $J = 7.4$, 6H, 2CH$_3$), 1.33 (d, $J = 6.2$, 6H, 2CH$_3$), 1.37–1.46 (m, 4H, 2CH$_2$), 1.63–1.69 (m, 4H, 2CH$_2$), 3.99–4.05 (m, 4H, 2OCH$_2$), 4.60–4.66 (m, 1H, OCH), $\delta_H$ [21] (CDCl$_3$): 0.65–1.88 (m, 2H), 3.63 (d, 2H, $J = 5.3$), 3.99 (dt, 4H, $J = 6.5$, 7.5). [M+Na]$^+$ found: 275.1386, [M+Na]$^+$ calculated: 275.1388.

3.4.4. Dibutyl-pentlyphosphate (7d)

$^{31}$P NMR (202.4 MHz, CDCl$_3$): $-0.68$, $^{13}$C NMR (125.7 MHz, CDCl$_3$): 13.5 (s, 2CH$_3$), 13.9 (s, CH$_3$), 18.6 (s, 2CH$_2$), 22.2 (s, CH$_2$), 27.5 (s, CH$_2$), 29.9 (d, $J = 6.8$, CH$_2$), 32.3 (d, $J = 6.9$, 2CH$_2$), 67.3 (d, $J = 6.2$, 2OCH$_2$), 67.6 (d, $J = 6.2$, OCH$_2$); $^1$H NMR (500 MHz, CDCl$_3$): 0.88–0.94 (m, 9H, 3CH$_3$), 1.31–1.36 (m, 4H, 2CH$_2$), 1.38–1.44 (m, 4H, 2CH$_2$), 1.62–1.69 (m, 6H, 3CH$_2$), 3.99–4.04 (m, 6H, 3OCH$_2$). [M+Na]$^+$ found: 303.1699, [M+Na]$^+$ calculated: 303.1701.

3.4.5. Dipentyl-ethylphosphate (8a)

$^{31}$P NMR (202.4 MHz, CDCl$_3$): $-0.75$; $^{13}$C NMR (125.7 MHz, CDCl$_3$): 13.9 (s, 2CH$_3$), 16.1 (d, $J = 7.0$, CH$_3$), 22.2 (s, 2CH$_2$), 27.6 (s, 2CH$_2$), 30.0 (d, $J = 7.0$, 2CH$_2$), 63.6 (d, $J = 5.9$, OCH$_2$), 67.7 (d, $J = 6.1$, 2OCH$_2$); $^1$H NMR (500 MHz, CDCl$_3$): $0.91$ (t, $J = 6.9$, 6H, 2CH$_3$), 1.33–1.38 (m, 11H, 4CH$_2$, CH$_3$), 1.66–1.71 (m, 4H, 2CH$_2$), 3.99–4.05 (m, 4H, 2OCH$_2$), 4.08–4.14 (m, 2H, OCH$_2$). [M+Na]$^+$ found: 289.1544, [M+Na]$^+$ calculated: 289.1545.

3.4.6. Dipentyl-proplyphosphate (8b)

$^{31}$P NMR (202.4 MHz, CDCl$_3$): $-0.70$; $^{13}$C NMR (125.7 MHz, CDCl$_3$): 10.0 (s, CH$_3$), 13.9 (s, 2CH$_3$), 22.2 (s, 2CH$_2$), 23.6 (d, $J = 6.9$, CH$_2$), 27.6 (s, 2CH$_2$), 30.0 (d, $J = 6.8$, 2CH$_2$), 67.6 (d, $J = 6.0$, 2OCH$_2$), 69.1 (d, $J = 6.0$, OCH$_2$); $^1$H NMR (500 MHz, CDCl$_3$): $0.91$ (t, $J = 7.1$, 6H, 2CH$_3$), 0.97 (t, $J = 7.4$, 3H, CH$_3$), 1.32–1.38 (m, 8H, 4CH$_2$), 1.66–1.74 (m, 6H, 3CH$_2$), 3.97–4.05 (m, 6H, 3OCH$_2$). [M+Na]$^+$ found: 303.1701, [M+Na]$^+$ calculated: 303.1701.

3.4.7. Dipentyl-isoproplyphosphate (8c)

$^{31}$P NMR (202.4 MHz, CDCl$_3$): $-1.62$; $^{13}$C NMR (125.7 MHz, CDCl$_3$): 13.9 (s, 2CH$_3$), 22.2 (s, 2CH$_2$), 23.6 (d, $J = 5.0$, 2CH$_3$), 27.6 (s, 2CH$_2$), 30.0 (d, $J = 7.1$, 2CH$_2$), 67.5 (d, $J = 6.2$, 2OCH$_2$), 72.3 (d, $J = 5.9$, OCH$_2$); $^1$H NMR (500 MHz, CDCl$_3$): $0.91$ (t, $J = 6.9$, 6H, 2CH$_3$), 1.26–1.40 (m, 14H, 4CH$_2$, 2CH$_3$), 1.66–1.72 (m, 4H, 2CH$_2$), 4.00–4.05 (m, 4H, 2OCH$_2$), 4.61–4.68 (m, 1H, OCH). [M+Na]$^+$ found: 303.1703, [M+Na]$^+$ calculated: 303.1701.
3.4.8. Dipentyl-butylphosphate (8d)

$^{31}$P NMR (202.4 MHz, CDCl$_3$) δ: −0.62; $^{13}$C NMR (125.7 MHz, CDCl$_3$) δ: 13.6 (s, CH$_3$), 13.9 (s, 2 CH$_3$), 18.7 (s, CH$_2$), 22.2 (s, 2CH$_2$), 27.6 (s, 2CH$_2$), 30.0 (d, J = 6.8, 2CH$_2$), 32.2 (d, J = 6.8, CH$_2$), 67.4 (d, J = 6.1, OCH$_2$), 67.7 (d, J = 6.1, 2OCH$_2$); $^{1}$H NMR (500 MHz, CDCl$_3$) δ: 0.93 (t, J = 7.2, 6H, 2CH$_3$), 0.96 (t, J = 7.7, 3H, CH$_3$), 1.33–1.40 (m, 8H, 4CH$_2$), 1.41–1.46 (m, 2H, CH$_2$), 1.67–1.72 (m, 6H, 3CH$_2$), 4.03–4.08 (m, 6H, 3OCH$_2$). [M+Na]$^+$ found: 317.1857, [M+Na]$^+$ calculated: 317.1858.

For the NMR spectra of the products, see the Supplementary Materials.

3.5. Theoretical Calculations

DFT computations at the M062X/6–311+G (d,p) level of theory were performed considering the solvent effect of the corresponding alcohol using the SMD solvent model with the Gaussian 09 program package [21–23]. The geometries of the molecules were optimized in all cases, and frequency calculations were also performed to ensure that the structures were in a local minimum or in a saddle point. The conformations of the reported structures were determined by conformational analysis. The solution-phase enthalpies and Gibbs free energies were obtained by frequency calculations as well. The H and G values obtained were given under 473 K, the corrected total energies of the molecules were taken into account. Entropic and thermal corrections were evaluated for isolated molecules using standard rigid rotor harmonic oscillator approximations, that is, the enthalpy and the Gibbs free energy were taken as the “sum of electronic and thermal free energies” printed in a Gaussian 09 vibrational frequency calculation. The standard state correction was taken into account. The transition states were optimized with the QST3 or the TS (Berny) method. The transition states were identified by having one imaginary frequency in the Hessian matrix, and IRC calculations were performed in order to prove that the transition states connected two corresponding minima.

For the details of the calculations, see the Supplementary Materials.

4. Conclusions

An MW-assisted protocol was developed for the esterification of monoalkylphosphates. The first step was the chemoselective direct esterification in the presence of [bmim][BF$_4$] as the catalyst. The second step was an alkylation esterification. Even phosphoric triesters with different alkyl groups were prepared. Additionally, quantum chemical computations showed that the activation enthalpy was high (on average 156.6 kJ mol$^{-1}$) for the monoesters, and even higher for the diesters, which agreed with the observed experimental data. In addition, the determining effect of entropy was pointed out in the esterifications. It is also noted that regarding direct esterifications, the overall energetics for the formation of diesters was more favorable than that for the formation of the triesters. As a whole, a new method was developed for the preparation of phosphate triesters avoiding the use of P-chlorides as the starting materials. The first, direct MW-assisted esterification step may be regarded as “green”. The experimental data were supported by theoretical calculations.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/molecules27154674/s1. $^{31}$P, $^{13}$C and $^{1}$H NMR spectra of the products, as well as the details for the quantum chemical calculations: coordinates, energetics and imaginary frequencies for the relevant species.

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References
1. De la Hoz, A.; Diaz-Ortiz, A.; Prieto, P. Microwave-assisted green organic synthesis. In Alternative Energy Sources for Green Chemistry; Stefanidis, G., Stankiewicz, A., Eds.; Royal Society of Chemistry: London, UK, 2016; Volume 47, pp. 1–33. [CrossRef]
2. Nasir Baig, R.B.; Varma, R.S. Alternative energy input: Mechanochemical, microwave and ultrasound-assisted organic synthesis. Chem. Soc. Rev. 2012, 41, 1559–1584. [CrossRef] [PubMed]
3. Nain, S.; Singh, R.; Ravichandran, S. Importance of Microwave heating in organic synthesis. Adv. J. Chem. A 2019, 2, 94–104. [CrossRef]
4. Sharma, N.; Sharma, U.K.; Van der Eycken, E.V. Microwave-assisted organic synthesis: Overview of recent applications. In Green Techniques for Organic Synthesis and Medicinal Chemistry, 2nd ed.; Zhang, W., Cue, B.W., Eds.; JohnWiley & Sons Ltd.: New York, NY, USA, 2018; pp. 441–468. [CrossRef]
5. Romanova, N.; Gravis, A.G.; Zyk, N.V. Microwave irradiation in organic synthesis. Russ. Chem. Rev. 2005, 74, 969–1013. [CrossRef]
6. Jolly, J. Microwave assisted synthesis in organic chemistry: A review of recent advances. Int. J. Chem. 2012, 4, 29–43. [CrossRef]
7. Dudley, G.B.; Stiegman, A.E. Changing perspectives on the strategic use of microwave heating in organic synthesis. Chem. Rec. 2018, 18, 381–389. [CrossRef] [PubMed]
8. Keglevich, G.; Mucsi, Z. Interpretation of the rate enhancing effect of microwaves. In Microwave Chemistry; Cravotto, G., Carnaroglio, D., Eds.; De Gruyter: Berlin, Germany, 2017; pp. 53–64. [CrossRef]
9. Keglevich, G.; Novák, T.; Vida, L.; Greiner, I. Microwave irradiation as an alternative to phase transfer catalysis in the liquid-solid phase, solvent-free C-alkylation of active methylene containing substrates. Green Chem. 2006, 8, 1073–1075. [CrossRef]
10. Keglevich, G.; Szekrényi, A. Eco-friendly accomplishment of the extended Kabachnik-Fields reaction; a solvent- and catalyst-free microwave-assisted synthesis of α-aminophosphonates and α-aminophosphine oxides. Lett. Org. Chem. 2008, 5, 616–622. [CrossRef]
11. Kovačs, T.; Urbanics, A.; Csatlós, F.; Keglevich, G. A study on the deoxygenation of trialkyl-, dialkyl-phenyl- and alkyl-diphenyl phosphine oxides by hydroxilanes. Heterotat. Chem. 2017, 28, e21376. [CrossRef]
12. Keglevich, G.; Jablonkai, E.; Balázs, L.B. A “green” variation of the Hirao reaction: The P–C coupling of diethyl phosphite, alkyl phenyl-H-phosphinates and secondary phosphine oxides with bromoarenes using a P-ligand-free Pd(OAc)₂ catalyst under microwave and solvent-free conditions. RSC Adv. 2014, 4, 22808–22816. [CrossRef]
13. Keglevich, G.; Forintos, H.; Körtvélyesi, T. Synthesis and reactions of β-oxophosphoranes/ylides containing a cyclic or acyclic P-moiety. Curr. Org. Chem. 2004, 8, 1245–1261. [CrossRef]
14. Quin, L.D. A Guide to Organophosphorus Chemistry; Wiley & Sons: New York, NY, USA, 2000; ISBN 978-0-471-31824-8.
15. Barton, D.; Ollis, W.D. (Eds.) Comprehensive Organic Chemistry, Phosphorus Compounds; Pergamon: Oxford, UK, 1979; Volume 2.
16. Kiss, N.Z.; Keglevich, G. Microwave-assisted direct esterification of cyclic phosphinic acids in the presence of ionic liquids. Tetrahedron Lett. 2016, 57, 971–974. [CrossRef]
17. Harsági, N.; Henyecz, R.; Ábrányi-Balogh, P.; Drahos, L.; Keglevich, G. Microwave-assisted ionic liquid-catalyzed selective monoesterification of alkylphosphonic acids—An experimental and a theoretical study. Molecules 2021, 26, 5303. [CrossRef] [PubMed]
18. Harsági, N.; Kiss, N.Z.; Keglevich, G. P-Chloride-free synthesis of phosphoric esters: Microwave-assisted esterification of alkyl- and dialkyl phosphoric ester-acids obtained from phosphorus pentoxide. Synthesis 2022, 54, 3047–3054. [CrossRef]
19. Mucsi, Z.; Kiss, N.Z.; Keglevich, G. A quantum chemical study on the mechanism and energetics of the direct esterification, thioesterification and amidation of 1-hydroxy-3-methyl-3-phospholene 1-oxide. RSC Adv. 2014, 4, 11948–11954. [CrossRef]
20. Zwierzak, A. Phase-transfer-catalysed phosphorylation of alcohols in a two-phase system. Synthesis 1976, 305–306. [CrossRef]
21. Frisch, M.J.; Trucks, G.W.; Schlegel, H.B.; Scuseria, G.E.; Robb, M.A.; Cheeseman, J.R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G.A.; et al. Gaussian 09, Revision D.01; Gaussian, Inc.: Wallingford, CT, USA, 2009.
22. Zhao, Y.; Truhlar, D.G. The M06 suite of density functionals for main group thermochemistry, thermochemical kinetics, noncovalent interactions, excited states, and transition elements: Two new functionals and systematic testing of four M06-class functionals and 12 other functionals. Theor. Chem. Acc. 2008, 120, 215–241. [CrossRef]
23. Petersson, G.A.; Bennett, A.; Tensfeldt, T.G.; Al-Laham, M.A.; Shirley, W.A. A complete basis set model chemistry. I. The total energies of closed-shell atoms and hydrides of the first-row elements. J. Chem. Phys. 1988, 89, 2193–2218. [CrossRef]