A Mechanistic Study on the Formation of Dronic Acids

Péter Ábrányi-Balogh 1,*, István Greiner 2* and György Keglevich 3,*

1 Research Centre for Natural Sciences, Medicinal Chemistry Research Group, 1117 Budapest, Hungary
2 Gedeon Richter Plc., 1475 Budapest, Hungary; i.greiner@richter.hu
3 Department of Organic Chemistry and Technology, Budapest University of Technology and Economics, 1521 Budapest, Hungary
* Correspondence: abranyi-balogh.peter@ttk.mta.hu (P.-B.); keglevich.gyorgy@vbk.bme.hu (G.K.); Tel.: +36-1-463-1111 (ext. 5883) (G.K.)

Abstract: Dronic acid derivatives, important drugs against bone diseases, may be synthesized from the corresponding substituted acetic acid either by reaction with phosphorus trichloride in methanesulfonic acid as the solvent or by using also phosphorous acid as the \( P \)-reactant if sulfolane is applied as the medium. The energetics of the two protocols were evaluated by high-level quantum chemical calculations on the formation of fenidronic acid and benzidronic acid. The second option, involving \((HO)_2P-O-PCl_2\) as the nucleophile, was found to be more favorable over the first variation, comprising \(Cl_2P-O-SO_2Me\) as the real reagent, especially for the case of benzdronate.

Keywords: dronic acid; carboxylic acid; phosphorus trichloride; phosphorous acid; solvents; mechanism; calculations

1. Introduction

Hydroxymethylenebisphosphonic (dronic) acid derivatives include important representatives that are used in the treatment of bone illnesses, such as osteoporosis, the Paget disease, and tumor-induced hypercalcemia [1–4]. The first-generation agents (etidronate, clodronate, and tiludronate) were only moderately potent, allowing a narrow therapeutic window regarding the desired inhibition and impairment of bone mineralization. Hence, they were replaced by second-generation (\(N\)-aliphatic) drugs, such as pamidronate, alendronate, and ibandronate [5–7], and third-generation (\(N\)-heterocyclic) species, such as risedronate and zoledronate, in clinical use [8,9]. The most important derivatives are shown in Figure 1.

The general method for the synthesis of dronic acid derivatives involves the reaction of the corresponding substituted acetic acid with phosphorus trichloride (PCl\(_3\)) or with PCl\(_3\) and phosphorous acid (P(OH)\(_3\)) in different solvents. The optimum conditions (molar ratios, solvent, temperature, and reaction time) as well as the role of the reagents and the mechanism were not described. Moreover, the purity of the products was not clarified and hence misleading yields were published. Keglevich, Grün, and Greiner, together with co-workers, investigated the chemistry of dronic derivatives in detail [4]. The optimum conditions were explored on the basis of the putative mechanisms substantiated by us [10]. According to this, for carrying out the reactions in methanesulfonic acid (MSA), there was the need for 3–3.2 equivalents of the PCl\(_3\). It was assumed that 1 equivalent of the PCl\(_3\) converts the substituted acetic acid to the corresponding chloride, while 2 equivalents are needed to provide the two P-functions. Both PCl\(_3\) and Cl\(_2\)P-O-SO\(_2\)Me (formed from PCl\(_3\) and MSA) were assumed to be the nucleophiles [10]. At the same time, applying sulfolane as the solvent, there was a need for at least 2 equivalents of both PCl\(_3\) and P(OH)\(_3\). In this case, Cl\(_2\)P-O-P(OH)$_2$ was found to be the nucleophile [10].
Results of the synthesis of the most important dronic acid derivatives applying the above-mentioned methods (PCl$_3$/MSA or PCl$_3$/H$_3$PO$_4$/sulfolane) are summarized in Table 1. On the basis of the diverse yields of the two methods, it is not possible to judge which one is to be preferred. It was, however, unambiguous that using sulfolane, a 2:3 or 2:4 ratio of PCl$_3$ and P(OH)$_3$, was in most cases advantageous.

Table 1. Preparative results of more important dronic acid derivatives.

| R          | Reagent(s) (equiv.) | Solvent | T (°C) | Workup                                      | Product                        | Purity (%) | Yield (%) | Ref. |
|------------|---------------------|---------|--------|---------------------------------------------|--------------------------------|------------|-----------|------|
| (CH$_2$)$_2$NH$_2$ | PCl$_3$ (3.2)       | MSA     | 75     | pH→1.8 purif. crystallization               | Pamidronate Na·2H$_2$O         | 99         | 57        | [11] |
|            | PCl$_3$/H$_3$PO$_4$ (2:2) | Sulfolane | 75     |                                              | Pamidronic acid                | 100        | 63        | [11] |
| (CH$_2$)$_3$NH$_2$ | PCl$_3$ (3.2)       | MSA     | 75     | pH→1.8 purif. pH→4.3 crystallization        | Alendronate Na·3H$_2$O         | 93         | 58        | [12] |
|            | PCl$_3$/H$_3$PO$_4$ (2:2; 3:2) | Sulfolane | 75     |                                              | Alendronate Na·3H$_2$O         | 100/99     | 46/52     | [13] |
| (CH$_2$)$_2$NMe$^a$Pent | PCl$_3$ (3.2)       | MSA     | 75     | pH→2 purif. pH→2 precipitation, digestion (MeOH) | Ibandronate Na                  | 99         | 46        | [12] |
|            | PCl$_3$/H$_3$PO$_4$ (2:2; 2:3; 2:4) | Sulfolane | 75     |                                              | Ibandronate 2Na                | 100        | 48/66/73  | [14] |
| CH$_2$-2-pyridyl | PCl$_3$ (3.1)       | MSA     | 75     | pH→2 filtration, washing crystallization, digestion (MeOH) | Risedronic acid                | 92         | 74        | [15,16], [17] |
|            | PCl$_3$/H$_3$PO$_4$ (2:2; 2:3; 2:4) | Sulfolane | 75     |                                              | Risedronic acid·H$_2$O         | 100/100/98 | 58/60/57 | [17] |
| CH$_2$-1-imidazoly | PCl$_3$ (3.1)       | MSA     | 80     | pH→1.8 recrystallization                    | Zoledronic acid                | 98/99      | 46/53     | [15,16] |
|            | PCl$_3$/H$_3$PO$_4$ (2:2; 2:3; 2:4) | Sulfolane | 75     |                                              | Zoledronic acid·2H$_2$O        | 100/99/99  | 74/63/66  | [18] |

As, with a few exceptions, the preparative results of the two methods for the different dronic acid derivatives were not comparable due to unreliable experiments, we wished to evaluate the energetics of the dronate formation on simple models using quantum chemical calculations. The two models selected were the formation of fenidronate and benzidronate from benzoic acid and phenylacetic acid, respectively, or from their derivatives.

2. Results and Discussion
2.1. A Study on the Formation of Fenidronic Acid

To have a simple model for the calculations, the reaction of benzoic acid with P-reagents was chosen. Version A involved the reaction with PCl$_3$ in MSA. Preparative experiments showed that the reaction of benzoic acid with 3.2 equivalents of PCl$_3$ in MSA at 75 °C/day, followed by hydrolysis at 105 °C/4 h, pH adjustment to 1.8 by NaOH/H$_2$O,
and precipitation with methanol afforded the disodium salt of fenidronic acid (fenidronate) in a 46% yield, in a pure form [19]. Version B for the theoretical study comprised the reaction of benzoic acid with \( \text{PCl}_3 \) and \( \text{P(OH)}_3 \) in sulfolane (Scheme 1).

![Scheme 1](image)

**Scheme 1.** Two models for the theoretical computations on fenidronic acid (FD).

Applying 3 equivalents of \( \text{PCl}_3 \) in MSA, benzoic acid itself, benzoyl chloride formed from the benzoic acid, and the mixed anhydride formed from benzoic acid and methane-sulfonyl chloride or from benzoyl chloride and MSA, under the conditions of the reaction may be regarded as the starting substrates undergoing addition of the P-nucleophile. The attacking P-reagents may be \( \text{PCl}_3 \) itself and the \( \text{Cl}_2\text{P-O-SO}_2\text{Me} \) species formed from \( \text{PCl}_3 \) and MSA. The variations outlined are summarized in Scheme 2. The anhydrides were assumed already in the earlier stage of our work [20]. We performed DFT-level computations at the M062X/6-311+G (d,p) level considering the solvent effect of water or DMSO simulating MSA and sulfolane, respectively, using the SMD solvent model with the Gaussian 09 program package. One can see that the most advantageous reaction variations were the ones starting from benzoyl chloride and \( \text{Cl}_2\text{P-O-SO}_2\text{Me} \) or \( \text{PCl}_3 \) as the P-nucleophiles (for the best case, see the framed part of Scheme 2). In any other case, the transition states (\( \text{TS1,2,5,6} \)) required an energy investment of higher than 200 kJ mol\(^{-1}\) and these reactions were more endothermic. It is also noted that starting from all the three benzoic acid derivatives, irrespective of whether the nucleophile is \( \text{PCl}_3 \) or \( \text{Cl}_2\text{P-O-SO}_2\text{Me} \), the intermediates contain a pentavalent pentacoordinated phosphorus atom. At the same time, the intermediate formed from benzoic acid or from the mixed anhydride is presumed to incorporate a three-membered oxaphosphirane ring.

![Scheme 2](image)

**Scheme 2.** Possible starting steps in the reaction of benzoic acid or its derivatives with \( \text{PCl}_3 \) in MSA (the numbers below the TSs mean the corresponding Gibbs free energy of activation).
For the formation of the bis adducts, we chose the energetically most favorable adduct 3 and adduct 4 as the starting intermediates. The protonation of these adducts 3 and 4 on the carbonyl oxygen seemed crucial, as without protonation, no reaction could be observed computationally. It was assumed that the MSA applied in large excess is responsible for the protonation. For the estimation of the protonation energy, we took the gas-phase Gibbs free energy of the proton [21] and took into account the computed Gibbs free energies of MSA and its conjugate base, methanesulfonate. The protonated intermediates ((adduct 3) + H⁺ and (adduct 4) + H⁺) were then reacted with PCl₃ or with Cl₂P-O-SO₂Me (Scheme 3).

The transition states (TS7–TS10) needed a further 85–98 kJ mol⁻¹ energy investment, as compared to the energies of the protonated adducts, and the reactions were endothermic, leading to bis adducts 1–4. The reaction with the lowest activation energy (TS10) was the one between adduct 4 and Cl₂P-O-SO₂Me, leading to bis adduct 4 (see the framed part of Scheme 3). Thereafter, the formation of fenidronic acid from bis adducts 1–4 was calculated. The elimination of HCl and/or MSA on the addition of water took place with an energy release of -390–420 kJ mol⁻¹. This means that the final hydrolysis is highly exothermic and might be the driving force for the whole reaction sequence. We have depicted the energetically most advantageous reaction pathway in Figure 2.

Scheme 3. Possible steps for the formation of bis adducts 1–4 (the numbers below the TSs mean the corresponding Gibbs free energy of activation).

The possible starting materials were assumed to be 2–2 equivalents of PCl₃ and P(OH)₃ in sulfolane, benzoic acid, and benzoyl chloride. As regards the P-nucleophile, Cl₂P-O-P(OH)₂ formed from PCl₃ and P(OH)₃ was regarded as the active agent. At the same time, (HO)₂P-PCI-P(OH)₂ could also be the nucleophile. Moreover, as 1 equivalent of PCl₃ covers the formation of PhC(O)Cl from PhC(O)OH, the involvement of the latter P-nucleophile is more probable. However, to simplify the situation, Cl₂P-O-P(OH)₂ was assumed in the calculations. A part of the possibilities mentioned can be seen in Scheme 4. The lowest Gibbs free energy belonged to the transition state of the reaction of benzoyl chloride and Cl₂P-O-P(OH)₂ (TS13), which resulted in the less endothermic adduct 9 among the adducts in the series (see the framed part of Scheme 4). Adduct 9 is formed by P-C addition and HCl elimination in one single step. On the departure of the HCl molecule from the reaction complex, the adduct is stabilized by further −20.2 kJ mol⁻¹. It is also seen that the -P(OH)₂ moiety of the Cl₂P-O-P(OH)₂ species is more nucleophilic than the -PCI₂ unit.
Figure 2. Gibbs free energy diagram for the formation of fenidronic acid from benzoyl chloride and Cl₂P-O-SO₂Me.

Scheme 4. Possible starting steps in the reaction of benzoic acid (or benzoyl chloride), PCl₃, and P(OH)₃ in sulfolane (the numbers below the TSs mean the corresponding Gibbs free energy of activation.).

The next adduct computed was formed from adduct 9 and a second molecule of Cl₂P-O-P(OH)₂. An important P-OH—O=P hydrogen bridge was present in TS14, with an activation energy of 94.0 kJ mol⁻¹, leading to bis adduct 5 in an exothermic reaction (Scheme 5). Again, the final step in this series was the exothermic hydrolysis. The energetically most advantageous reaction pathway is depicted in Figure 3.
2.2. A Study on the Formation of Benzidronic Acid

After investigating the formation of fenidronic acid, we turned our attention to benzidronic acid. The use of 2 equivalents of PCl$_3$ gave benzidronate in a yield of 36% (Scheme 6). Further adding 1 equivalent of H$_3$PO$_3$, the yield increased to 74%. Applying 3.2 equivalents PCl$_3$ led to a yield of 46%. When there was also 1 equivalent of H$_3$PO$_3$, the yield was 81% [22]. The positive effect of H$_3$PO$_3$ was surprising. The formation of the (HO)$_2$P-O-PCl$_2$ intermediate must be assumed. In MSA as the solvent, there is only a slight chance that PCl$_3$ will react with H$_3$PO$_3$ to provide (HO)$_2$P-O-PCl$_2$, as due to the excess of MSA, the probability of the formation of MeSO$_2$-O-PCl$_2$ is greater. However, the phenylacetyl derivatives may be more capable of reacting with (HO)$_2$P-O-PCl$_2$ present only in a low concentration.
During the calculations, we took into consideration phenylacetyl chloride as the starting component reacting with PCl$_3$ or with Cl$_2$P=O-SMe in MSA (Scheme 7). The transition states (TS15 and TS16) were of 116.1 and 134.7 kJ mol$^{-1}$, respectively. The values were similarly low as in the reaction with benzoyl chloride, although in this case, the route involving PCl$_3$ was the more favorable option (see the framed part of Scheme 7).

Both energetically similar pathways were calculated further. The protonation and formation of the corresponding bis adducts from adducts 10 and 11 was computed assuming both PCl$_3$ and Cl$_2$P=O-SMe as the nucleophiles (Scheme 8). Transition states TS17–TS20 required less (54–71 kJ mol$^{-1}$) further energy investment than those in the analogous steps of fenidronic acid formation, and bis adducts 6–9 had much lower energy levels (between 115 and 165 kJ mol$^{-1}$) as compared to the range of 193–212 kJ mol$^{-1}$ obtained for bis adducts 1–4 (Scheme 3). In this case, again PCl$_3$ was the most favorable reagent (see the framed part of Scheme 8). Notably, taking a look over the energy value of the final dronic acids, one may conclude that the last hydrolysis is again a highly exothermic step (−390–420 kJ mol$^{-1}$). We have depicted the most advantageous reaction pathway in Figure 4.

In the case of the other reaction setup with sulfolane as the solvent, phenylacetyl chloride was reacted with Cl$_2$P=O-P(OH)$_2$ (Scheme 9). The activation energy required for the first and second additions (TS21 and TS22) were lower for both cases than that for the reaction with benzoyl chloride (TS13 and TS14) (75.0 vs. 137.5 kJ mol$^{-1}$ and 52.8 vs. 94.0 kJ mol$^{-1}$), and both steps were found to be exothermic. The HCl elimination in this case led to an energy gain of −43.9 kJ mol$^{-1}$. The final hydrolysis was again highly exothermic. We have shown the plausible reaction pathway in Figure 5.
Scheme 8. Possible steps for the formation of bis adducts 6–9 (the numbers below the TSs mean the corresponding Gibbs free energy of activation).

Figure 4. Gibbs free energy diagram for the formation of benzidronic acid from phenylacetyl chloride and PCl₃.

Scheme 9. Possible steps for the formation of bis adduct 10 (the numbers below the TSs mean the corresponding Gibbs free energy of activation).
The reported yields for benzidronate, in general, were higher than those for fenidronate, which is in accord with the results of the computations suggesting lower activation Gibbs free energies for the formation of benzidronate and steps that are more exothermic before the final hydrolysis. Moreover, in the case of benzidronate, the improving effect of H$_3$PO$_3$ was shown experimentally, suggesting that the formation of the Cl$_2$P-O-P(OH)$_2$ reactant is realistic, and results in increased yields. This is also supported by the lower activation energy in the reaction with Cl$_2$P-O-P(OH)$_2$ as compared to the case with Cl$_2$P-O-SMe as the nucleophile. Notably, in all cases, the acyl chloride was suggested to be the most favorable reactant, implying that the carboxylic acid, in the first step, is transformed by PCl$_3$ to the corresponding chloride.

![Gibbs free energy diagram for the formation of benzidronic acid from phenylacetyl chloride and Cl$_2$P-O-P(OH)$_2$.](image)

**Figure 5.** Gibbs free energy diagram for the formation of benzidronic acid from phenylacetyl chloride and Cl$_2$P-O-P(OH)$_2$.

### 3. Conclusions

The possible mechanistic pathways leading to fenidronic acid and benzidronic acid were computed considering the reaction of benzoic acid or phenylacetic acid and derivatives with PCl$_3$ in MSA or with PCl$_3$/P(OH)$_3$ in sulfolane. It was found that the corresponding acyl chlorides should be considered as the starting compounds and PCl$_3$ or its condensed derivative with MSA or H$_3$PO$_4$ (Cl$_2$P-O-SO$_2$Me or Cl$_2$P-O-P(OH)$_2$, respectively) may be the nucleophile. The multistep formation of the bis adducts was in most cases endothermic, and the exothermic final hydrolyses could be the driving force for the series of reactions. In the case of benzidronic acid, the activation Gibbs free energies were lower for all steps than that for fenidronic acid. It is noteworthy that in the case of using PCl$_3$/P(OH)$_3$ in sulfolane, the formation of the adducts was exothermic. It unambiguously turned out that the setup with PCl$_3$/P(OH)$_3$ in sulfolane involving (HO)$_2$P-O-PCl$_2$ as the nucleophile is the energetically more preferable option. Hence, regarding the synthesis of dronic acid derivatives, the PCl$_3$/P(OH)$_3$/sulfolane method is recommended.
4. Computational Protocol

DFT-level computations at the M062X/6-311+G (d,p) level were performed considering the solvent effect of water (\(\varepsilon = 78.4\)) or DMSO (\(\varepsilon = 46.8\)) simulating MSA (no \(\varepsilon\) is available). However, the physical properties of MSA are similar to that of sulfuric acid (\(\varepsilon_{\text{H}_2\text{SO}_4} = 84\)) [23,24] and sulfolane (\(\varepsilon = 43.4\)) [25] on using the SMD solvent model with the Gaussian 09 program package. The actual solvents were chosen based on their similar dielectric constants. The popular M062x method was chosen for its known accuracy for main group thermochemistry and the computation of barrier heights [26]. The geometries of the molecules were optimized in all cases (see Supplementary Material), and frequency calculations were also performed to assure that the structures are in a local minimum or in a saddle point. This was followed by single-point measurements at the M062X/6-311++G (3df,3pd) level, which resulted in the energy values presented in Table S1 and used for the figures of the manuscript. The solution-phase Gibbs free energies were obtained by frequency calculations as well. The G values obtained were given under standard conditions, and 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 Gibbs free energy was taken as the “sum of electronic and thermal free energies” printed in a Gaussian 09 vibrational frequency calculation. Standard state correction was taken into account. The transition states were optimized with the QST3 or the TS (Berny) method. Transition states were identified by having one imaginary frequency in the Hessian matrix and connecting two corresponding minima.

Supplementary Materials: The best preparative procedures, together with compound characterization; details of theoretical calculations: Table S1: X, Y, Z Coordinates of the computed structures (columns are in this order), Table S2: Energy (Hartree) and entropy (cal molK–1) values obtained for the computations together with imaginary 2150 frequencies (1/s).

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