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Toward an Understanding of the Hydrolysis of Mg−PP$_i$. An *ab Initio* Study of the Isomerization Reactions of Neutral and Anionic Mg−Pyrophosphate Complexes

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Abstract: *Ab initio* calculations were performed to study the stability of various pyrophosphate species in the gas phase: $H_4P_2O_7$, $H_3P_2O_7^-$, $H_2P_2O_7^{2-}$, $HP_2O_7^{3-}$, $P_2O_7^{4-}$, and their complexes with Mg^{2+}. It is found that the metal cation allows the existence of highly charged anions in the gas phase. We also study the isomerization reactions $Mg{\cdot}H_2P_2O_7 \rightarrow (H_2PO_4{\cdot}Mg{\cdot}PO_3)$, $(Mg{\cdot}HP_2O_7)^- \rightarrow (HPO_4{\cdot}Mg{\cdot}PO_3)^-$, and $(Mg{\cdot}P_2O_7)^{2-} \rightarrow (PO_4{\cdot}Mg{\cdot}PO_3)^{2-}$, at the self-consistent-field (SCF) and second-order perturbation (MP2) levels of the theory, using a 6-31+G** basis set with diffuse and polarization functions. Other basis sets, including one of valence triple ζ plus polarization (vTZP) quality, were employed to check for the convergence of the results. It is found that the same mechanism occurs for the isomerizations of the three species: one of the P−O bridging bonds of the reactant is longer than the other, and the route to the products proceeds through its elongation. This asymmetry is induced by the metal cation in the case of the evenly charged anions. In all cases the metal cation coordinates the transition states and the leaving groups. The structures found for the complexes $(H_2PO_4{\cdot}Mg{\cdot}PO_3)$, $(HPO_4{\cdot}Mg{\cdot}PO_3)^-$, and $(PO_4{\cdot}Mg{\cdot}PO_3)^{2-}$ are different from those reported previously, the metal cation being enclosed by the two phosphates. The activation barrier increases with the charge of the anion, from $\Delta G^{\circ\ddagger} = 5.6$ kcal/mol for the neutral complex $Mg{\cdot}H_2P_2O_7$, to $\Delta G^{\circ\ddagger} = 10.4$ kcal/mol for the monoanion $(Mg{\cdot}HP_2O_7)^-$, to $\Delta G^{\circ\ddagger} = 13.5$ kcal/mol for the dianion $(Mg{\cdot}P_2O_7)^{2-}$. The positive value found for the energy of the isomerization $(Mg{\cdot}P_2O_7)^{2-} \rightarrow (PO_4{\cdot}Mg{\cdot}PO_3)^{2-}$, $\Delta G^{\circ\ddagger} = 1.8$ kcal/mol, predicts the synthesis to be spontaneous in the gas phase, opposite of what occurs in the aqueous solution. This result supports the view that the hydration energy makes a large contribution to the energy of hydrolysis. The gas-phase hydrolysis reaction $H_2O + Mg^{2+} + H_2P_2O_7^{2-} \rightarrow Mg^{2+} + H_2PO^{4-} + H_2PO^{4-}$ is also studied as a multistep reaction, involving the isomerization of $H_2O + (Mg{\cdot}H_2P_2O_7) \rightarrow H_2O + (PO_3{\cdot}Mg{\cdot}H_2PO_4)$ as an intermediate step. It is found that the equilibrium in the gas phase yields $H_2PO_4{\cdot}Mg{\cdot}H_2PO_4$ as the final species; an energy input is required for separating the metal cation from the phosphate anions.

1. Introduction

Due to the ubiquity of the hydrolysis of phosphoanhydryde bonds in biosynthetic processes,[1] a large effort has been made to understand the various intra- and intermolecular contributions to the energy of the hydrolysis reactions. Since the early theories about the "high energy" of the P∼O−P bond, which considered only intramolecular effects,[2−5] a number of data have been pointing to the relevance of intermolecular interactions:[6] The results obtained calorimetrically by George et al.[7] for the hydrolysis reactions of various pyrophosphate species, and the changes of the observed equilibrium constants, K_{obs}, for the hydrolysis of pyrophosphate in solution when the reaction occurs in a mixture of an organic aprotic solvent (e.g., dimethyl sulfoxide) with water,[6,8−11] have been used as arguments to support the proposal of George et al.[7] that the difference in hydration energies between reactants and products has a major contribution to the free energies of the hydrolysis reactions. Also, the only reported numerical simulation of pyrophosphate in aqueous solution[12] shows important differences in the hydration layers of $H_4P_2O_7$ and H_3PO_4, but is not accurate enough to yield quantitative results of the hydration energies.

On the other hand, there have been several theoretical studies to estimate the heat of the reaction $H_4P_2O_7 + H_2O \rightarrow H_3PO_4 + H_3PO_4$ in the gas phase.[13−18] Although the first attempts yielded

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values ranging from −13.6 kcal/mol to −0.4 kcal/mol, the most recent reports[17,18] exhibit a convergence to thermoneutrality and show that the previous estimates were lacking the effect of intramolecular hydrogen bonding, which stabilizes the $H_4P_2O_7$ molecule. This result seemed to corroborate George's hypothesis,[7] but when the anions are considered, the behavior is opposite the measurements in aqueous solution: the estimates of the enthalpies $\Delta H°$ predict the reactions to be more exothermic as the charge of the anion increases, with the exception of the hydrolysis of $H_3P_2O_7^-$ which is endothermic. This last result is due to the existence of intramolecular hydrogen bonds in the monoanion and the lack of charge in one of the resulting orthophosphates, H_3PO_4. The estimates for the free energies $\Delta G°$ have the same trend.[17,18] The main criticism to the calculations of anions is that they are expected to be unstable in the gas phase, due to their low ionization energies,[16−18] whereas in the aqueous solution they are stabilized by hydration and counterions: the free energy depends on the pH and the concentration of magnesium.[6−11] The possible existence of multivalent anions in the gas phase is interesting to the understanding of enzymatic catalysis because the microenvironment at the active sites is different from the bulk of the solution.[19]

Furthermore, there is compelling evidence[20−23] that the biologically active pyrophosphate species is the hydrated complex with magnesium $(Mg\cdot(H_2O)_4\cdot P_2O_7)^{2-}$ and the mechanism proposed for the hydrolysis in the active site of the enzyme is a nucleophilic attack of a deprotonated metal bound water molecule at the phosphorus center, which yields *cis*-[Mg-(Pi)$_2$], through a pentacoordinated intermediate.[24,25] This is to be compared with a recent extensive study of the $Mg\cdot H_2P_2O_7$ complex, in which Ma et al.[26] propose a mechanism for the hydrolysis of pyrophosphate in the gas phase through a metaphosphate intermediate. Both schemes involve the elongation of one of the P−O bonds with the bridging oxygen. However, it is worth noting that the relevant species in aqueous solution are the anions $(Mg\cdot HP_2O_7)^-$ and $(Mg\cdot P_2O_7)^{2-}$, whereas the neutral species is virtually nonexistent at pH 7.0 and higher.[27]

To allow for a better understanding of the role of magnesium and the behavior of the negatively charged species, in this work we present *ab initio* calculations of the magnesium−pyrophosphate complexes $Mg\cdot H_2P_2O_7$, $(Mg\cdot HP_2O_7)^-$, and $(Mg\cdot P_2O_7)^{2-}$ to look into the stabilization of the corresponding pyrophosphate anions $H_2P_2O_7^{2-}$, $HP_2O_7^{3-}$, and $P_2O_7^{4-}$ by means of an analysis of the molecular orbital energies. We also compute the enthalpies and the energy barriers of the isomerization reactions

$$(Mg\cdot H_2P_2O_7) \rightarrow (H_2PO_4\cdot Mg.PO_3) \qquad (1)$$

$$(Mg\cdot HP_2O_7)^- \rightarrow (HPO_4\cdot Mg\cdot PO_3)^- \qquad (2)$$

$$(Mg\cdot P_2O_7)^{2-} \rightarrow (PO_4\cdot Mg\cdot PO_3)^{2-} \qquad (3)$$

to test an extension of the mechanism proposed by Ma et al.[26]

To show that these are relevant intermediate steps in the gas-phase hydrolysis of the corresponding Mg−pyrophosphate complexes, we study the four-step reaction

$$H_2O + Mg^{2+} + H_2P_2O_7^{\ 2-} \rightarrow H_2O + (Mg\cdot H_2P_2O_7) \qquad (4)$$

$$H_2O + (Mg\cdot H_2P_2O_7) \rightarrow H_2O + (H_2PO_4\cdot Mg\cdot PO_3) \qquad (5)$$

$$H_2O + (H_2PO_4\cdot Mg\cdot PO_3) \rightarrow (H_2PO_4\cdot Mg\cdot H_2PO_4) \qquad (6)$$

$$(H_2PO_4\cdot Mg\cdot H_2PO_4) \rightarrow Mg^{2+} + H_2PO_4^{\ -} + H_2PO_4^{\ -} \qquad (7)$$

2. Computational Details

The GAUSSIAN-92/DFT program[28] was employed to perform *ab initio* calculations with its standard 6-31+G** basis set: one diffuse function of s symmetry on each non-hydrogen atom, one s polarization function on hydrogen, and p and d polarization functions on each non-hydrogen atom. Geometry optimizations were performed at the SCF/6-31+G** level of theory for all the molecular species studied. Because the 6-31+G** basis set is not yet saturated, an analysis of convergence was made with various other basis sets: the internal 6-31G, 6-31G*, and 6-31G** of the HONDO 8.5 program.[29] This latter code was also used to perform calculations with its internal effective core potentials which permitted the use of other basis sets: valence double ζ with polarization (vDZP) and valence triple ζ plus polarization (vTZP). As a further test of convergence of the structure, the SCF/6-31G optimal geometries were used as the starting points for MP2/6-31G optimizations.

The estimates of the energies ΔE_e^{SCF} of the isomerizations 1−3 were computed with the above-mentioned basis sets, using the SCF/6-31+G** optimized geometries. The energy barriers were computed with the 6-31+G** basis, and the correlation energy was computed at the MP2/6-31+G** level.

3. Results and Discussion

As stated in the previous section, the convergence of the structural parameters was tested by performing geometry optimizations with various basis sets. The deviations with respect to the SCF/6-31+G** geometries were found to be small for all molecular species studied. The corresponding data on bond lengths, bond angles, and dihedral angles of SCF/6-31+G** are given as Supporting Information. Thus, unless otherwise stated, the geometries discussed in this section are SCF/6-31+G** optimals.

3.1. Pyrophosphate Equilibrium Structures. The structures obtained in this work for $H_4P_2O_7$, $H_2P_2O_7^{2-}$, and $HP_2O_7^{3-}$ are in good agreement with those reported previously[17,18] (Figure 1). However, for the monoanion $H_3P_2O_7^-$ a different configuration is found (Figure 2): instead of a strong single hydrogen bond between an oxygen in one moiety and a hydrogen in the other[17,18] (structure **2b**), the oxygen makes a bifurcated hydrogen bond with the two hydrogens of the opposite moiety (structure **2a**). The structure **2a** has an energy 3.3 kcal/mol lower than

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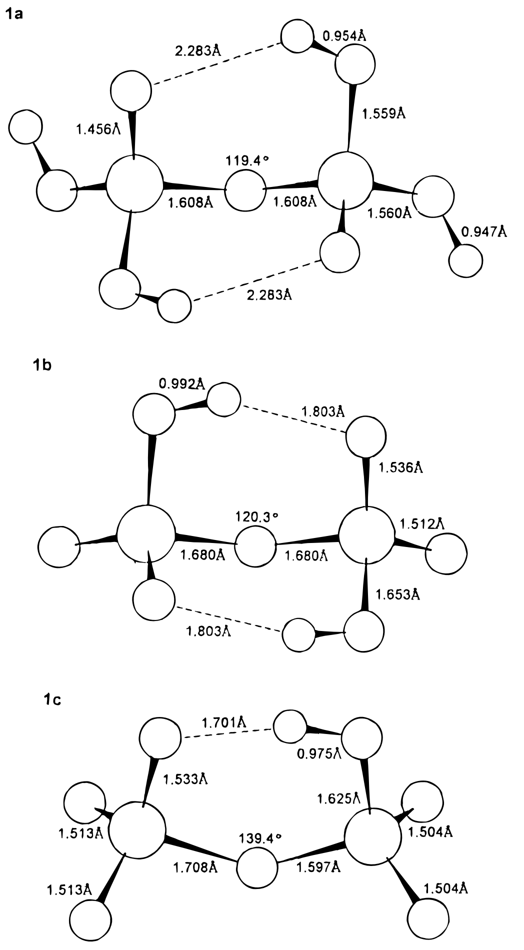

Figure 1. Optimal structures found for $H_4P_2O_7$ (**1a**), $H_2P_2O_7^{2-}$ (**1b**), and $HP_2O_7^{3-}$ (**1c**). They are stabilized by intramolecular hydrogen bonding.

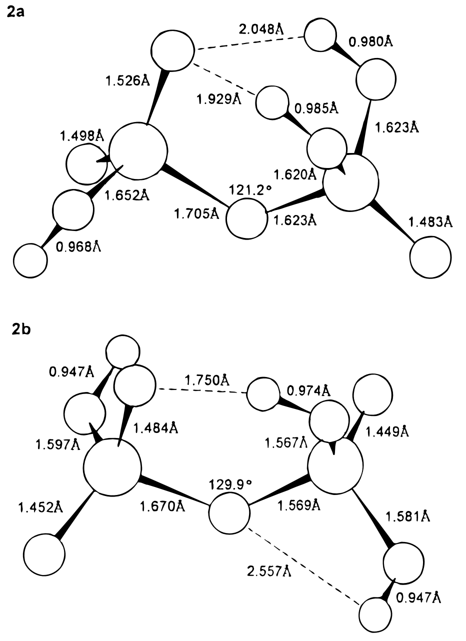

Figure 2. Optimal structures of $H_3P_2O_7^-$: structure **2b** has been reported in the literature[17,18] as the global minimum, but structure **2a** has an energy 3.3 kcal/mol lower (SCF/6-31+G**). It is stabilized by a double hydrogen bond.

structure **2b**, and its P−O−P bond angle is more acute, 121° vs 130°. This result does not invalidate the conclusion that the hydrolysis is endothermic[17,18] (with $\Delta E_e^{SCF} = 22.3$ kcal/mol), but shows that the current methods for geometry optimization have limitations. This fact encouraged us to make a more thorough study of the geometries of Mg−pyrophosphate complexes and their isomerization products (see below).

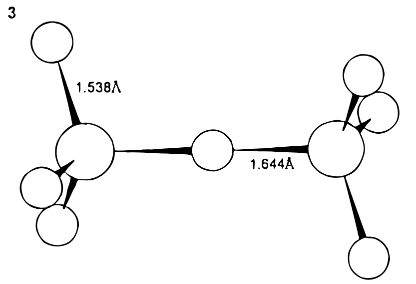

Figure 3. Optimal structure found for $P_2O_7^{4-}$. The P−O−P angle is linear, $\phi = 180°$, due to the strong electrostatic repulsion. This molecular species should not be stable in the gas phase.

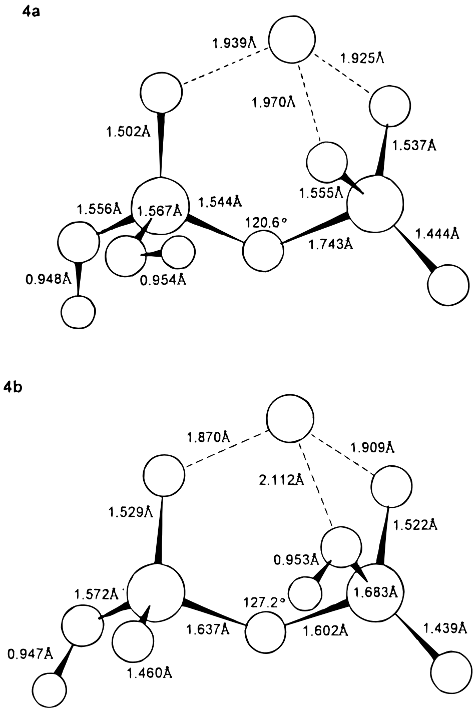

Figure 4. Optimal structure of $Mg{\cdot}H_2P_2O_7$: structure **4a** is the same as found by Ma et al.,[25] with the two hydrogens at the same moiety, whereas structure **4b** has one hydrogen at each moiety and a weak hydrogen bond between moeities. Both structures have an activated P−O bond, and the metal cation coordinates three oxygen atoms.

The quadruply charged anion $P_2O_7^{4-}$ (Figure 3) shows a staggered configuration with a linear P−O−P angle due to the strong electrostatic repulsion, and D_{h3} symmetry. It can be seen that, in the unevenly charged anions $H_3P_2O_7^-$ and $HP_2O_7^{3-}$ (structures **1c** and **2a**,**b**), the electrostatic interactions induce an asymmetry in the bridging P−O bonds and that the P−O−P angles are more acute than in the evenly charged anions.

3.2. Mg−Pyrophosphate Complexes. The $Mg{\cdot}H_2P_2O_7$ complex (Figure 4) has been extensively studied by Ma et al.,[26] and the results presented here are in good agreement with their findings for the equilibrium geometry (structure **4a**): the two hydrogens are located in the same moiety, and the bridging P−O bond of the opposite moiety is longer than the other. The Mg^{2+} cation coordinates three oxygen atoms, and this holds true even for a suboptimal configuration ($\Delta E = 2.7$ kcal/mol above the energy of structure **4a**) with one hydrogen in each moiety (structure **4b**). In this latter configuration a weak hydrogen bond is also present. It is worth noting that the asymmetry of the electrostatic intramolecular interactions of structure **4a** is induced by the Mg^{2+} cation, with the concomitant elongation of one of

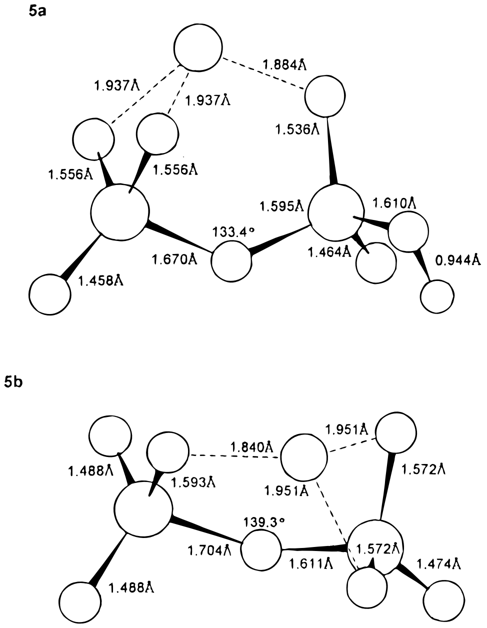

Figure 5. Optimal structures of the anions $(Mg{\cdot}HP_2O_7)^-$ (**5a**) and $(Mg{\cdot}P_2O_7)^{2-}$ (**5b**). Both should be stable in the gas phase. They both have an activated P−O bond, but in the case of the dianion the activated bond corresponds to the moiety that has only one oxygen coordinated by the metal cation.

the P−O bonds, as compared to the corresponding dianion $H_2P_2O_7^{2-}$ (structure **1b**).

The structures found for the anions are shown in Figure 5; both complexes $(Mg{\cdot}HP_2O_7)^-$ (structure **5a**) and $(Mg{\cdot}P_2O_7)^{2-}$ (structure **5b**), have several features in common with the $Mg{\cdot}H_2P_2O_7$ complex: one of the two bridging P−O bonds is longer than the other, and the Mg^{2+} cation coordinates three oxygen atoms. The P−O−P angle increases with the charge of the complex, due to the stronger electrostatic repulsion. In the case of $(Mg{\cdot}HP_2O_7)^-$ (structure **5a**) the difference between the lengths of the bridging P−O bonds is smaller than in the corresponding $HP_2O_7^{3-}$ anion (structure **1c**), 0.075 Å vs 0.111 Å, but the P−O−P angle becomes more acute, 133° vs 139°. The singly charged anion $H_3P_2O_7^-$ also has a P−O bond (structure **2a**) which is 0.082 Å longer than the other, and an even more acute P−O−P angle than the complex $(Mg{\cdot}HP_2O_7)^-$. On the other hand, the metal cation makes $(Mg{\cdot}P_2O_7)^{2-}$ (structure **5b**) quite asymmetric, as compared to $P_2O_7^{4-}$ (structure **3**). An important feature that distinguishes the anion $(Mg{\cdot}P_2O_7)^{2-}$ is that the longest bridging P−O bond corresponds to the moiety with only one oxygen coordinated to the cation, opposite the two other species where the longest bridging bond corresponds to the moiety with two oxygens coordinated to the metal cation.

3.3. Orbital Energies. An important question, even a controversial one, is the very existence of the charged species in the gas phase. An analysis of the energies of the molecular orbitals allows an assessment of the stability of each molecule. The data shown in Table 1 are in agreement with previous results:[17,18] all the occupied orbitals of the pyrophosphates $H_4P_2O_7$, $H_3P_2O_7^-$, and $H_2P_2O_7^{2-}$ have negative energies, whereas $HP_2O_7^{3-}$ and $P_2O_7^{4-}$ have several occupied orbitals with positive energies. Thus, they should not be stable in the gas phase. But when they coordinate to the Mg^{2+} cation, the picture changes dramatically: all occupied orbitals of the complexes $Mg{\cdot}H_2P_2O_7$, $(Mg{\cdot}HP_2O_7)^-$, and $(Mg{\cdot}P_2O_7)^{2-}$ have negative energies, and for $Mg{\cdot}H_2P_2O_7$ even the lowest unoccupied molecular orbital has a negative energy. This shows that the multiply charged anions are stabilized by the counterion.

Table 1. Highest Occupied (HOMO) and Lowest Unoccupied (LUMO) Molecular Orbital Energies (hartrees) Computed at the SCF/6-31+G** Level of Theory[a]

complex	HOMO	LUMO	complex	HOMO	LUMO
$H_4P_2O_7$	−0.49368	0.05013	$P_2O_7^{4-}$	0.23076	0.51471
$H_3P_2O_7^-$	−0.29033	0.17353	$Mg{\cdot}H_2P_2O_7$	−0.43546	−0.03960
$H_2P_2O_7^{2-}$	−0.12476	0.30356	$(Mg{\cdot}HP_2O_7)^-$	−0.21205	0.05514
$HP_2O_7^{3-}$	0.13454	0.39887	$(Mg{\cdot}P_2O_7)^{2-}$	−0.08366	0.16285

[a] The triply and quadruply charged pyrophosphate anions have positive energies and thus should be unstable in the gas phase; however, when coordinated to Mg^{2+}, even the fully deprotonated complex is predicted to be stable in the gas phase.

Table 2. Contributions to the Enthalpies $\Delta H°$ of the Isomerization Reactions of Mg−Pyrophosphate Complexes[a]

reaction	ΔE_e^{SCF}	ΔE_e^{MP2}	ΔE_{th}^{298}	$\Delta H°$	$\Delta E_e^{SCF,\ddagger}$	$\Delta E_e^{MP2,\ddagger}$	$\Delta E_{th}^{298,\ddagger}$	$\Delta H^{\circ\ddagger}$
1	−11.5	−1.5	−0.3	−13.3	10.8	−3.0	−0.9	6.9
2	−6.4	−3.8	0.2	−10.0	17.1	−6.7	1.0	11.4
3	7.1	−2.2	−0.8	4.1	20.2	−5.4	−0.9	13.9

[a] The numbers in the first column correspond to the reactions indicated in the text. ΔE_e^{SCF} is computed at the SCF/6-31+G** level of theory; ΔE_e^{MP2} is the contribution of the correlation energy, computed at the MP2/6-31+G** level of theory; ΔE_{th}^{298} includes the zero-point vibrational energy, ΔE_{ZPE}, and the energies of the various degrees of freedom at $T = 298$ K. The last four columns correspond to the activation barriers. All energies and enthalpies are given in kcal/mol.

Table 3. Reaction and Activation Enthalpies, Entropies, and Free Energies of the Isomerization Reactions of the Mg−Pyrophosphate Complexes, for $T = 298$ K, Computed with Basis 6-31+G**[a]

reaction	$\Delta H°$	$\Delta S°$	$\Delta G°$	$\Delta H^{\circ\ddagger}$	$\Delta S^{\circ\ddagger}$	$\Delta G^{\circ\ddagger}$
1	−13.3	11.9	−16.8	6.9	4.4	5.6
2	−10.0	9.1	−12.7	11.4	3.2	10.4
3	4.1	7.6	1.8	13.9	1.6	13.5

[a] The numbers in the first column correspond to the reactions indicated in the text. The energy barrier is higher for the charged species. For the doubly charged anion the isomerization is spontaneous toward synthesis, opposite the other two cases, which are spontaneous toward splitting. Enthalpies and free energies are in kcal/mol, and entropies in cal/(mol·K).

Therefore, it is physically meaningful to study the isomerization in the gas phase to gain insight into possible mechanisms for the enzymatic catalysis.

3.4. Isomerization Reactions. The calculation of the enthalpies included the zero-point energy, ZPE, and the thermal energy at $T = 298$ K, ΔE^{298}, both computed with a harmonic approximation:

$$\Delta H° = \Delta E_e^{SCF} + \Delta E_e^{MP2} + \Delta E_{ZPE} + \Delta E^{298} \qquad (8)$$

The reference state is at $P = 0.1$ MPa. The various contributions (computed with the 6-31+G** basis) are shown in Table 2. The entropies were also computed with a harmonic approximation, and then the free energies as the difference:

$$\Delta G = \Delta H - T\Delta S \qquad (9)$$

The reaction enthalpies, entropies, and free energies of the three isomerization reactions (computed with the 6-31+G** basis) are presented in Table 3. Ma et al.[26] also computed the activation barrier for the reaction $HP_2O_7^{3-} \rightarrow HPO_4^{2-} + PO_3^-$, using the longest bridging P−O bond as the reaction coordinate, and found the activation energy 3 times as large as that for reaction 1; on this basis, they propose that the metal cation not only produces an asymmetry in the bridging P−O bonds, but it also induces such a strain as to lower the activation barrier. Thus, the longest bridging P−O bond is said to be "activated".

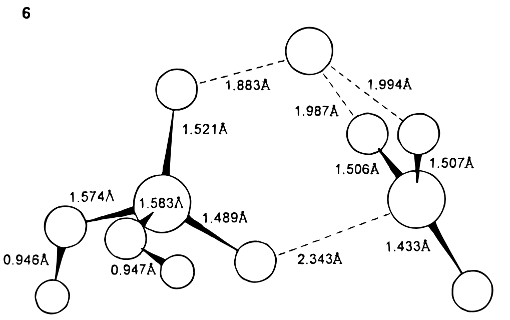

Figure 6. Transition state of the isomerization reaction 1. The metal cation coordinates three oxygen atoms.

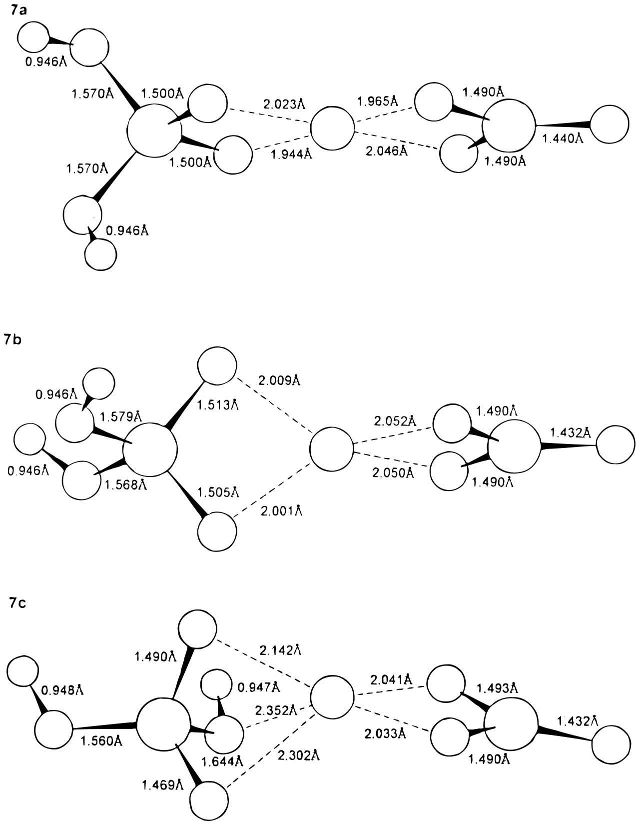

Figure 7. Optimal structures of the ($H_2PO_4{\cdot}Mg{\cdot}PO_3$) complex: structure **7a** is reported by Ma et al.[25] as the global minimum, but structure **7b** has a lower energy (see Table 4). In this latter structure, the four oxygen atoms coordinated by the metal cation lie in two orthogonal planes. Structure **7c** was also tested as the initial configuration for an optimization, and it converged to structure **7b**.

(1) Isomerization of the Neutral Complex: ($Mg{\cdot}H_2P_2O_7$) → ($H_2PO_4{\cdot}Mg{\cdot}PO_3$). This isomerization was extensively studied by Ma et al.[26] with an even-tempered basis set of DZP quality, which employs p orbitals for polarization instead of the usual d orbitals, and does not include diffuse functions. At the SCF level they found an activation energy of $\Delta G^{\circ\ddagger} = 6.7$ kcal/mol, through a transition state in which the Mg^{2+} ion coordinates three oxygen atoms. In this work we found a somewhat lower barrier of $\Delta G^{\circ\ddagger} = 5.6$ kcal/mol (see Table 3) and a shorter value of the reaction coordinate for the transition state, the P−O distance being 2.343 Å instead of 2.474 Å (Figure 6).

On the other hand, the product of the isomerization (Figure 7) found by Ma et al.[26] has a C_{2v} symmetry in which four oxygen atoms lie in the same plane as the Mg (structure **7a**). It is here that our results differ substantially from theirs: the equilibrium geometry found for ($H_2PO_4{\cdot}Mg{\cdot}PO_3$) has the oxygens of the metaphosphate in a plane orthogonal to that of the oxygen of the orthophosphate (structure **7b**). Although we found that Ma's geometry is a local minimum, its energy is 6 kcal/mol higher than that of structure **7b** at both the SCF/6-31+G** and MP2/6-31+G** levels of the theory. Ma's estimate for the energy of the isomerization from structure **4a** to structure **7a** is $\Delta E_e^{SCF} = -8.9$ kcal/mol with the DZP basis,[26] but we found a value of only $\Delta E_e^{SCF} = -5.5$ kcal/mol at the SCF/6-31+G** level of theory. However, when we use structure **7b** instead of **7a**, our prediction of the reaction is $\Delta E_e^{SCF} = -11.5$ kcal/mol, and the estimate of the free energy of the reaction is $\Delta G^\circ = -16.8$ kcal/mol (Table 3).

Table 4. Energy Difference (kcal/mol) between Structures **7a** and **7b**, $\Delta E_{a,b} = E(\mathbf{7a}) - E(\mathbf{7b})$, Computed with Various Basis Sets[a]

	6-31G	6-31G*	6-31G**	6-31+G**	vDZP	vTZP
$\Delta E_{a,b}$	4.7	6.1	6.1	6.0 (5.7)	4.7	5.4

[a] The numbers in parentheses are computed at the MP2 level of theory. The energy of structure **7b** is consistently lower for all basis sets tested.

Table 5. Estimates of the Energy ΔE_e^{SCF} (kcal/mol) for Reaction 1, Using as the Final Product Structures **7a** and **7b** with Various Basis Sets[b]

structure	6-31G	6-31G*	6-31G**	6-31+G**	DZP[a]	vDZP	vTZP
7a	15.7	−7.8	−8.2	−5.5	−8.9	−12.4	−11.
7b	10.9	−13.9	−14.3	−11.5		−17.1	−16.4

[a] This is the value reported by Ma et al.[25] [b] Except the result with basis 6-31G, all values are negative and structure **7b** yields a lower energy.

Being conscious of the difficulty of finding the global minimum, we took care of searching for other possible low-energy geometries, such as structure **7c**. The optimization procedure converged to structure **7b**. Then we computed the energies of the two structures **7a** and **7b** with various basis sets and found the energy of **7b** to be consistently lower for all the basis sets (Table 4).

To test the convergence of the estimate for the energy of the reaction, ΔE_e^{SCF}, we used as final products both structures **7a** and **7b** with various basis sets (Table 5). The 6-31G basis without polarization functions yields a positive value, very different from the results of the others. But even discarding that result, the dispersion of values is somewhat large; however, it remains negative for both structures, and the results with structure **7b** are consistently lower. It is worth noting the smaller absolute value predicted with basis 6-31+G**, which is the only basis with diffuse functions. Because an anion is involved, this should be the most reliable estimate due to a better description of the effects of charge delocalization; the coordination of the oxygen atoms by the metal cation is not only produced by a strong electrostatic interaction, but also by the transference of charge. Thus, the notation $Mg^{2+}{\cdot}H_2P_2O_7{}^{2-}$ and $H_2PO_4{}^{-}{\cdot}Mg^{2+}{\cdot}PO_3{}^{-}$ used by Ma et al.[26] is misleading.

(2). Isomerization of the Monoanionic Complex: ($Mg{\cdot}HP_2O_7$)$^-$ → ($HPO_4{\cdot}Mg{\cdot}PO_3$)$^-$. This isomerization reaction is also energetically favorable, $\Delta G^\circ = -12.7$ kcal/mol, but with a higher activation barrier, $\Delta G^{\circ\ddagger} = 10.4$ kcal/mol (Table 3). The transition state (structure **8a**) and the final product (structure **8b**) are shown in Figure 8. The geometry of the ($HPO_4{\cdot}Mg{\cdot}PO_3$)$^-$ complex is similar to that of the ($H_2PO_4{\cdot}Mg{\cdot}PO_3$) complex.

(3) Isomerization of the Dianionic Complex: ($Mg{\cdot}P_2O_7$)$^{2-}$ → ($PO_4{\cdot}Mg.PO_3$)$^{2-}$. The energy computed for this isomerization reaction is positive, $\Delta G^\circ = 1.8$ kcal/mol (Table 3), showing that it favors the synthesis of pyrophosphate. This result is in agreement with the experimental observation[6] that the synthesis of PP$_i$ depends on pH. The transition state

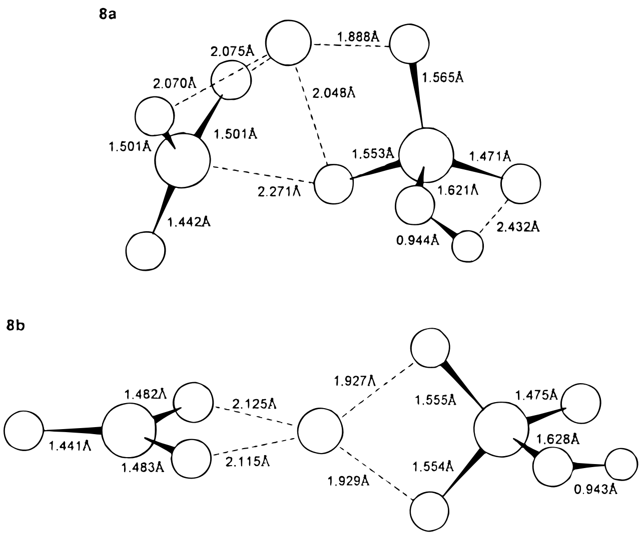

Figure 8. Transition state (**8a**) and final product (**8b**) of the isomerization reaction 2. The metal cation coordinates four oxygen atoms in both cases. In the final product, the four oxygen atoms coordinated by the metal cation lie in two orthogonal planes.

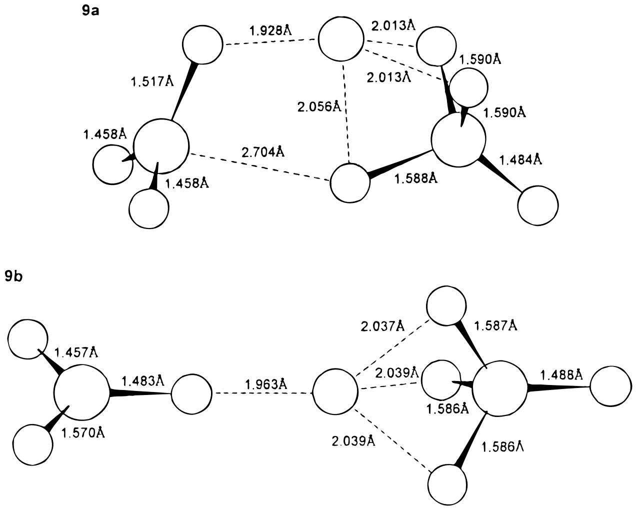

Figure 9. Transition state (**9a**) and final product (**9b**) of the isomerization reaction 3. The metal cation coordinates four oxygen atoms in both cases. In the final product, the metal cation coordinates one oxygen of the metaphosphate and three of the $PO_4{}^{3-}$ moiety.

Table 6. Estimates of the Energies ΔE_e^{SCF} (kcal/mol) for Reactions 2 and 3 with Various Basis Sets[a]

reaction	6-31G	6-31G*	6-31G**	6-31+G**	vDZP	vTZP
2	12.0	−5.9	−5.8	−6.4	−8.8	−8.4
3	17.9	9.9	9.9	7.1	4.8	5.2

[a] Except the result with basis 6-31G, reaction 2 is predicted to be exothermic, whereas reaction 3 should be endothermic.

(structure **9a**) and the final product (structure **9b**) are shown in Figure 9. The geometry of the $(PO_4 \cdot Mg \cdot PO_3)^{2-}$ complex is different from the final complexes of reactions 1 and 2: the Mg^{2+} cation coordinates only one oxygen of the metaphosphate, and three of the $PO_4{}^{3-}$ moiety.

Table 6 shows the ΔE_e^{SCF} energies computed with various basis sets for reactions 2 and 3. As it happens with reaction 1, there is a large dispersion of values. Nevertheless, the energy for reaction 2 is consistently negative (except with basis 6-31G), and the energy for reaction 3 is consistently positive. As stated for reaction 1, the results with basis 6-31+G** should be the most reliable, and the results with basis 6-31G are unreliable.

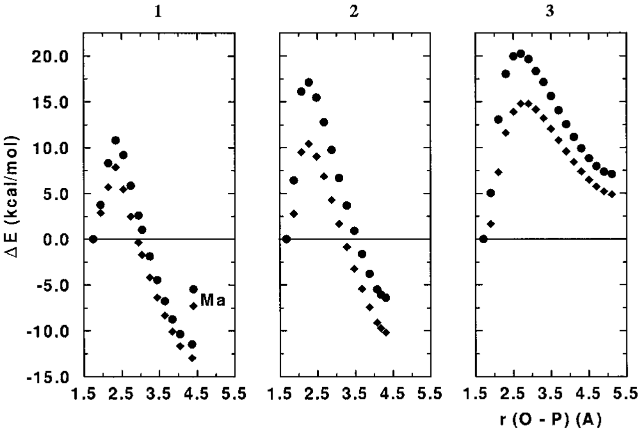

Figure 10. Energy as a function of the reaction coordinate, the activated P−O bond, for isomerizations 1−3. The number at the top of each graph corresponds to the respective reaction. The last point of each graph was obtained from full optimizations using the preceding geometry as the starting point. To check for convergence, several optimizations starting from other points were also performed. The filled circles are for energies computed at the SCF/6-31+G** level and the filled diamonds include the correlation energy at the MP2/6-31+G** level. In graph 1, the points corresponding to the geometry reported by Ma et al.[25] are labeled Ma.

Figure 10 shows the behavior of the energy, computed with basis 6-31+G**, as a function of the reaction coordinate, the activated P−O distance, for each of the above isomerization reactions. Each point in the graphs was computed as the energy of the optimal geometry for the given P−O distance; that is, the P−O distance was kept fixed, and all other parameters were optimized. Care was taken to check that each of the three transition states has only one imaginary frequency. The last point of each graph was obtained from full optimizations using the preceding geometry as the starting point. To check for convergence, several optimizations starting from other points were also performed.

The three isomerization reactions have the same features: upon elongation of the P−O distance, a transition state is found in which the Mg^{2+} cation coordinates four oxygen atoms. This coordination is due not only to electrostatic interactions, but also to charge transfer. However, in the final products of reactions 1 and 2 the oxygen atoms lie in two orthogonal planes, whereas the final product of reaction 3 has a different geometry. Though the pathways found for the isomerizations are somewhat different from Ma's proposal,[26] our results also support the existence of a metaphosphate intermediate in the hydrolysis of Mg−pyrophosphate complexes in the (anhydrous) gas phase.

To show that this is the case, we studied the hydrolysis of the neutral species as the four-step reaction 4−7. The geometry of the $H_2PO_4 \cdot Mg \cdot H_2PO_4$ complex was optimized in the same way as the other molecular species in this work. It has basically the same structural features as the $PO_3 \cdot Mg \cdot H_2PO_4$ complex: the oxygen atoms coordinated by the metal cation lie on orthogonal planes enclosing it (Figure 11).

The computed energies for reactions 4−7 are presented in Table 7. The sum yields an estimate of $\Delta E_e^{SCF} = -52.0$ kcal/mol for the hydrolysis $H_2O + Mg^{2+} + H_2P_2O_7{}^{2-} \rightarrow Mg^{2+} + H_2PO_4{}^{-} + H_2PO_4{}^{-}$, which is in agreement with previous calculations.[17,18] In this case the metal cation is assumed to act as a catalyst, so it should not have any effect on the equilibrium. However, this way of writing the reaction neglects the strong electrostatic interactions between the ions; this can be seen in the very large values of the energies for reactions 4 and 7, which show that the complexes with the metal cation are much more stable than the isolated molecules. In fact, the most stable species is the $H_2PO_4 \cdot Mg \cdot H_2PO_4$ complex.

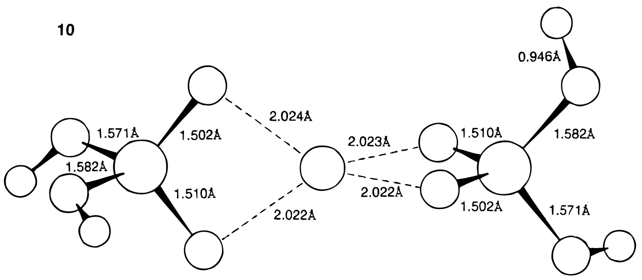

Figure 11. Optimal structure for the $H_2PO_4{\cdot}Mg{\cdot}H_2PO_4$ complex. The oxygens coordinated by the metal cation lie on orthogonal planes enclosing it.

Table 7. Reaction Enthalpies, Entropies, and Free Energies for the Hydrolysis of Pyrophosphate, Considered as a Four-Step Reaction[a]

reaction	ΔE_e^{SCF}	$\Delta H°$	$\Delta S°$	$\Delta G°$
4	−550.1	−542.9	5.2	−544.4
5	−11.5	−13.3	11.9	−16.8
6	−50.4	−40.2	−36.9	−29.2
7	560.0	549.2	33.4	539.2
total	−52.0	−47.2	13.4	−51.2

[a] The last line is the sum of the four reactions. Enthalpies and free energies are in kcal/mol, and entropies in cal/(mol·K). Though the overall hydrolysis is predicted to be spontaneous, the equilibrium species in the gas phase should be the $H_2PO_4{\cdot}Mg{\cdot}H_2PO_4$ complex.

4. Conclusions

We have studied various pyrophosphate complexes, with and without Mg^{2+}, to find their stability in the gas phase. The analysis of the molecular orbitals shows that the singly and doubly charged anions should be stable and that this stability is enhanced by the coordination to Mg^{2+}. Furthermore, the triply and quadruply charged pyrophosphate anions are stabilized by the cation. Then we explored the mechanism of isomerization of Mg−pyrophosphate complexes, and found that not only the $Mg{\cdot}H_2P_2O_7$ neutral complex but also the anionic complexes $(Mg{\cdot}HP_2O_7)^-$ and $(Mg{\cdot}P_2O_7)^{2-}$ follow the same pathway as the neutral species in the gas phase, involving a metaphosphate intermediate. The facts that all the complexes have one bridging P−O bond longer than the other and that the activation energies of the isomerizations are lower than in the case without the metal cation support the hypothesis that metal cations induce strain on the reactants. In all cases where it is present, the Mg^{2+} cation coordinates both the transition state and the leaving group. However, the structures of the corresponding final products are different from those reported previously.[26] We also found that the description of all Mg−PP$_i$ complexes requires basis sets with diffuse functions.

The mechanism described above is as yet inconsistent with the proposal of a pentacoordinated phosphorus prior to hydrolysis.[25] This latter proposal is based on NMR data of the hydrolysis in the aqueous solution, where the Mg−pyrophosphate complex is hydrated. The role of water in the hydrolysis is still unknown and will require further study. However, an important point to notice is the positive energy for the isomerization of the $(Mg{\cdot}P_2O_7)^{2-}$ complex, favoring the synthesis as opposite of what occurs in aqueous solution. This result supports the view that the hydration energy makes a large contribution to the energy of hydrolysis.

It is worth mentioning that the full hydrolysis reactions in the gas phase involve one water molecule as a reactant, for instance

$$H_2O + Mg^{2+} + H_2P_2O_7{}^{2-} \rightarrow Mg^{2+} + H_2PO_4{}^- + H_2PO_4{}^- \quad (10)$$

In this case the metal cation is assumed to act as a catalyst, so it should not have any effect on the equilibrium. However, this way of writing the reaction neglects the strong electrostatic interactions between the ions. It is better to consider it as a four-step reaction:

$$H_2O + Mg^{2+} + H_2P_2O_7{}^{2-} \rightarrow H_2O + (Mg{\cdot}H_2P_2O_7) \quad (4)$$

$$H_2O + (Mg{\cdot}H_2P_2O_7) \rightarrow H_2O + (H_2PO_4{\cdot}Mg{\cdot}PO_3) \quad (5)$$

$$H_2O + (H_2PO_4{\cdot}Mg{\cdot}PO_3) \rightarrow (H_2PO_4{\cdot}Mg{\cdot}H_2PO_4) \quad (6)$$

$$(H_2PO_4{\cdot}Mg{\cdot}H_2PO_4) \rightarrow Mg^{2+} + H_2PO_4{}^- + H_2PO_4{}^- \quad (7)$$

where the isomerizations studied here are intermediate steps. The estimates for the energies of reactions 4 and 7 support the statement made in the last paragraph. Furthermore, the results of this work show the $(H_2PO_4{\cdot}Mg{\cdot}H_2PO_4)$ complex to be quite stable, so it is unlikely that the reaction proceeds until separation of the metal cation from the phosphate anions. Therefore, the Mg^{2+} cation should not be acting simply as a catalyst; an energy input should be required to separate it from the $H_2PO_4{}^-$ anions in the gas phase.

In the case of the anionic species $(Mg{\cdot}HP_2O_7)^-$ and $(Mg{\cdot}P_2O_7)^{2-}$ the electrostatic interactions are stronger and the isolated pyrophosphates are not even stable in the gas phase, so the equilibria should also go toward the complexes. The various equilibra and activation energies of the preceding scheme have yet to be determined, a subject of current research at our laboratory.

A final caveat about the structures found in this work, and others, is that the current optimization procedures do not guarantee finding global minima. Moreover, due to the large increase in the number of degrees of freedom when more molecules are considered, a thorough sampling of the configuration space becomes unfeasible with the current methods of *ab initio* calculations. This calls for the development of new algorithms.

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Supporting Information Available: Tables listing the bond lengths, bond angles, and dihedral angles of the structures shown in this paper in the Z-matrix form (11 pages). See any current masthead page for ordering and Internet access instructions.

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