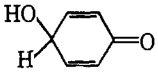
This estimate of the excess energy is *ca.* 0.9 ev (~21 kcal mole^{-1}).

To estimate whether reaction 9a is feasible, we write the sequence

$$C_6H_5O\cdot \longrightarrow HOC_6H_4\cdot \qquad \Delta H = 12\ \text{kcal mole}^{-1}$$

$$HOC_6H_4\cdot + H_2O \longrightarrow HOC_6H_4OH + H \qquad \Delta H = 12\ \text{kcal mole}^{-1}$$

$HOC_6H_4OH \longrightarrow$



$(\Delta H = 18\ \text{kcal mole}^{-1})^{37}$

Summing the enthalpies, we find that process 9a is endothermic by 42 kcal mole^{-1}. Therefore, any excess vibrational energy in the range 21–32 kcal mole^{-1} does not seem sufficient to allow phenoxyl to react with water.

Acknowledgment. We wish to acknowledge helpful discussions with Professor L. I. Grossweiner and to thank Professor E. F. Zwicker for his assistance with the flash photolysis experiments.

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The Electronic Structure of Phosphate Esters

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Abstract: A simple self-consistent molecular orbital method is used to calculate the charge distributions and energies arising from 2p–3d orbital interactions in phosphates. Application of the method to different conformations of phosphate aliphatic esters gives energy values which can be correlated with the known structural features of these esters and the thermochemical data available for the heats of saponification of the acyclic and cyclic forms. The resulting charge distributions are in accord with the reaction rate data for these compounds and they offer a possible explanation for the exceptionally high reactivity of the cyclic esters. The theory implies that the rate of nucleophilic attack on the phosphorus atom is sensitive to the conformation of the ester groups about this atom and suggests that these conformational changes may be important factors in determining the reactivity of phosphates and polyphosphates.

Although phosphorus is an important constituent of biological systems and appears to play a fundamental role in metabolic processes, an understanding of its chemical behavior in living systems has been retarded by the lack of a sound conceptual scheme to describe the bonding within phosphate and polyphosphate esters. In this paper an attempt is made to develop a scheme that will be applicable to a study of both the chemistry and conformation of phosphate esters and the esters of pyro- and triphosphates as well as analogous compounds based on silicon, sulfur, and chlorine. The first application will be to diester and triester phosphates—particularly to an interpretation of their neutral and basic hydrolysis rates and their conformation in the solid state.

Molecular oribital calculations of the Hückel type have been carried out on phosphates by a number of workers,[2–4] but the calculations all suffer from the lack of explicit consideration of the geometry of the phosphate group.

Pauling[5] was probably the first to suggest that the 3d orbitals on the central atom could be involved in π-type bonds with the oxygen atoms in the tetrahedral MO_4^{-n} ions. These ideas have been extended by Van Wazer[6] to account for the properties of a large variety of phosphorus compounds. A more explicit proposal for 2p–3d bonding in tetrahedral ions has been put forward by Cruickshank[7] in which the geometrical properties of two of the five 3d orbitals were introduced in a qualitative manner and used to account for the bond distances and geometries of a large number of compounds in which Si, P, S, and Cl were involved in tetrahedral bonding.

The work to be reported here goes one step beyond the qualitative picture of Cruickshank. The basic idea of the importance of 2p–3d π-type bonding, superimposed on a σ-bond skeleton made up of sp^3-hybrid orbitals on the central atom, has been used. The formulation has been generalized by the removal of symmetry restrictions and by the introduction of all five 3d orbitals into the calculation, not just the two strong-bonding ones. A simple Hückel molecular orbital treatment has been used with self-consistent features to refine the Hückel parameters and both net charges and π-electron energies have been derived. The former quantity is used to interpret chemical reactivity; the latter to interpret thermodynamic quantities and conformation. Such an unsophisticated treatment of complex phenomena cannot be expected to give a complete quantitative understanding of phosphate chemistry, but, as will appear later, certain rather gross chemical and structural features can be correlated by such a treatment and implications arise which may be

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(1) Present address: Department of Radiation Biology and Biophysics, University of Rochester School of Medicine and Dentistry, Rochester, N. Y.

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pertinent to enzyme-catalyzed reactions involving phosphates.

Method of Calculation

The σ-Bond System. The theoretical treatment will be applied to phosphorus atoms surrounded tetrahedrally by four oxygen atoms, and with compounds of this type it is reasonable to assume that the 3s and 3p orbitals on the central atom hybridize to form four sp^3 orbitals pointing toward the oxygens. The sp^3 orbitals will overlap strongly with appropriate orbitals on oxygen.

The hybridization scheme on oxygen will depend on its environment. For an oxygen bound only to the central atom, one 2p orbital will be assumed to point toward the central atom and form the σ bond while the 2s orbital contains a lone pair of electrons. This will leave two p orbitals at right angles to the σ bond available for π-type bonding with the central atom. Other hybridization schemes that lead to weaker π bonding might be induced by intermolecular interactions with the oxygen such as hydrogen bonding and ionic interactions. However, such effects will be neglected in this first study.

When the oxygen is joined to another atom as well as the central atom (*e.g.*, to hydrogen or carbon), the bond angles ($\angle$POC or POH) are usually close to 120°. This implies sp^2 hybridization on the oxygen with only one p orbital available for π bonding to the central atom.

The σ system will consist of these hybrid orbitals on the oxygen and central atom overlapping along the interatom axis, each σ bond containing two electrons. In addition, it also includes a lone pair of electrons on each oxygen occupying the nonbonding orbitals, either an s orbital or an sp^2 hybrid.

Because of the difference in electronegativity between oxygen and phosphorus, it is unlikely that the σ bonds are homopolar, and an attempt has been made to include this expected polarity in the σ bonds by assuming a flow of electrons from the central atom to the oxygen proportional to the difference in electronegativity, as suggested by Pauling.[5] Pauling's calculations give a polarity of 0.32 electron for a P–O bond. A similar shift of 0.32 electron in the direction of oxygen is assumed for C–O bonds. This polarity will make an important direct contribution to the final charge distribution, and it will have an additional effect on the assignment of molecular orbital parameters in the treatment of the π-type bonding. Pauling's relation between polarity and electronegativity difference has been criticized,[8] and its quantitative indications of charge distributions are probably unreliable. However, since the σ-bond polarity makes a fairly constant contribution to the different molecules treated here, the exact numerical values are of little importance, especially when comparisons are made between molecules with the same σ skeleton.

The π-Bond System. One important assumption made in treating the π electrons is that the only interactions between the σ and π systems will be through the σ-bond polarity and the screening effects of these σ electrons on the π electrons. The orbitals available for π bonding are taken to be the five 3d orbitals on the phosphorus atom and the 2p orbitals on the oxygens not involved in the σ system. Since aliphatic esters only are considered, there will be no π-electron contribution from the ester groups. Interactions such as those between the 3p orbitals on the central atom and the 2p orbitals on oxygen and between the 2p orbitals on different oxygens will be neglected in this elementary treatment. Some justification for the explicit neglect of such interactions comes from molecular orbital calculations on $F_2NSO_2NF_2$[9] in which the 3s and 3p orbitals on the sulfur and the 2s and 2p orbitals on nitrogen were included in the basis set and all interactions treated. The results showed that the essential nature of the rotational barrier about the N–S bonds could be attributed to p–d interactions and that all other interactions made a much smaller contribution.

The phosphorus atom will contribute one electron to the π system. An oxygen bonded only to the phosphorus atom will contribute three π electrons while an oxygen with two σ bonds will contribute two π electrons.

The Molecular Orbital Parameters. The simple Hückel molecular orbital theory which we propose to use has been described elsewhere in applications to hydrocarbons and heterocycles.[10,11] Two types of parameter enter into the calculations; a coulomb integral, $\alpha_r = \int \phi_r H_{eff} \phi_r dv$, and a resonance integral, $\beta_{rs} = \int \phi_r H_{eff} \phi_s dv$, where ϕ_r and ϕ_s are atomic orbitals, H_{eff} is an effective one-electron Hamiltonian, and the integrals are evaluated over all space. In general, these integrals are not calculated directly but are treated as empirical parameters to be evaluated from experimental data. Unfortunately, there are not enough experimental data of a suitable kind to allow all the parameters to be evaluated empirically for the molecules in which we are interested. Instead, a theoretical approach will be necessary, but the results will be calibrated against similar Hückel parameters that have been established empirically for other atoms and molecules.

The resonance integrals are assumed to be proportional to the overlap integral,[12] that is, $\beta_{rs} = kS_{rs}G_{rs}$, where $S_{rs} = \int \phi_r' \phi_s' dv$, the orientation of ϕ_r' and ϕ_s' being taken to give maximum π-type overlap. G_{rs} is determined by the relative orientation in space of the 2p and 3d orbitals for any particular molecular conformation.[13]

Values of S_{rs} based on Slater orbitals have been tabulated by Jaffé[13] for 2p–3d overlap. Although Slater orbitals are probably a poor approximation to 3d orbitals, Cruickshank[7] showed how the Slater orbital exponents could be adjusted to give agreement with Hartree self-consistent-field results. The orbital exponents derived by Cruickshank together with Jaffé's tables and the geometrical factors peculiar to each different molecule have been used to evaluate β_{rs}. The constant k is determined by comparison with the

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carbon–carbon resonance integral in benzene and the known carbon–carbon overlap integral.[14] Thus

$$\beta_{rs} = \frac{S_{rs}G_{rs}\beta_{cc}}{0.245} \qquad (1)$$

In evaluating the Slater exponents, screening by inner shell electrons and the σ electrons (including the electron shift due to bond polarity) is included. The π-electron distribution obtained after the first molecular orbital calculation is also included in the screening, and subsequent iterations are carried out until the resonance integrals remain unchanged.

It is convenient to write the coulomb integral, α_r, as

$$\alpha_r = \alpha_c + \delta_r\beta_{cc} \qquad (2)$$

where α_c is the coulomb integral of a carbon atom and δ_r is the coulomb parameter for the r'th atom. The coulomb integrals are assumed to be proportional to the potential energy of a π electron in the field of the nucleus and its associated electrons.[11] If the electron distribution about an atom is approximated by a Slater orbital and the π electron is considered to be at a distance from the nucleus corresponding to the maximum in the radial distribution function derived with Slater orbitals, then its potential energy is proportional to Z^2/n^2 where Z is the effective charge experienced by the π electron and n is an effective principal quantum number. This expression for the potential energy is closely related to one of Gordy's definitions of electronegativity[15] and thus, in a sense, the coulomb integral is being set proportional to an effective electronegativity for the π electron.

Equation 2 can be written as

$$\delta_r = \frac{A}{\beta_{cc}}\left(\frac{Z_r^2}{n_r^2} - \frac{Z_c^2}{n_c^2}\right) \qquad (3)$$

This equation has been plotted in Figure 1 using δ_r values from the compilation of Pullman and Pullman[11] for carbon, nitrogen, and oxygen and a more recent value for the δ_r of sulfur.[16] The straight line confirms the approximate validity of the proportionality between δ_r and Z_r^2/n_r^2. The point for sulfur is low but a value of $n_s = 2.71$ rather than 3.00 brings it into line. This is taken as an indication that with atoms using third shell orbitals for bonding the effective principal quantum number should be 2.71.

The screening attributed to the π electrons can be written as $\epsilon(Q - 1)$ where Q is the total π-electron charge on the atom and ϵ is the screening parameter. The value of ϵ for a 2p electron is taken as 0.35 and for a 3d electron it is taken as 0.30.[7] We can then write

$$\delta_r = \frac{A}{\beta_{cc}}\left[\frac{(Z_r' - \epsilon_r(Q_r - 1))^2}{n_r^2} - \frac{Z_c^2}{n_c^2}\right] \qquad (4)$$

where Z_r' is the charge on nucleus r corrected for the screening effect of the non-π electrons associated with atom r. The constant, A/β_{cc}, is given the value 0.48 from the slope in Figure 1. Equation 4 is the prescription for evaluating δ_r and it contains terms that depend on the π-electron distribution. Again, as with β_{rs}, this introduces a self-consistent feature.

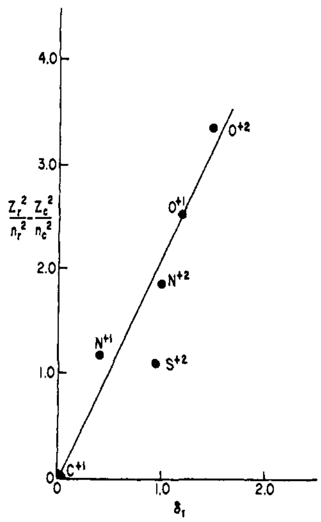

Figure 1. Plot of $(Z_r^2/n_r^2) - (Z_c^2/n_c^2)$ *vs.* δ_r for carbon, nitrogen, oxygen, and sulfur. See eq 3.

The parameters derived in the rough manner described above, although related to experimentally derived parameters from other systems, cannot be expected to give a precise description of the electron distribution until they have been refined and thoroughly tested against experimental data. On the other hand, the methods used should give a rough ordering of the appropriate parameters and will take into account in an approximate manner the screening effects expected when a large number of π electrons occur on a small number of atomic centers, as is the case in the molecules treated here. This should be sufficient to lead to a reliable calculation of relative charge distributions among similar molecules and hence to a comparison of gross differences in chemical properties among similar molecules.

Calculations. The calculations were performed with a digital computer program that solves the Hückel secular equation in the orthogonal approximation, calculates the Q_r values, recalculates new δ_r values according to eq 4, and then repeats the calculation with these new δ_r values. This cycling is continued until successive Q_r values for all atoms agree to within any preassigned amount (within 0.002 electron for the calculations reported here). The resonance integrals also depend on the Q_r values since these affect the shielding and hence the value of Z occurring in the Slater orbitals used to calculate S_{rs}. Such corrections to S_{rs} are made by hand in between sets of refinement on δ_r. Values of S_{rs} for different conformations of the same molecule are very close and in the calculations reported here they are taken to be identical. The calculations always converge and are finally consistent with respect to all Q_r, δ_r, and β_{rs} values.

Molecular Models. Since the chemical reactivity of the phosphate di- and triesters in both acyclic and cyclic forms will be pertinent to this study, calculations have been performed on models which are expected to approximate these structures. The models have been referred to a left-hand cartesian coordinate system with the phosphorus atom at the origin (Figure 2). Oxygen

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Table I. Net Charges and π-Electron Energies for Various Conformations of Phosphate Esters

Model	θ_2, deg	θ_3, deg	θ_4, deg	Molecular relations	π-Electron energy in units of β_{cc}	Net charge				
						O_1	O_2	O_3	O_4	P
					Diester anions					
1	. . .	0	0		19.4018	−0.6152	−0.6152	−0.3657	−0.3657	+0.3219
2	. . .	90	90		19.7910	−0.5454	−0.5454	−0.3573	−0.3573	+0.1655
3	. . .	110	110	Diethyl phosphate anion	19.7769	−0.5516	−0.5516	−0.3503	−0.3503	+0.1639
4	. . .	140	140	Trimethylene phosphate anion	19.6497	−0.5791	−0.5791	−0.3413	−0.3413	+0.2008
5	. . .	182	192	Ethylene phosphate anion	19.1729	−0.6502	−0.6420	−0.3324	−0.3312	+0.3159
					Triester					
6	150	0	113	Dibenzylphosphoric acid	16.8300	−0.4866	−0.3130	−0.3105	−0.2850	+0.4351
7	0	182	192	Methyl ethylene phosphate	16.5764	−0.5212	−0.3095	−0.3179	−0.3200	+0.5085

atoms 3 and 4 are in the *YZ* plane and oxygen atoms 1 and 2 are in the *XZ* plane. The bond lengths for all molecules are taken as P–O = 1.44 A and P–O(C) = 1.57 A. These are close to the distances in methyl ethylene phosphate[17] and dibenzylphosphoric acid.[18] In the acylic esters the ∠OPO angles are taken as 109° 28′ but in the 5-cyclic structures this angle in the ring is reduced to 99° in accord with the crystal structure results on methyl ethylene phosphate.[17] These distances and angles are probably rather poor approximations for the diester phosphate anion but at this stage detailed adjustments of these parameters are of doubtful significance. In any case, the conclusions will not be affected by reasonable variations of bond distances or ∠OPO angles.

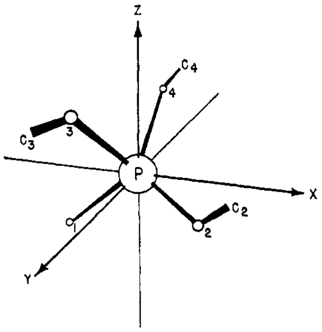

Figure 2. Coordinate system in relation to the molecular models for phosphate esters. $C_3O_3PO_4C_4$ are all in the *YZ* plane while $O_1PO_2C_2$ are in the *XZ* plane. The conformation illustrated here has $\theta_2 = \theta_3 = \theta_4 = 0°$.

On the nonesterified oxygen atoms one 2p orbital involved in the π-bonding is taken parallel to the +*Y* direction while the other is taken perpendicular to it and the σ bond. The 2p π-bonding orbital on an esterified oxygen atom is taken perpendicular to the COP plane. The relative orientation of this p orbital with respect to the d orbitals on the phosphorus atom, and hence the magnitude of the various 2p–3d G_{rs} factors, will depend on the orientation of the ester group about the P–O bond. The angular degree of freedom for each esterified oxygen atom is specified by the angle θ between the normal to the COP plane and the +*X* axis for θ_3 and θ_4 and between the normal to the plane and the +*Y* axis for θ_2; $\theta_3 = 0°$ and $\theta_4 = 0°$ correspond to conformations where the respective carbon atoms lie in the *YZ* plane and point away from the *Z* axis as in Figure 2; $\theta_2 = 0°$ corresponds to the conformation where C_2 is in the *XZ* plane pointing away from the *Z* axis as in Figure 2. A positive angle corresponds to a clockwise rotation looking down the O–P σ bond from O to P.

The values θ_3 and θ_4 for the 5-cyclic esters in both the anion and neutral molecule are taken equal to the corresponding angles found in methyl ethylene phosphate.[17] The values for the 6-cyclic trimethylene phosphate anion are derived from a structure assembled with Courtauld atomic models. Values of θ_3 and θ_4 for the acyclic diester are taken from the structure of barium diethyl phosphate while the angles θ_2, θ_3, and θ_4 for the acyclic triester are assumed, for lack of any other model, to be equal to those in dibenzylphosphoric acid.[18]

Results

The self-consistent parameters for the diester phosphate monoanion (model 2, see Table I) are typical of those obtained in these calculations and are given in Table II.

Table II. Self-Consistent Hückel Parameters

Overlap Integrals, S_{rs}	
P–O	0.322
P–O(C)	0.295
Coulomb Parameters, δ_r	
P	−0.719
O	1.015
O(C)	1.087

There are three general features of the results (Table I) which appear to be significant. First, model 2 has the greatest π-electron energy (a negative quantity) of all the diester models tested and a qualitative consideration of orbital overlaps shows that all other orientations of the ester groups would lead to a smaller π-electron energy. This is roughly the structure found in barium diethyl phosphate.[19] A plot of π-electron energy *vs.* θ for symmetrical diester phosphates (Figure 3) shows a broad minimum and this suggests that the conformation of the diester within 20° of the minimum might be sensitive to other factors such as the neglected intramolecular interactions and the environment of the

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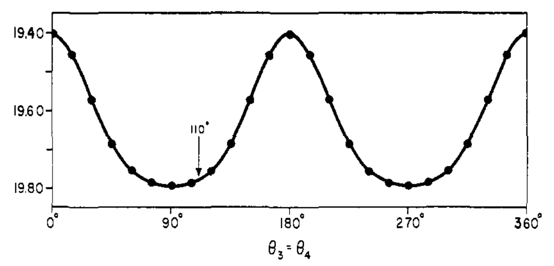

Figure 3. π-Electron energy (E_π) in units of β_{cc} *vs.* θ for the symmetrical phosphate diester models. The value of $\theta = 110°$ corresponds to the observed angle in barium diethyl phosphate.

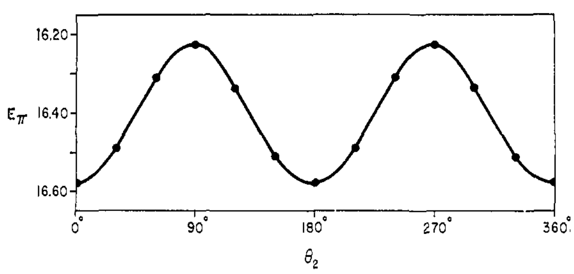

Figure 4. π-Electron energy (E_π) in units of β_{cc} *vs.* θ_2 for 5-cyclic triester models. θ_3 and θ_4 are held fixed at their values in methyl ethylene phosphate as θ_2 is varied. The observed θ_2 in methyl ethylene phosphate is 356.4°.

molecule. Second, as the conformation of the ester group about the phosphorus–oxygen bond changes, there is a relatively large change in the net charge on the phosphorus atom but only a small change in the charge on the esterified oxygens. Third, the change in π-electron energy with change in conformation is relatively small–about 2% of the β-term contribution.

Discussion

There is little point in an exhaustive discussion of the stable conformation and bond distances in phosphate esters until more crystal structure determinations are available. For the diester anion the maximum π energy occurs for $\theta_3 = \theta_4 = 90°$ but this conformation places carbon atoms C_3 and C_4 closer to one of the nearest nonbonded oxygens than the other. The symmetric position where the O–C bond bisects the angle $\angle$OPO formed by nearest nonbonded oxygens (Figure 2) corresponds to $\theta_3 = \theta_4 = 120°$. The observed θ_3, θ_4 angles in barium diethyl phosphate are close to 110° and thus it appears that the actual conformation may be a compromise between maximum π bonding and minimum interaction between the ethyl groups and close nonbonded oxygens. Reasonably accurate crystal structure information is available for potassium O,O-dimethylphosphordithioate[20] where the bonding would be expected to be qualitatively similar to that in a diester phosphate. Here the pertinent angles are $\theta_3 = \theta_4 = 88.3°$, close to the theoretical position of maximum π energy. It is also of interest that the energy difference between structures 1 and 3 can be attributed entirely to interactions between the 2p orbital on oxygen and the "weakly bonding" 3d orbitals on phosphorus that Cruickshank omitted from his discussion. That is, if calculations are performed omitting the three weakly bonding d orbitals, the π-electron energies for the 1 and 3 forms are identical.

A plot of E_π *vs.* θ_2 for the cyclic methyl ethylene phosphate is shown in Figure 4. The actual value of θ_2 in the solid state is $\theta_2 = 356.4°$, which is quite close to a position of maximum π energy ($\theta_2 = 357.5°$). In this case the value of θ_2 for maximum π-energy corresponds closely to the angle that places C_2 midway between its nearest nonbonded oxygen atoms.

The attack of nucleophilic agents, primarily H_2O and OH^-, on di- and triester phosphates in both their acyclic and cyclic forms has been studied intensively. The anion of dimethyl phosphate is fairly unreactive and hydrolyzes slowly, even at 100°, by a combination of C–O fission (nucleophilic attack on carbon) and P–O fission (nucleophilic attack on phosphorus).[21,22] In contrast, the hydrolysis of the cyclic ethylene phosphate anion is enormously faster than that of the acyclic dimethyl phosphate anion and occurs predominantly through attack on phosphorus. An enhancement by a factor of 10^8 in the rate of attack on the phosphorus in the cyclic over the acyclic form has been observed. There is no comparable enhancement of attack on carbon and it may be that the rate of this attack is roughly the same in both forms.

The triester phosphate is similar to the diester in that the phosphorus in the cyclic form (*e.g.*, methyl ethylene phosphate) is much more sensitive to nucleophilic attack than in acyclic form.[23] Also, there is a shift of about −18 ppm in the ^{31}P nmr spectrum in the 5-cyclic forms of various phosphate triesters relative to the acyclic forms[24,25] that may reflect a relative deshielding of the nuclear charge on phosphorus.

At first this kinetic acceleration of attack on the phosphorus atom was attributed to strain in the five-membered ring since the six-membered ring compound, trimethylene phosphate, reacts only slightly faster than dimethyl phosphate.[26] Further support for the existence of strain in methyl ethylene phosphate was provided by measurements of the heats of saponification of the acyclic and 5-cyclic compounds.[23] These showed that the 5-cyclic compound has a heat of saponification 7 to 9 kcal/mole higher than the acyclic analog. This figure has been revised downward to 5.5 kcal/mole in more recent work.[27] Further evidence based primarily on the hydrolysis of cyclic phosphites and sulfites suggested that strain in the five-membered ring may not be the main reason for the high reactivity of the cyclic compounds and the suggestion was advanced that the acyclic ester might be stabilized relative to the cyclic ester by π-type bonding that involves the 3d orbitals on the central atom.[27] More recently the argument ap-

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pears to have swung back toward minimizing the importance of 2p–3d bonding.[28]

The correct procedure for the theoretical study of reaction rates involves evaluation of transition-state as well as ground-state energies. Since the geometries of the transition states for the reactions considered here are not known this procedure cannot be used as yet. However, some model calculations on a trigonal bipyramid pentacovalent transition state[22] for the attack of a hydroxyl ion on a diester phosphate anion suggest that the π energy of the transition state may be relatively insensitive to the conformation of the ester groups. Variation of the ester orientation from $\theta_3 = \theta_4 = 0°$ to $\theta_3 = \theta_4 = 90°$ makes a change of only $0.013\beta_{cc}$ in the π energy of the transition state with this model while the same change in conformation in the ground state leads to a change of $0.39\beta_{cc}$ (see Table I) in the π energy. The following discussion of chemical reactivity is based on ground-state properties only, and, although rather limited theoretical calculations lend some support to this procedure in the treatment of phosphate ester hydrolysis, the basic justification must reside in the agreement between the theoretical and experimental results.

In order to discuss the experimental facts of chemical reactivity in terms of electronic structure two simple criteria for reactivity will be used. Since the reactions of interest proceed through nucleophilic attack, an increase in positive charge on the attacked atom might be expected to increase the rate of this process (rule 1). However, when this charge is constant on the atom attacked then the adjacent atom should play a predominant role and increased positive charge would be expected to increase the rate of bond fission between this atom and the one subjected to nucleophilic attack (rule 2). There is some relation between this picture and the "dispositivity" relation suggested by Pullman and Pullman[29] in connection with similar reactions. Since our calculations are rough and the atom charges depend to a great extent on the σ-bond polarity assumptions, whether an atom charge is positive or negative (especially the charge on the ester oxygen) is of doubtful significance. However, the direction of change in charge (and to a lesser extent the magnitude of this change) is significant when a series of similar compounds is compared.

On applying these simple ideas to the diester phosphate anions, it can be seen from Table I that when an ester goes from its stable acyclic form (model 3) toward the 5-cyclic form (model 5) there is a large increase in positive charge on the central atom which would be expected by rule 1 to lead to the increased reactivity that is actually observed. Rule 2 tells us that the bond broken will be the O(C)–P bond rather than the O–P bond since in the latter case the oxygen is much more negative than in the former. This is in agreement with experiment since ^{18}O exchange with the unesterified oxygen atoms is not observed in either diester phosphate anion form.[22] The constant charge on carbon and the relatively constant charge on the ester oxygen are consistent with the lack of any observed kinetic acceleration in C–O fission on going from the acyclic to cyclic form.

The charge distribution of the 6-cyclic form lies close to that of the acyclic structure and thus the reactivity would be expected to lie close to that of the acyclic ester, in accordance with experiment.

The results in Table I for methyl ethylene phosphate are also in accord with the general increased reactivity of phosphorus in the cyclic ester and the observed ^{31}P nmr shift. It may well be that dibenzylphosphoric acid is not a particularly good model for the acyclic triester. Certainly there are other conformations that will give increased π-bonding energy (and decreased positive net charge on the phosphorus) but a better treatment of the problem must await the crystal structure analysis of an acyclic triester.

In the 5-cyclic triester the net charges on the ring oxygen atoms are -0.3179 and -0.3200. These are very slightly more negative than on the noncyclic esterified oxygen, -0.3095. The exclusive splitting of the P–O ring bond in basic aqueous solution is in disagreement with the theoretical predictions on this point. However, when nucleophilic attack by water is carried out in aprotic solvents on certain 5-cyclic triesters hydrolysis occurs primarily at the noncyclic ester oxygen.[30] The limited experimental work suggests that in the cyclic triester phosphates the particular P–O bond that is broken during nucleophilic attack on phosphorus depends on secondary conditions, such as solvent, which have not been considered in the present theoretical treatment. The close similarity in net charges for the ring and nonring esterified oxygen in the 5-cyclic triester makes such a change in bond breaking with experimental conditions appear plausible.

On the simple picture developed here the difference in heats of hydrolysis between a cyclic and acyclic triester should be primarily equated with the difference in π energy between the two forms plus the difference in σ energy associated with the angle distortions in the cyclic structure. The σ-energy changes cannot be allowed for in the present scheme but it is possible to estimate the π-energy changes. The difference in π energy (Table I) for models 6 and 7 is $0.2536\beta_{cc}$. If β_{cc} is taken equal to -16 kcal/mole, a value obtained from a comparison of empirical and calculated resonance energies of aromatic compounds,[10] the predicted difference in π energy is 4.1 kcal/mole. The difference in heat of saponification (ΔH of ethylene ester minus ΔH of acyclic ester) is close to 5.5 kcal/mole.

The agreement between the calculated and observed quantities should not be construed as a quantitative justification for the theory. The encouraging feature is the fact that the calculated π energy is not greater than the observed difference in heats of saponification. Changes in the σ energy associated with bond distortion may still be important. It should be noted that the p orbitals on oxygen involved in the π bonding with phosphorus are always taken to be perpendicular to the POC plane. This is reasonable when the $\angle$POC angles are close to 120°, as they probably are in the acyclic structures. The corresponding angles on the ring oxygens in methyl ethylene phosphate are 112°,[17] closer to what one might expect for sp^3 hybridization. The treatment in this paper implies that the hybridization on all the ring atoms in the cyclic structures remains

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(30) F. Ramirez, O. P. Madan, N. B. Desai, S. Meyerson, and E. M. Banas, *J. Am. Chem. Soc.*, **85**, 2681 (1963).

unchanged from that of the acyclic structures and this in turn implies that the σ orbitals on the oxygen and phosphorus atoms of the ring deviate from the internuclear axis by about 4°. A satisfactory resolution of the relative importance of hybridization changes, σ-bond changes, and π bonding cannot be obtained by the elementary approach used here. On the other hand, this treatment does present one way of looking at the problem of bonding in phosphate esters which is in general agreement with experimental results.

The theory has some implications which may be of importance in understanding the role of phosphates in biochemical systems. The calculations suggest that with a small expenditure of energy (less than 10 kcal/mole), conformational changes can be brought about which alter the 2p–3d interaction sufficiently to cause large changes in charge distribution which in turn lead to large changes in chemical reactivity. In molecules more complex than the simple aliphatic esters, conformational changes of the type described here might be brought about by interaction with the surroundings through hydrogen bonding or ionic attraction. Conformational changes and their effect on 2p–3d π-type bonding in phosphates and polyphosphates may be significant factors in the catalytic activity of enzymes, metal ions, and surfaces on biochemical reactions involving phosphorus.

Addendum

After this manuscript had been submitted for publication the crystal structure analysis of methyl pinacol phosphate by Newton, Cox, and Bertrand[31] came to my attention. Dr. Newton was kind enough to furnish information on this structure in advance of publication. This compound has a five-membered ring, as does methyl ethylene phosphate, but presumably because of steric hindrance with the methyl groups attached to the ring the methyl ester group does not lie between the ring oxygen atoms as in methyl ethylene phosphate but is rotated almost 180°. In terms of the angular coordinate used in this paper, θ_2 for methyl pinacol phosphate lies in the energy minimum near 180° rather than in the minimum at 0° as in methyl ethylene phosphate (see Figure 4). More detailed considerations of the methyl pinacol phosphate structure show that θ_2 is actually 160°—a deviation of about 20° from the calculated energy minimum—but such a deviation involves an increase in energy of only $0.03\beta_{cc}$ (0.5 kcal/mole) relative to the energy minimum. Presumably this deviation can be attributed to repulsion between the methyl ester group and the nonesterified oxygen on phosphorus.

Newton, Cox, and Bertrand discussed the conformation and high chemical reactivity of methyl pinacol phosphate and methyl ethylene phosphate in qualitative terms making use of the same basic arguments on 2p–3d π bonding that are used in this paper. Although there are some formal differences between their interpretations and those in this paper (particularly with regard to chemical reactivity) both conclude that π bonding in phosphate esters is an important factor in determining their conformation and chemical reactivity.

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