Mechanism of Hydrolysis of Cyclic Phosphate Esters

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Abstract: Molecular orbital calculations are carried out on cyclic and acyclic phosphate esters, and corroboration is found for the main features of the mechanism advanced by Westheimer to explain the reactivities of the cyclic compounds toward hydrolysis and oxygen exchange. Ring strain lowers the occupation of the P 3d orbitals and favors nucleophilic attack at P leading to a trigonal bipyramidal pentaoxyphosphorane with the entering and leaving groups in apical positions. The adduct of methyl ethylene phosphate and water can undergo pseudorotation with a computed upper limit to the barrier of about 12–15 kcal/mol when the phosphoryl oxygen remains in a basal position. Protonation of the intermediate is predicted to occur most easily at the apical, ring oxygen.

Model systems for the hydrolytic action of ribonuclease on polyribonucleotides are provided by five-membered cyclic triesters of phosphoric acid. The geometrical constraints[1] on these esters are such as to make them highly reactive toward hydrolysis and oxygen exchange. The five-membered cyclic esters, such as methyl ethylene phosphate, hydrolyze[2] 10^6–10^8 times faster than corresponding acyclic esters, and also much faster than six- or seven-membered[3,4] cyclic esters. Westheimer and coworkers have proposed that the strain in the five-membered rings facilitates the formation of a trigonal bipyramidal intermediate which can undergo pseudorotation. Their mechanism is based on the following hypotheses or rules. (1) The hydrolyses proceed *via* a nucleophilic attack on phosphorus leading to a trigonal bipyramidal intermediate.[2] (2) The five-membered ring spans one apical and one basal position.[5,6] (3) Groups enter and leave from apical positions.[5] (4) Pseudorotation of the trigonal bipyramid can take place leading to exchange of the apical and basal positions.[5,7] (5) The pseudorotation occurs subject to the preference of less electronegative substituents (*e.g.*, carbon in tetraoxyalkylphosphoranes) to occupy basal positions and of the more electronegative substituents (*e.g.*, oxygen) to occupy apical positions.[5,8] (6) The phosphoryl oxygen prefers a basal position.[9] The experimental findings which these hypotheses correlate and explain are reviewed elsewhere.[1]

The purpose of this paper is to examine the mechanism and rules outlined above by carrying out extended Hückel[10,11] molecular orbital calculations on cyclic and acyclic esters of phosphoric acid. Methyl ethylene phosphate, whose structure[12,13] and chemistry[1] are well established, is used as a model for studying nucleophilic attack and hydrolysis. Even though the enhanced hydrolysis rates are usually either acid- or base-catalyzed, reagents which are neutral and unsolvated are used for computing potential surfaces in order to avoid possible uncertainties associated with applying extended Hückel theory to ions.[14] Nevertheless, the major features of the reaction between water and a phosphate ester are expected to emerge in essentially the same form as would be obtained from treating ionic species by some more elaborate theory. Whereas a study of phosphonates and phosphinates would be needed to test hypothesis 5, there exists a theoretical interpretation[15] for the experinental evidence[1] indicating that the more electronegative substituents occupy apical positions about pentavalent phosphorus. Consequently, the present study concerns pentaoxyphosphoranes.

Previous theoretical work[16] on alkyl phosphate esters was aimed at the molecular conformations and their relation to reactivity. Although not all valence electrons and overlap integrals were included (unlike the extended Hückel method here employed), charge distributions of the phosphate esters were, in general, found to be harmonious with the relative reaction rates and nmr shifts. In particular, the phosphorus atom was found to be more positive in the cyclic compounds than in the acyclic compounds. Only a cursory investigation of a trigonal bipyramidal intermediate was made.

Method of Calculation

The extended Hückel method[11] of computing LCAO molecular orbitals is in such widespread use that only the geometrical and orbital parameters which enter the computations need be discussed here. The geometries used are based on X-ray crystallographic structure determinations of the following esters: methyl ethylene

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[15] P. C. Van Der Voorn and R. S. Drago, *J. Am. Chem. Soc.*, 88, 3255 (1966).

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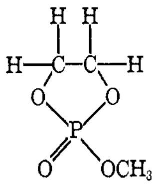

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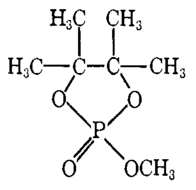

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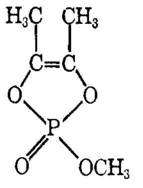

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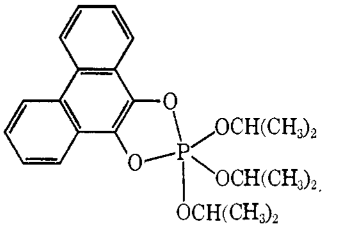

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phosphate (MEP, **1**),[12] methyl pinacol phosphate (MPP, **2**),[17] acetoinenediol cyclophosphate (ACP, **3**),[18] and dibenzyl phosphoric acid.[19] The structure determination[6,20] of a pentaoxyphosphorane, 2,2,2-triisopropoxy-4,5-(2′,2″-biphenyleno)-1,3,2-dioxaphospholene (**4**), provides a model for constructing trigonal bipyramidal intermediates. Hydrogens and other necessary atoms are added to the molecules using reasonable bond angles and lengths. The structure of the nucleophile water is well known.[21] The geometries of the transition states are discussed in more detail later.

The orbital parameters entering the extended Hückel theory, namely, the valence-state ionization potentials and orbital exponents, are the same as those which worked well in a molecular orbital study of adenosine 5′-triphosphate.[22] The Wolfsberg–Helmholz constant is taken as 2.0; the orbital exponents are just the Slater values, except for the H 1s and P 3d orbitals, for which the values of 1.2 and 1.4, respectively, are taken from self-consistent-field optimization calculations.[23] The carbon and hydrogen valence state ionization potentials are those in common usage,[11] and the phosphorus and oxygen values of -18.57 eV (P 3s), -13.98 (P 3p), -8.48 (P 3d), -37.59 (O 2s), and -14.62 (O 2p) are taken from self-consistent-field eigenvalues[23] of PO. In compounds where oxygen is not bonded to phosphorus, these oxygen parameters correspond to a very electronegative oxygen, which is actually desirable when using water as the nucleophile.

Within the extended Hückel framework, it has been found[22,24] that half the sum over electrons of the molecular eigenvalues, $0.5\Sigma_i\epsilon_i$, is more appropriate for comparing molecular energies than the sum, $\Sigma_i\epsilon_i$. Hence in this work, energies and energy differences refer to $0.5\Sigma_i\epsilon_i$.

Results and Discussion

Characteristics of Alkyl Phosphate Esters. We initially discuss the conformations of the esters and then proceed to examine the bonding and hybridization of phosphorus in these compounds. In later sections the potential surface for the reaction of MEP and water is investigated.

Both MEP[12] and ACP[18] crystallize with the methyl group positioned over the ring, equidistant from the two ring oxygens, and roughly coplanar with the P=O bond. On the other hand, MPP[17] exists in a conformation with the methyl group rotated approximately 180° from this position. We find for MEP and ACP the expected threefold barriers to rotation about the P—OCH_3 bond and compute the crystalline-state conformations to be most stable. The barriers encountered when the methyl group eclipses the P–O bonds are in the range 2–4 kcal/mol, except in MPP. For this molecule the steric crowding from the ring methyl groups makes the barrier essentially twofold; the barrier to eclipsing the P=O bond is almost negligible (0.4 kcal/mol), whereas a huge, perhaps exaggerated, barrier of 21–26 kcal/mol exists against placing the methyl group over the ring with fixed bond angles. Because of a possible overemphasis[11] of steric effects, the theory indicates a gain in stability of about 1 kcal/mol when the methyl group of MPP is rotated 67° from the crystalline-state position[25] so that the methyl carbon, C_8, and the ring oxygen, O_3, are *anti*. Nevertheless, we find in agreement with previous conclusions[16–18] that P-OCH_3 π bonding, moderated by steric effects in the crystal, determines the observed methyl positions in the five-membered cyclic esters. Strong π bonding in the phosphoryl bonds of triesters of phosphoric acid is manifested in short P=O internuclear distances of 1.38–1.46 Å.[12,17,18,26–28] Thus, the fact that in MEP, ACP, and MPP the methoxyl group is nearly coplanar with the P=O and the P—OCH_3 bond length is no longer than the P—OC bond lengths in the ring suggests that the methoxyl oxygen is trying to take advantage of π-type orbitals on P used in the P=O bond. It is not surprising then that we find the P—OCH_3 π overlap populations to be greatest when the methoxyl group and phosphoryl group are coplanar.

The most prominent characteristic of the electronic structures (Figure 1) of the five-membered cyclic esters is the large net atomic charge on phosphorus.[16] Charges on P are typically about 0.04 more positive in the cyclic esters than in the comparable acyclic compounds for both the di- and triesters. This difference is predominantly due to a lowered occupation of the outer P orbitals, *i.e.*, the 3d orbitals. In each of the cyclic triesters the charge on P becomes still more positive by about 0.03 when the methoxyl group is rotated 90° away from the crystalline state position. The P is more positive in the triesters than in the diesters of

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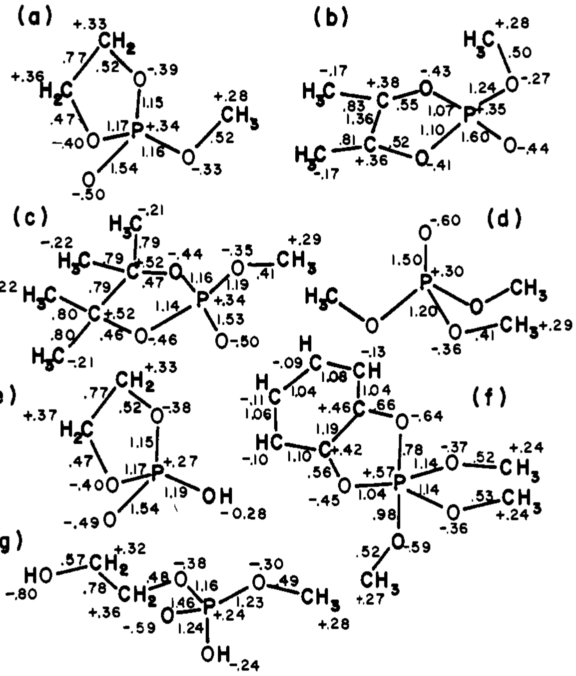

Figure 1. Net atomic charges (signed numbers) and overlap populations (unsigned numbers) for (a) methyl ethylene phosphate (MEP), (b) acetoinenediol cyclophosphate (ACP), (c) methyl pinacol phosphate (MPP), (d) trimethyl phosphate (geometry based on a threefold rotation of the methoxyl group about the P=O bond of MPP), (e) hydrogen ethylene phosphate (based on geometry of MEP), (f) 2,2,2-trimethoxy-4,5-benzo-1,3,2-dioxaphospholene (based on geometry of ref 20), (g) methyl-2-hydroxyethyl phosphate (based on geometry of ref 19). The hydrogens have charges of about +0.05 when bonded to carbon and +0.4 when bonded to oxygen; overlap populations are about 0.8 for C-H bonds and 0.6 for O-H bonds.

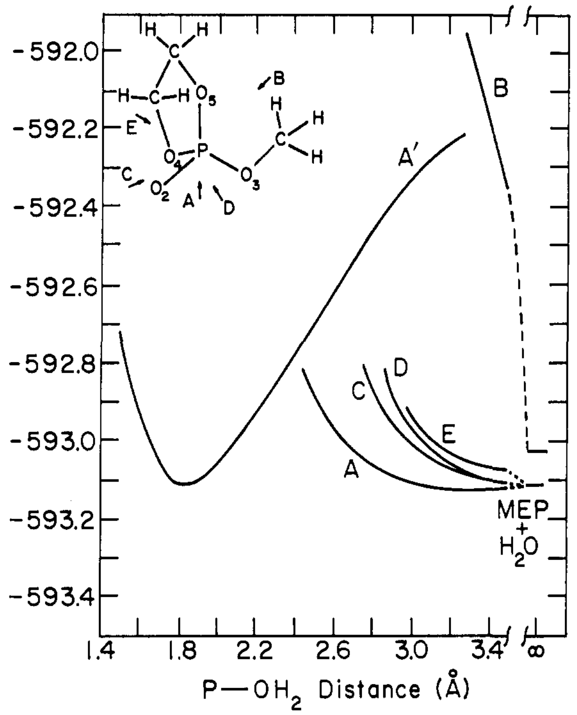

Figure 2. Potential curves (eV) for the approach of water toward MEP. See text for description.

Figure 1, and the former are known to hydrolyze more rapidly.[2,29–32] Thus, the large charge on P has a direct bearing on the reactivity of cyclic esters toward nucleophilic attack, and we shall return to this subject later. The low electron density around P also may correlate[16] with the observed[33,34] nmr deshielding relative to acyclic compounds.

One of the arguments supporting the formation of pentacoordinated phosphorus intermediates in the hydrolysis of phosphate esters is the existence of many stable pentaoxyphosphoranes.[35] The electronic structure of one such compound (Figure 1) indicates that the phosphorus is very positive when surrounded by five electronegative oxygen atoms. The apical oxygen in the five-membered ring is quite negative because of the long P–O distance (1.75 Å). The π overlap populations in the basal P–O bonds (0.37–0.45) are considerably greater[20,36] than in the two apical bonds (0.20 and 0.32) due to π bonds lying in the basal plane. Contributions of P 3d orbitals amount to 24–31% of the σ P–O overlap populations and 77–85% of the π P–O overlap populations, which is consistent with the recognized ability of 3d orbitals to form π bonds.[23]

Path of Attack by a Nucleophile. The proposed mechanism for hydrolysis and oxygen exchange of strained cyclic phosphate esters is investigated by allowing the nucleophile water to approach MEP. The high positive charge on phosphorus, noted above,[16] enhances the rate of nucleophilic attack at this atom relative to the rate of attack at phosphorus in unstrained esters or to the rate of attack at carbon. Potential surfaces (Figure 2) indicate that attack is particularly favorable on the back sides of P–O bonds in the ring. In fact, in the approach on the back side of the P–O_5 bond (path A) a very slight potential minimum (0.12 kcal/mol compared to the infinitely separated molecules) occurs at a P–OH_2 distance of 3.25 Å. Attack on the back side of the P–O_4 is similar to path A, but the minimum occurs near 3.5 Å and is not as deep. Path A′ is in the same direction as A, but the ester is in a trigonal pyramidal geometry; the actual reaction path may be a smooth fit of curves A and A′ made in the region 2.2–2.6 Å. Path B is on the back side of the P=O_2 bond with the methoxyl group rotated 180° out of the way. Path C roughly bisects the O_4–P–O_2 bond angle, whereas path D roughly bisects the O_2–P–O_3 bond angle. Path E is on the back side of the P–O_3 bond.

The reason for the minimum in path A of Figure 2 is not obvious from examination of the Mulliken population analysis or from the known characteristic of MO theory to perform poorly at long nonbonded distances. However, an explanation is provided by the electron density map (Figure 3) which shows that although the

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(32) T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms," Vol. 2, W. A. Benjamin, Inc., New York, N. Y., 1966, pp 1–21.

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net atomic charge on the oxygen of water has not changed greatly from that of the infinitely separated water, there is a large transfer of electron density from the negative to the positive lobe of the O $2p_z$ orbital (assuming water attacks P along the $-z$ axis). The stabilization resulting from this incipient bond more than offsets the destabilization from the steric repulsions at the long P–OH_2 distance of 3.25 Å. In addition to the obvious steric reasons, path A is most favorable because of the character of the lowest empty MO (Figure 4) of MEP. This molecular orbital consists principally of lobes on the back sides of the P–O ring bonds, and hence it can interact with the approaching electron pair from water. Moreover, the highest occupied MO of MEP has mainly lone-pair character on the ring oxygens, and hence it interferes little with nucleophiles. As will be seen later, path A leads to one of the most stable trigonal bipyramidal intermediates with the phosphoryl oxygen being basal and the ring spanning an apical and basal position. The other curves (Figure 2) rise sharply in the region 2–3 Å where the complex distorts to a trigonal bipyramid because they force the phosphoryl oxygen into an energetically unfavorable apical position or force the ethylene to span two basal positions.

The nucleophilic attack by water on an acyclic triester, trimethyl phosphate (Figure 1) involves a more sharply rising repulsive potential than that encountered in MEP at short P—OH_2 distances. The approach of water on the back side of the P—OC bond is found to be preferred over approach on the back side of the P═O bond.

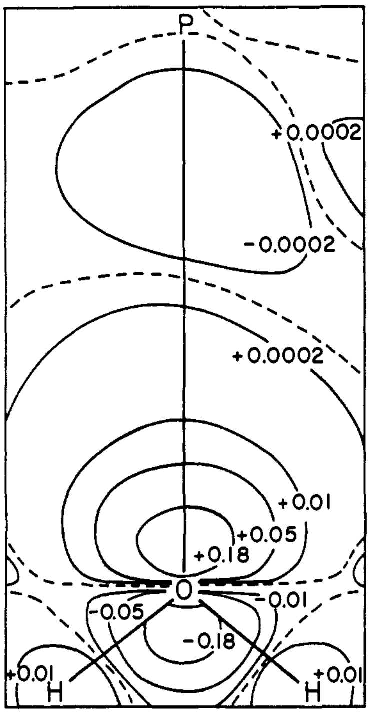

Figure 3. Electron density *difference* map obtained by substracting the density of water and tetrahedral MEP from that of the MEP-H_2O system at a P–OH_2 distance of 3.25 Å. The contours are in units of electronic charge with positive numbers corresponding to regions gaining electron density, and the nodal surfaces are denoted by dotted lines. The map, covering an area of 2 × 4 Å, shows the density in the plane of the water molecule, P, and O_5 (off the map at the top).

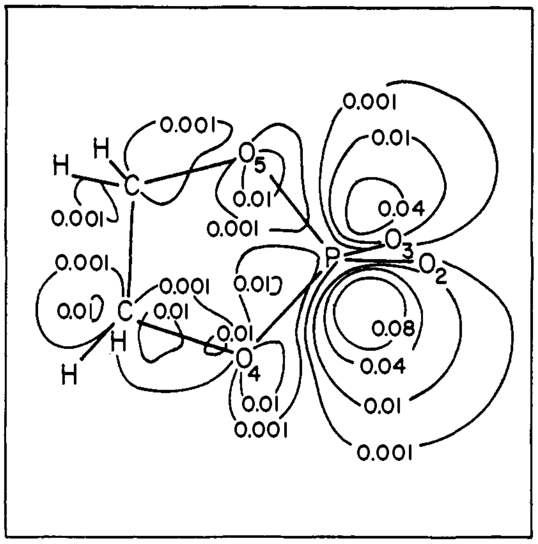

Figure 4. Electron density map of the lowest empty molecular orbital of tetrahedral MEP computed from $D(\mathrm{x}) = 2\Sigma_{p,q}C_{p\mathrm{LEMO}}C_{q\mathrm{LEMO}}\chi_p(\mathrm{x})\chi_q(\mathrm{x})$, where the C are coefficients of the basis functions χ. A complicated set of nodal surfaces is not shown for sake of clarity. The map, covering an area of 6 × 6 Å, is of the density in the plane of O_4, P, and O_5. The projections of other atoms on this plane are shown; the methyl carbon bonded to O_3 lies directly above P.

The Intermediates and Pseudorotation. An initial geometry for a trigonal bipyramidal intermediate is arrived at by assuming the reaction follows path A (Figure 2). Hence the approach of water on the back side of the P–O_5 bond of MEP simply causes the methoxyl group and phosphoryl oxygen to rotate up to the incipient basal plane (perpendicular to the P–O_5 bond), and the –OCH_2CH_2O– group translates until O_4 is also in this plane. The basal P–OC distances are initially taken as 1.58 Å and the P–OC apical distance[20] as 1.75 Å. The apical P–OH_2 bond (Figure 5) is optimized at a reasonable 1.80 Å. The following optimum bond distances are subsequently found for the intermediates of Figure 6: apical P–O bonds in the ring are 1.75 Å, apical P–OR (R = H_2, H, CH_3) bonds outside the ring are 1.80 Å, basal P–O^- bonds are 1.44 Å, the apical P–O^- bond is 1.65 Å (model VIII), the basal P–OH_2 bond is 1.50 Å (model VIII), the basal P–OH bond is 1.44 Å (model VII), and the basal P–O (methanol) bond is 1.58 Å (model VI). The methoxyl groups of models I and II prefer *anti* conformations relative to the basal, ring oxygens.

Energies (Figure 6) of various intermediates indicate that the apical, esterified oxygen prefers to be protonated, even though the charge distributions (Figure 7) indicate that this oxygen and the phosphoryl oxygen are both very negative in the intermediate (model IV) prior to pseudorotation or proton transfer. It is especially interesting that several of the isomers examined (models I–III) are more stable than the infinitely separated reactants, suggesting the possibility of experimentally detecting an intermediate.

Pseudorotation[5,7] is a bond-bending process in which one basal bond of a trigonal bipyramid is chosen as pivot, and the other two basal bonds are bent toward the pivot, reducing the O_p–P–O_b angles from 120 to 90°, and the two apical bonds are bent away from the pivot, increasing the O_p–P–O_a angles from 90 to 120°. Thereby the molecule goes through a tetragonal pyramid with the pivot oxygen O_p at the apex, and the apical and two basal substituents exchange positions. Rather than doing an elaborate optimization of all geometrical parameters and finding the location of a saddle point on the potential surface, a rough estimate of the barrier to pseudorotation is obtained by the following procedure. A geometry for a tetragonal pyramid is arrived at by choosing the phosphoryl oxygen of the pentaoxyphosphorane III (Figures 6 and 7) as pivot and distorting the O_p–P–O angles to about 105° where the other four oxygens are almost coplanar. The choice of the P–O^- bond as pivot is logical because it does not like to be apical (Figure 6). Moreover, the force constants for the P–OR (R = H, C) bonds are computed to be lower than for the P–O^- bond, and hence it is reasonable that the former are more easily deformable and that the latter serves as pivot. The P–OR bonds are taken at an intermediate value of 1.67 Å, and the other bond distances are kept about the same as in MEP.[12] The calculations indicate that the P–O_p distance shows no tendency to lengthen beyond[12] 1.44 Å in the tetragonal pyramid, even if this oxygen is singly protonated. The energy of the tetragonal pyramid (Figure 7) derived from model III lies 12 kcal/mol above that of III. The continuation of the pseudorotation process produces (after proton transfer) models I and II (Figures 6 and 7) which are apparently more stable than III. We interpret 12–15 kcal/mol as an upper limit to the barrier to pseudorotation because optimization of the geometry of the tetragonal pyramid would lower the apparent activation energy. The upper limit is in line with those estimated for phosphorus halides.[37] The energy of a tetragonal pyramid derived from model VII (Figure 6), where the pivot oxygen is protonated, lies 5–6 kcal/mol above that of VII.

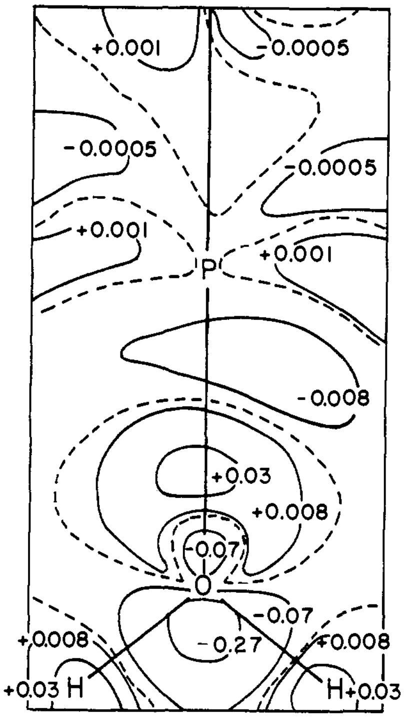

Figure 5. Electron density *difference* map, analogous to Figure 3, obtained by subtracting the density of water and trigonal pyramidal MEP from that of the trigonal bipyramidal MEP–H_2O system at an equilibrium P–OH_2 distance of 1.80 Å.

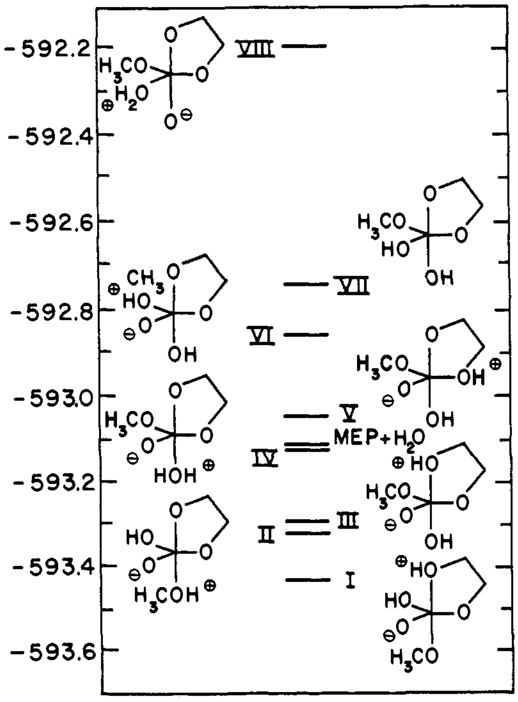

Figure 6. Energies (eV) of trigonal bipyramidal intermediates. The sum of energies of the infinitely separated reactants, MEP and H_2O, is shown for comparison.

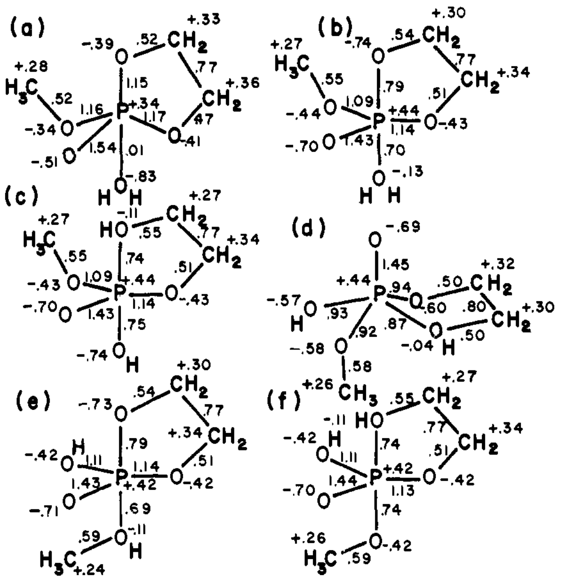

Figure 7. Net atomic charges and overlap populations for (a) water and tetrahedral MEP at the optimized P–OH_2 distance of 3.25 Å, (b) model IV, (c) model III, (d) tetragonal pyramidal intermediate to pseudorotation, (e) model II, and (f) model I.

Modes of Decomposition of the Intermediates. Paths of decomposition (Figure 8) of the trigonal bipyramidal intermediates indicate that the groups leaving from apical positions encounter the least resistance. Path F represents model I (Figure 6) decomposing by rotation of the apical $-CH_2OH^+$ group about the C–C axis, and

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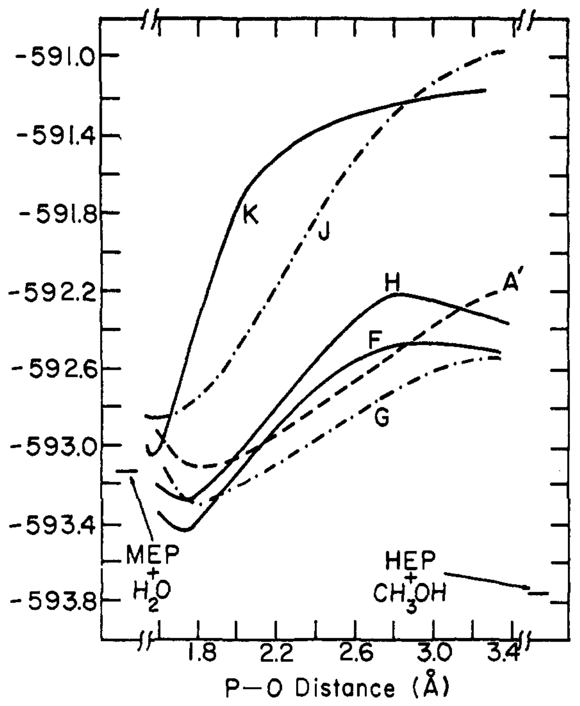

Figure 8. Potential curves (eV) for the departure of hydroxyl oxygens from trigonal bipyramidal intermediates. See text for description. Path A′, which depicts the departure of water from an apical position, is reproduced from Figure 2. The energy of methyl-2-hydroxyethyl phosphate (−594.34 eV) lies below the sum of the energies of hydrogen ethylene phosphate (HEP) and methanol shown in the figure.

path H represents the same process in model III. Path G depicts the departure of methanol in model II by translation along the apical axis, and path J shows the translation of methanol from a basal position in model VI. Path K represents ring opening by a rotation of the basal $-CH_2OH^+$ group about the C–C axis of model V.

Since the calculations indicate the most stable pentaoxyphosphorane to be model I (Figure 6), where a hydrogen is covalently bonded to the apical, ring oxygen, the hydrolysis is expected to proceed primarily with ring opening (path F, Figure 8). This is, indeed, observed to be the case; acid-catalyzed hydrolysis of MEP gives mainly ring opening.[1] The second most stable intermediate, model II, decomposes with retention of the ring (path G, Figure 8). Whereas path G is computed on the basis of a simple translation of methanol away from phosphorus, path F is computed from a rotation of the $-CH_2OH^+$ group about the C–C axis. Probably a more complicated set of bond twistings would lower path F (and also H and K) at P–O distances greater than about 2 Å in Figure 8. Of course, the pertinent region of Figure 8 is at short P–O distances (less than about 2.4 Å) because as the hydroxyl group moves away from phosphorus, the molecule will not stay fixed in a trigonal bipyramidal geometry, but will become tetrahedral. Also in regard to Figure 8, it is no small success of the theory to predict the energies of the reactants, intermediates, and products to be in the apparent proper relative order.

Summary

The ring strain in the five-membered cyclic phosphate esters results in lowered occupation of the P 3d orbitals, and the resulting deshielding of the phosphorus nucleus accounts for the high rate of nucleophilic attack in hydrolysis and oxygen exchange. The lowest activation energies are involved in the following mechanism. (1) The nucleophile approaches the phosphate ester on the back-side of one of the P–O ring bonds. (2) This bond lengthens to an apical bond and the other P–OC bonds become basal bonds of a trigonal bipyramidal intermediate. (3) The intermediate undergoes pseudorotation most easily when the phosphoryl oxygen serves as pivot (*i.e.*, remains in a basal position). (4) The apical oxygens prefer to be protonated. (5) The hydroxyl group formed in step 4 moves away from phosphorus. (6) The local geometry at phosphorus relaxes toward tetrahedral. Thus, the hypotheses advanced earlier are corroborated. Moreover, predictions about the nature of the intermediates are apparent from this work.

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