J. Am. Chem. Soc. 1984, 106, 7825–7831

Stereoelectronic Effects on the Basicity and Nucleophilicity of Phosphites and Phosphates. Ab Initio Molecular Orbital Calculations and the α-Effect

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Abstract: Ab initio molecular orbital calculations on phosphites, protonated phosphites, and protonated phosphates reveal important stereoelectronic effects. In the phosphites, an antiperiplanar lone pair on oxygen to the phosphite lone pair raises the energy of the molecule by 3.3 kcal/mol relative to a phosphite conformation with no antiperiplanar lone pairs to the phosphite lone pair. Upon phosphorus protonation of the phosphite the relative energy difference between the conformations reverses. The conformation with lone pairs on oxygen antiperiplanar to the P–H bond is now more stable than the conformation without this antiperiplanar lone-pair interaction. Finally, the origin of the α-effect, the enhanced nucleophilicity of a base possessing a heteroatom with an adjacent unshared electron pair, is suggested to arise from the stereoelectronic effect. This is attributed to a transition-state stereoelectronic effect. Whereas oxygen lone pairs antiperiplanar to the P–H$^+$ in the ground-state protonated phosphite stabilize the structure by only 1 kcal/mol at a P–H distance of 1.4 Å, this stereoelectronic stabilization rises to $>$12 kcal/mol, at a P–H distance of $\sim$3 Å, falls off again at even longer P–H bond distances, and finally reverses energies for the two confirmations of the neutral phosphites.

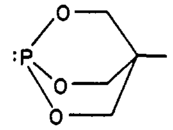
The role of orbital orientation in organic and enzymatic reactions has been of considerable current interest.[1-10] Deslongchamps and co-workers[2] in studying tetracovalent carbon species have demonstrated selective cleavage of bonds which are trans-antiperiplanar (app) to lone pairs on directly bonded oxygen and nitrogen atoms. Molecular orbital calculations have provided theoretical justification for these stereoelectronic effects in tetracovalent carbon and phosphorus species and pentacovalent phosphoranes.[5-11] Thus, as has been shown in molecular orbital calculations on the X_1–Y–X_2 (X = O, N; Y = P, C) structural fragments, the X_1–Y bond is strengthened (as indicated by an increase in the Mulliken overlap population) while the Y–X_2 bond is weakened when the X_1 atom lone pair is app to the Y–X_2 (Structure A, Figure 1) bond. In the gauche, trans (*g*, *t*) conformation of dimethoxymethane (Structure A, Figure 1, X = OCH_3, Y = CH_2) the overlap population for the trans C–O (Y = C, X_2 = O) bond is 0.022 electron lower than the overlap population for the gauche C–O bond. In the *g*,*t*-dimethoxymethane one lone pair (shaded in A) on the gauche bond oxygen is app to the trans C–O bond, while no lone pairs on the trans bond oxygen are app to the gauche bond. Thus, the Y–X_2 bond is weaker than the X_1–Y bond because it has one app lone pair on X_1 and no lone pairs on X_2 app to the X_1–Y bond.[8] Lehn[5,6] and Pople[7] and co-workers have shown similar overlap population differences in related systems.

Molecular orbital calculations on phosphate esters (Figure 1, X_1, X_2 = OCH_3, Y = PO_2^-) and tetrahedral carbon intermediates (Figure 1, X_1 = NH_2, X_2 = OH, Y = CHOH) have also provided confirmation for the stereoelectronic effect.[6,8-10] Ab initio molecular orbital calculations[11] on the reaction profile for the base-catalyzed hydrolysis of dimethyl phosphate in various ester conformations have provided support for this stereoelectronic theory.

$$(CH_3O)_2PO_2^- + {}^-OH \rightarrow (CH_3O)_2PO_3H^{2-} \rightarrow (CH_3O)PO_3H^- + CH_3O^- \quad (1)$$

Separate transition states were observed for the first addition step and the second elimination step. A metastable pentacovalent intermediate [$(CH_3O)_2PO_3H^{2-}$] was established along the reaction coordinate. Significantly, for the methoxide elimination step the transition state which has an antiperiplanar lone pair to the methoxide leaving group is ca. 11 kcal/mol lower in energy than the transition state without this app lone pair.

Phosphite as well as phosphate esters undergo marked changes in properties (basicity, nucleophilicity, rate of hydrolysis, spectra) upon inclusion of the phosphorus atom into a monocyclic or a bridgehead bicyclic system.[12-16] We demonstrate both theoretically and experimentally in this and the accompanying paper that stereoelectronic effects play an important role in these properties.



bicyclic
phosphite

Finally, the origin of the α-effect, the enhanced nucleophilicity of a base possessing a heteroatom with an adjacent unshared electron pair, has been much debated. We emphasize that the α-effect may also be considered a stereoelectronic effect.

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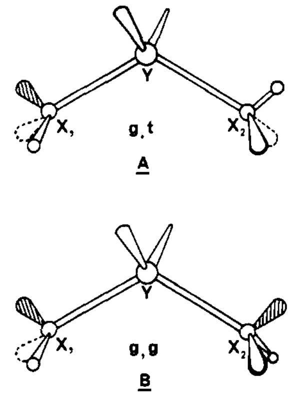

Figure 1. Conformations *g,t* (structure A) and *g,g* (structure B). Dihedral angles about the X_1Y and X_2Y bonds are defined by the $-X_1-Y-X_2-$ structural fragment and are gauche (*g*, dihedral angle ±60°) or trans (*t*, dihedral angle 180°). For $X_1 = X_2$ = divalent oxygen, the sp^3-hybridized lone pairs are also shown, with the antiperiplanar lone pairs being shaded.

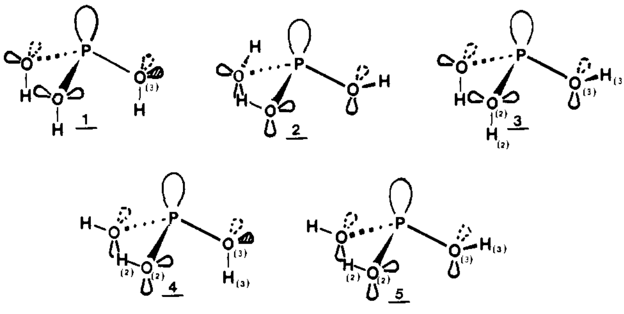

Figure 2. Structures for different conformations of phosphites.

Methods of Calculation

The SCF LCAO-MO ab initio calculations utilized the GAUSSIAN 70 and 80 series of programs generally with a STO-3G minimal basis set[17] (although a 6-21G basis set also was used for single point calculations). Except for some of the partially protonated phosphites, standard scale factors were used where indicated using the geometry optimized at the STO-3G level. In the other structures, which would not converge with the standard scale factors, the valence shell scale factors were optimized and then sequentially in three groups: phosphorus 3sp, ester oxygen 2sp, and proton 1s. The molecular geometries were optimized either by sequentially varying a set of geometrical parameters until the total energy had been effectively minimized (<0.1 kcal/mol) or utilizing the geometry optimization routine of GAUSSIAN 80 (both procedures yielded identical geometries where tested). The final geometries for phosphites and protonated phosphite and phosphate esters are given in Table I.

All calculations were carried out on an IBM 4341 computer.

Results and Discussion

Ground-State Stereoelectronic Effects in Phosphites. Shown in Table I are the relative energies for various conformations of phosphites (see Figure 2 for structures). The results are basically consistent with the ground-state anomeric, stereoelectronic effect.[1,7] Similar results are obtained with STO-3G or 6-21G basis sets. Although other interactions are operative[18] and it is not our intent to discuss them here, in general it is energetically more favorable to have a conformation about the P–O bond which allows an oxygen lone pair to be trans, antiperiplanar (app) to an adjacent polar bond (P–OR). This ground-state stereoelectronic effect is presumed to arise from the favorable orbital interaction of the oxygen lone pair orbital, n, with the antibonding P–O σ* orbital.[1]

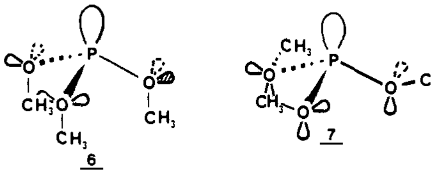

Figure 3. Structures for different conformations of trimethyl phosphites.

This two-electron interaction of these two orbitals is stabilizing. In contrast, it is destabilizing to have an oxygen lone pair orbital app to the phosphorus lone pair orbital. This is a four-electron, lone-pair–lone-pair interaction which is overall destabilizing.[18] Thus **4** is 3.3 kcal/mol lower energy than **5**. The conformations differ in rotation about only one of the three P–O bonds. In **4** both lone pairs on O-3 are app to the adjacent polar P–O bonds while in higher energy **5**, one of the lone pairs on O-3 is app to the phosphorus lone pair. **5** has one more destabilizing four-electron orbital interaction and one less two-electron stabilizing orbital interaction. Similarly **2** is 3.0 kcal/mol higher energy than **3**. Again **3** has two more n $\leftrightarrow$ σ* favorable interactions and two less $n_O \leftrightarrow n_P$ (O, oxygen; P, phosphorus) unfavorable interactions. An exception to this analysis is seen in comparing **1** and **3** which differ in conformation only about P–O_3. Phosphite **1**, which has the same conformation as the bicyclic phosphite, is higher energy than **3** in spite of the more favorable lone pair orientation on O-3 in **1** relative to **3**. Actually, as has been shown earlier for phosphate and tetrahedral carbon species,[5,8] a secondary "counterbalancing" stereoelectronic effect probably is responsible for some of these energy differences (particularly between **1** and **3**). Thus, interaction of a lone pair app to an adjacent acceptor bond is favored if the acceptor bond oxygen is not participating in any stereoelectronic interactions with an adjacent polar bond. Note in **3**, O-3 has one fewer oxygen lone pair app to adjacent polar bonds than in **1**. Thus the P–O-3 bond is a more effective acceptor bond. Bond length differences (Table I) and population analyses and atomic charges (Table II) support this counterbalancing stereoelectronic effect.

This difference could also be attributed to either an unfavorable 1,3-steric interaction between the hydrogens or unfavorable dipole interaction in "bicyclic" **1**. Note in Table I, (see Figure 3 for structures) large 1,3-steric interactions between the methyl groups of the trimethyl phosphite esters are presumably responsible for the much higher energy of **6** (comparable conformation to **1**) relative to **7** (comparable conformation to **2**).

Indeed in spite of this unfavorable steric or dipole interaction in **1**, it is still 1.4 kcal/mol lower energy than **2**. **1** has three additional favorable two-electron interactions relative to **2** and three fewer unfavorable lone-pair–lone-pair interactions. Eliminating the unfavorable steric or dipolar interactions in **1**, and assuming a similar 3.3 kcal/mol stabilization per orbital interaction as in the **4**/**5** pair, **1** should be 3.3–9.9 kcal/mol rather than just 1.4 kcal/mol more stable than **2**. The actual stereoelectronic stabilization of **1** relative to **2** is thus *at least* 1.4 kcal/mol and possibly much greater. In fact, at the 6-21G level of calculation, **1** is 5.5 kcal/mol lower in energy than **2**.

Stereoelectronic Effects in Protonated Phosphites. This relative energy differences between conformations **1** and **2** *reverses* upon protonation of the phosphite. As shown in Table I using both STO-3G and 6-21G (Figure 4) basis sets, **9b** (comparable conformation about the P–O bonds to **2**) is now 4.6 kcal/mol *lower* energy than **8b** (comparable conformation to **1**) at a P–H$^+$ distance of 1.8 Å.[19] This reversal is graphically depicted in Figure 5. This is exactly the stereoelectronically expected result since **9** has three oxygen lone pairs app to the polar P–H$^+$ bond (analogous to a polar P–O bond). A similar energy difference was observed for the protonated phosphates (**10** and **11**),[20] where the protonated "acyclic" phosphate **11** is 3.9 kcal/mol more stable than the

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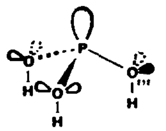
(19) The proton and phosphorus distance was arbitrarily chosen to be 1.8 Å, and the geometries of the "bicyclic" and protonated phosphates were not optimized.

(20) All O–H bond distances were assumed to be 1.0 Å.

Table I. STO-3G Optimized Geometries and Relative Energies for Phosphites, Protonated Phosphites, and Protonated Phosphates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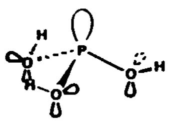
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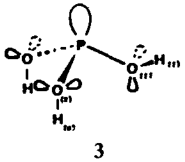
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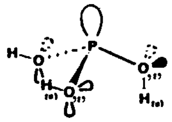
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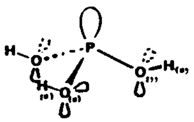
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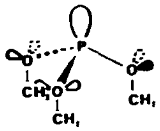
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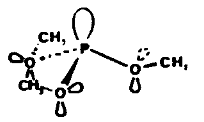
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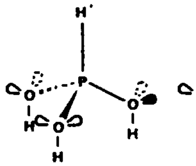
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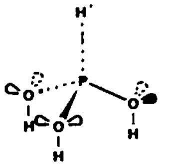
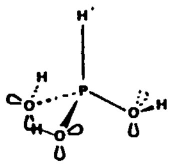

8b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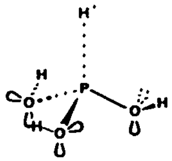
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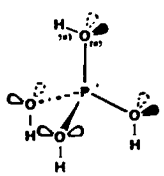
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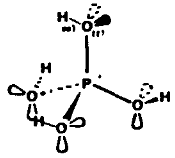
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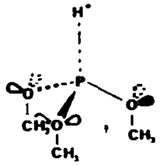
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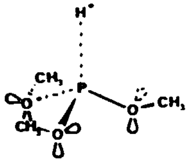
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conformation	1	2	3	4	5	6	7	8a	8b	9a	9b	10	11	12	13
P-O	1.677	1.689	1.672	1.690	1.683	1.671	1.689	1.657	1.658	1.657	1.656	1.651	1.649	1.655	1.653
$\angle OPO_2$: θ	98.9	95.3	99.7	96.6	98.4	106.0	94.6	112.9	112.1	107.4	106.6	112.9	107.938	115.1	106.8
$\angle PO\begin{bmatrix}H\\C\end{bmatrix}:\psi$	109.3	105.9	108.4	106.8	105.9	126.8	114.3	109.7	109.0	108.4	108.6	110.1	108.7	120.4	114.7
$\angle\begin{bmatrix}\text{lone pair}\\H^+\\O\end{bmatrix}PO$: ϕ	118.7	121.4				112.7	122.0	105.8	106.7	111.5	112.2	105.7	111.0	103.0	112.1
$\tau\begin{bmatrix}\text{lone pair}\\H^+\\O_3\end{bmatrix}PO\begin{bmatrix}H\\C\end{bmatrix}$	180.0	60.0				180.0	60.0	180.0	180.0	60.0	60.0	180.0	60.0	180.0	60.0
$P-O_2$			1.680	1.690	1.692										
$P-O_3$			1.690	1.664	1.678							1.646	1.654		
$\angle O_2PO_3$			97.2	94.5	94.4										
$\angle OPO_3$: ζ			94.7	94.5	91.9										
$\angle PO_2H_2$			108.6	106.8	106.6										
$\angle PO_3H_3$			105.7	106.5	105.7							107.5	108.9		
τH_3O_3PO			180.0[a]	48.5	180.0[a]							180.0[a]	180.0[a]		
$P-H^+$								1.386	1.8[a]	1.396	1.8[a]			1.8[a]	1.8[a]
relative energy, kcal/mol	0.0	1.4[b]	−1.6[b]	−1.6[b]	1.7[b]	0.0	−19.8[c]	−39.6[d]	0.0	−40.4[d]	−4.6[d]	0.0	−3.9[e]	0.0	−10.0[f]

total E (1) = −560.17078 (STO-3G), −566.68300 (6-21G)
total E (6) = −675.87615 (STO-3G)
total E (**8b**) = −560.47218 (STO-3G), −566.91636 (6-21G)
total E (**10**) = −560.38078 (STO-3G)
total E (**12**) = −676.21332 (STO-3G)

O–H = 1.0,[a] C–O = 1.43,[a] $\angle$OCH = 109.5[a]
τPOCH[a] = 30, 150, 270°

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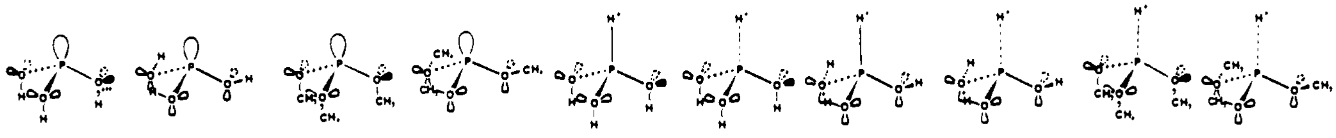
[a] Assumed. [b] Relative to 1. [c] Relative to 6. [d] Relative to **8b**. [e] Relative to 10. [f] Relative to 12 (STO-3G).

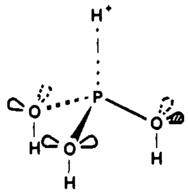
Table II. Population Analyses and Atomic Charges for Phosphates, Protonated Phosphites, and Protonated Phosphates

Conformation

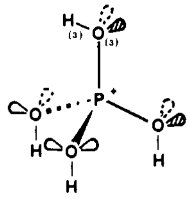


1 2 6 7 8a 8b 9a 9b 12 13

	1	**2**	**6**	**7**	**8a**	**8b**	**9a**	**9b**	**12**	**13**
					Population Analyses					
P–O	0.3910	0.3756	0.3680	0.3786	0.4074	0.3970	0.4200	0.4124	0.3966	0.4182
O–H	0.4854	0.4932	0.5196	0.5236	0.5116	0.5080	0.5148	0.5146	0.5114	0.5122
H^+–P					0.6762	0.5020	0.6026	0.4576	0.5058	0.4506
					Atomic Charges					
P	+0.8652	+0.7924	+0.8956	+0.8357	+1.1784	+1.1219	+1.1800	+1.1306	+1.1457	+1.152
O	−0.4271	−0.4199	−0.4106	−0.3896	−0.3295	−0.3355	−0.3318	−0.3347	−0.3246	−0.317
H (C)	+0.1387	+0.1558	−0.0756	−0.0764	+0.2470	+0.2400	+0.2632	+0.2608	−0.0700	−0.073
H^+					+0.0693	+0.1647	+0.0256	+0.0913	+0.1269	+0.069



8a,b



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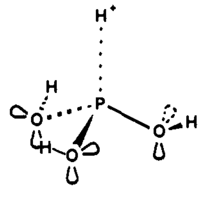
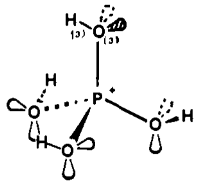


9a,b



11

Figure 4. Structures for different conformations of protonated phosphites and protonated phosphates.

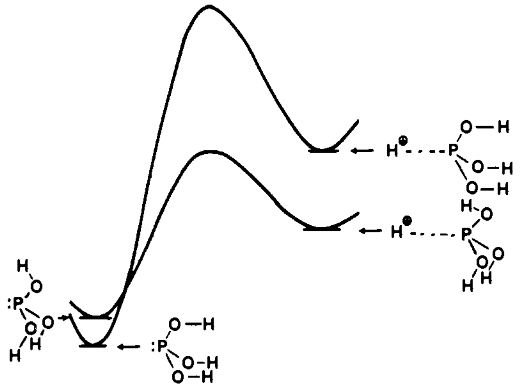
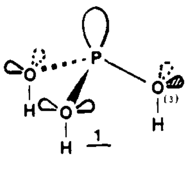
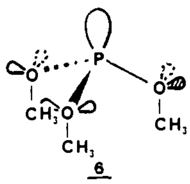
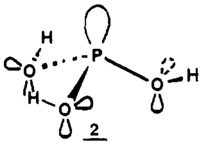
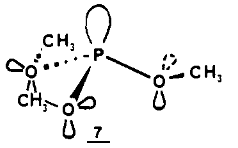


Figure 5. Graphical depiction of relative energies of phosphites, protonated phosphites, and solution phase transition states.

Table III. Calculated HOMO Ionization Potentials for Phosphites

structure	IP, eV	structure	IP, eV
	9.17,[a] 10.3[b]		8.17[a]
	7.17[a]		6.94[a]

[a] Calculated, this work. [b] Calculated, ref 16c, based upon full bicyclic phosphite structure.

protonated "bicyclic" phosphate **10** presumably for the same stereoelectronic argument.

This energy difference between the two protonated geometries would have been greater if methyl groups could have been used in place of hydrogen in both "bicyclic" and "acyclic" phosphites (and also phosphates). The basis for stabilization of the "acyclic" molecules is the stereoelectronic (anomeric-type) two-electron stabilizing interaction of the vicinal nonbonding orbitals with the antibonding orbital of the incipient P–H^+ bond. On the basis of one-electron molecular orbital theory, the two-electron stabilization resulting from the interaction of a doubly occupied MO(ζ) with a vacant nondegenerate MO(σ^*) may be approximated as being inversely proportional to the energy separation of the two MO's and directly proportional to the square of their overlap

$$\mathrm{SE}(\zeta,\sigma^*) \propto \frac{S^2_{\zeta\sigma^*}}{\Delta E_{\zeta\sigma^*}} \qquad (2)$$

In the above example the doubly occupied MO(s) is a nonbonding orbital (ζ = n) on oxygen, however, ζ can be $\sigma_{\mathrm{O-H}}$, $\sigma_{\mathrm{O-C}}$, $\sigma_{\mathrm{C-H}}$, $\sigma_{\mathrm{C-C}}$, etc, and it is expected that SE(n,σ^*) > SE($\sigma_{\mathrm{O-H}}$,σ^*), and SE(n,σ^*) > SE($\sigma_{\mathrm{C-H}}$,σ^*) > SE($\sigma_{\mathrm{C-C}}$,σ^*).[21] This implies that electron donation from the $\sigma_{\mathrm{O-H}}$ and $\sigma_{\mathrm{C-H}}$ bonds into the σ^* bond are better than the $\sigma_{\mathrm{O-C}}$ and $\sigma_{\mathrm{C-C}}$, respectively.

In spite of the fact that the $\sigma_{\mathrm{O-H}}$ bonds in the "bicyclic" analogue **1** can effectively donate electrons to the incipient σ^* bond upon protonation, the protonated "bicyclic" analogue **8b** is still calculated to be 4.6 kcal/mol higher energy than the protonated acyclic analogue **9b**. Therefore, the energy difference between protonated bicyclic and acyclic geometries is expected to be greater if hydrogens are replaced by alkyl groups because there is much less electron donation from the OC bonds in the bicyclic geometry.

Ionization Potentials. The stereoelectronic effect provides an explanation for the difference in ionization potentials of the phosphites. Assuming the validity of Koopmans' theorem, each ionization potential (IP_j) is simply equal in magnitude to an orbital energy (ϵ_j): $\mathrm{IP}_j = -\epsilon_j$. Calculated IP's for "bicyclic" (**1** and **6**) and "acyclic" (**2** and **7**) phosphites are listed in Table III and some experimental values for a few phosphites in Table IV.[16] Earlier ab initio MO calculations[16b] (see also ref 14c) with similar basis set as ours (but including 3d functions on phosphorus) indicated

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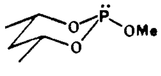
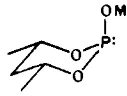
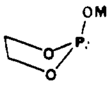
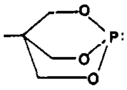
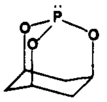
[21] Cieplak, A. S. J. Am. Chem. Soc. **1981**, 103, 4540.

Table IV. Experimental Vertical Ionization Potentials and Proton Affinities of Phosphites

no.	compd	IP[a]	PA[a]
14	$P(OCH_3)_3$	196 (8.50)	229.9
15		192 (8.34)	227.5
16		200 (8.69)	224.9
17		209 (9.06)	215.6
18		216 (9.35)	212.4
19		217 (9.42)	215.6
20		224 (9.72)	200.4

[a] From ref 14b in kcal/mol. Values in parentheses in eV.

that the phosphorus a_1 orbital is the HOMO orbital and is assigned to the lowest energy photoelectron band (lowest IP). Our own calculations agree with this assignment, although with a slightly poorer basis set our calculated IP's are slightly lower than Yarborough and Hall's and the experimental values. Qualitatively, however, there is good agreement between the relative energy differences.

Basicity of Phosphites. Measurements of gas-phase proton affinities,[14] and solution-phase basicities[13] of phosphites have revealed both bond angle and conformational effects. The gas-phase proton affinity (PA), which is defined as the hetereolytic bond dissociation energy for loss of a proton from the acid BH^+

$$BH^+ \rightarrow B + H^+ \qquad \Delta H = PA$$

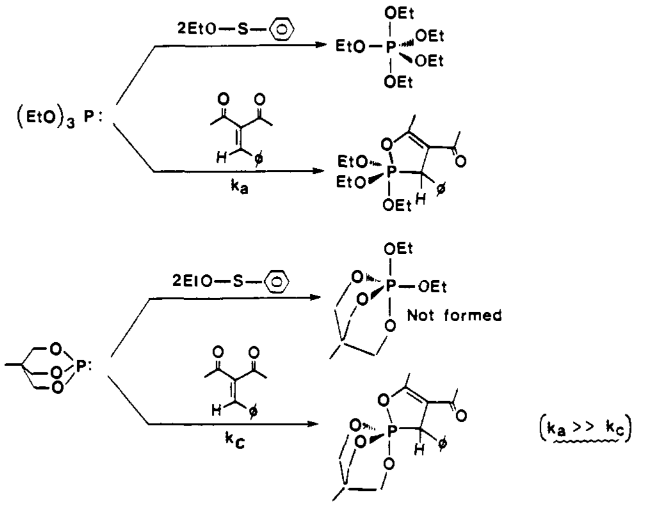
for various phosphites is listed in Table IV. As pointed out by Hodges et al.,[14a] the proton affinity decreases as the phosphorus lone pair ionization potential increases, a not uncommon relationship.[14a] Indeed the proton affinity is thermodynamically related to the base ionization potential, with

$$PA = D(B^+H) + IP(H) - IP(B)$$

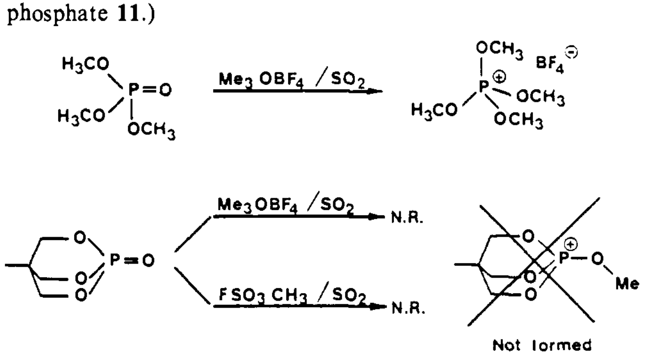
where $D(B^+H)$ is the homolytic bond dissociation energy and IP(H) is the ionization potential of the hydrogen atom. As discussed previously phosphorus-lone-pair–oxygen-lone-pair repulsion in the phosphite will raise the energy of the phosphorus lone pair orbital and hence decrease the IP and increase the PA.[12-14] In the protonated phosphite, oxygen lone pair overlap with the σ^* orbital (σ^*_{P-H}) will similarly affect the PA. Comparison of the experimental values in Table IV confirms these predictions. Clearly (O–P–O and P–O–C) bond angle is one factor (compare **17** vs. **15** and **20** vs. **18**) and is likely attributable to a "Hinge Effect" offered by Verkade[12,13] where hybridization changes with bond angles. Similarly as shown by our ab initio calculations and earlier CNDO/2 calculations,[14b] oxygen-lone-pair–phosphorus-lone-pair repulsion will vary with P–O torsional angles and hence orbital orientation. Note in particular that **15** has a lone pair on each of the ring oxygens which is app to the phosphorus lone pair. In **16** none of the oxygen lone pairs is app to the phosphorus lone pair, and significantly the phosphorus lone pair orbital is lower in energy (higher IP; Table IV). In contrast to the destabilizing interaction of an oxygen app lone pair to the phosphorus lone pair in the neutral phosphite, in the protonated phosphite, the oxygen lone pair will now be app to the P–H+ bond and this stereoelectronic effect will be stabilizing.

As supported by measured proton affinities (Table IV), the PA for bicyclic phosphite **1** is calculated to be 2.4 kcal/mol higher energy than that of the acyclic phosphite **2**. While a portion of the calculated PA difference is attributed to the IP difference of the neutral phosphites (likely also a reflection of the stereoelectronic effect), a portion is also due to the ground-state stereoelectronic effect in the protonated phosphites. Note that the bicyclic protonated phosphites **8a** is calculated to be 1.0 kcal/mol higher energy than the acyclic protonated phosphite **9a**, whereas the bicyclic phosphite **1** is 1.4 kcal/mol *lower* energy than the acyclic phosphite **2**.

Nucleophilicity and the α-Effect. As described in the accompanying paper, these results provide an explanation for the poor nucleophilicity of the bicyclic phosphite: The poor nucleophilicity of the bicyclic phosphite is likely due to the stereoelectronic effect. Verkade, while acknowledging the importance of these orbital interactions,[12] has also attributed these properties to a "Hinge Effect": ring constraint produces hybridization changes at the alkoxy oxygens which result in alteration of the π donating ability on oxygen lone pairs to the d-orbitals on phosphorus.[12-14] Our own analysis emphasizes the stereochemistry of proper orbital overlap between alkoxy oxygen lone pairs and the incipient σ* orbital of the newly forming bond to phosphorus, besides lone-pair–lone-pair repulsion in the neutral phosphite. Protonation at phosphorus will increase the O–P–O angle and the resulting increase in ring strain in the "bicyclic" transition state is also possibly partially responsible for the low nucleophilicity of the bicyclic phosphite.[22]



Similar considerations can also rationalize the resistance to alkylation of the bicyclic phosphate observed in this lab[23] and others.[24] (Note protonated "bicyclic" phosphate **10** is 3.9 kcal/mol higher energy than the protonated "acyclic" conformation of phosphate **11**.)



The "α-effect", the enhanced reactivity of nucleophiles possessing a pair of electrons α to the nucleophilic atom, can be viewed as a stereoelectronic effect. Although numerous explanations have

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[22] Emsley, J.; Hall, D. "The Chemistry of Phosphorus"; Wiley: New York, 1976.

[23] In preparation.

[24] Finley, J. H.; Denney, D. Z.; Denney, D. B. *J. Am. Chem. Soc.* **1969**, *91*, 5826.

been provided for the "α-effect" (see ref 25–27 and ref therein), one explanation that comes closest to the stereoelectronic orbital interaction picture is the one developed by Hudson[28] and Klopman.[29] Lone-pair–lone-pair orbital mixing (such as oxygen and phosphorus lone pairs in phosphites) will raise the energy of the HOMO and mixing with the lowest unoccupied molecular orbital (LUMO) will be enhanced. The major emphasis in these MO α-effect theories has been lone-pair–lone-pair interaction[12,28,29] rather than our stereoelectronic interpretation of *transition-state magnification* of adjacent lone-pair–σ^* interactions.[8,9] Indeed, as pointed out by Heaton[30] these "ground-state destabilization" arguments do not accord with the calculated and actual HOMO energies. His ab initio MO calculations instead emphasize the importance of the antibonding characteristics and higher polarizability of the α-effect HOMOs. All of these studies (including Heaton's) suffer from their emphasis on ground-state properties of α-effect nucleophiles. As we have emphasized the stereoelectronic effect (and likely the α-effect) is largely a transition-state phenomenon.[31] Significant mixing of n and σ^* is possible only in the transition state. It is this specific lowering of the transition-state energy by α-effect lone pair electrons that presumably is responsible for a significant fraction of the enhanced reactivity of these α-effect nucleophiles.

Our calculations strongly support the transition-state stereoelectronic effect basis for the α-effect. Although the strongly exoergic protonation of the phosphite does not proceed via a transition state in these gas-phase calculations (Figure 6A), we can still address the importance of the stereoelectronic effect on a structure that would likely resemble the solution phase transition state for electrophilic attack on a phosphite (Figure 5). Since the ionization potential of the neutral hydrogen atom is 13.6 ev,[33] and the ionization potentials for the phosphites are 8.5–9.7 eV (cf. Table IV) in order to prevent "premature" electron transfer from the phosphite to the proton, the scale factor on the 1s orbital of the proton was reduced at longer P–H distances. In this way we achieved convergence to a ground state with charge still largely on the proton at large (>4 Å) separation of the proton from the phosphites. In solution, of course, solvation of the proton would ensure that charge transfer would not occur until the approach of the proton was close enough. This distance depended upon the choice of the hydrogen orbital scale factor and for a hydrogen scale factor of 0.84, charge transfer and hence the "transition state" occurred around 3–4 Å. Again, in the gas-phase calculations no true transition state is found in this region (3–4 Å, Figure 6A). Note, however, that the stereoelectronic effect is maximized in this region (Figure 6B) which we are defining as the "transition state". It is likely significant that in other phosphorus reaction surfaces which we have calculated (ref 8, 9, and unpublished) true transition states were obtained at P–X internuclear separation of ~3 Å.

It is most important that the energy *difference* between the partially protonated "bicyclic" and "acyclic" phosphites reaches a maximum at a P–H distance of 3.0 Å ((Figure 6A,B), geometries in Table I). Again, the lowest energy conformation has the phosphite oxygen lone pairs app to the translating P–H bond. Thus in the ground state of the protonated phosphite oxygen lone pairs app to the P–H bond stabilizes the molecule by only 1 kcal/mol (compare **9a** vs. **8a**). In contrast, conformation **9** (corresponding to the "acyclic" structure) is at least 12 kcal/mol (with a STO-3G basis set) lower in energy than **8** (corresponding to the "bicyclic" phosphite) at a P–H bond distance of 3.0–4.0 Å (depending on the scale factors and basis set used in the calculations; the energy difference is 8.2 kcal/mol at 3-Å separation and calculated with the 6-21 basis set).

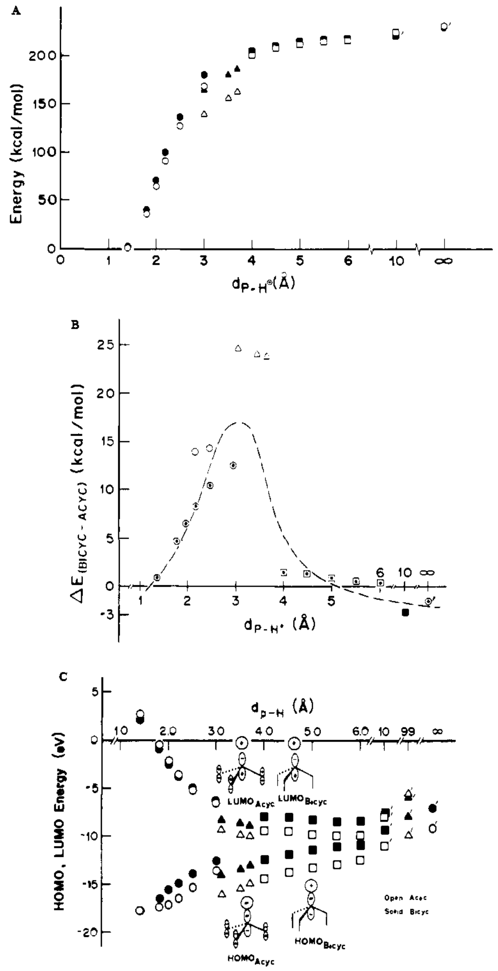

Figure 6. (A) Relative energies (STO-3G basis set) of protonated bicyclic, **8** and acyclic, **9** phosphites as a function of P–H bond distance. (○, ●) Open symbols, acyclic conformation **9**, closed symbols, bicyclic conformation **8**, standard scale factors at $d_{P-H} \leq 3$ Å. (△, ▲) Scale factors optimized at 3.5 Å. (□, ■) Scale factors used at 6.0 Å (see legend to Figure 6B). (□′, ■′) Scale factors adjusted for acyclic system at d_{P-H} = 10.0 Å, phosphite geometry. (○′, ●′) Standard scale factors, phosphite geometry, no proton. (B) Energy difference between protonated phosphite conformations **8** and **9** as a function of P–H bond distance. (⊙) d_{P-H^+} = 1.8 Å geometry. Standard scale factors: P_{3sp} = 1.90, O_{2sp} = 2.25, H_{1s} = 1.24. (○) Phosphite geometry ($d_{P-H^+} = \infty$), Standard scale factors. (△) Phosphite geometry, scale factors optimized at d_{P-H^+} = 3.5 Å for bicyclic system: P_{3sp} = 1.885, O_{2sp} = 2.229, H_{1s} = 0.842 (for the translating proton). (▣) Phosphite geometry, scale factors adjusted for both systems at d_{P-H^+} = 6.0 Å: acyclic P_{3sp} = 1.853, O_{2sp} = 2.226, H_{1s} = 0.44; bicyclic P_{3sp} = 1.866, O_{2sp} = 2.219, H_{1s} = 0.55. (■) Phosphite geometry, scale factors adjusted for acyclic system at d_{P-H^+} = 10.0 Å. (⊙′) Phosphite geometry, standard scale factors. Dashed line is drawn only for visualization. (C) HOMO/LUMO energies for protonated phosphite conformations **8** and **9** as a function of P–H bond distance. See captions to Figure 6 for structures and scale factors used.

According to eq 2, the stereoelectronic effect provides the greatest stabilization energy at this putative "transition state" P–H bond distance with the greatest $n_O \leftrightarrow \sigma^*$ (HOMO/LUMO) mixing. Indeed, as shown in Figure 6C, at a P–H distance of 3–4 Å, the LUMO for both "cyclic" **8** and "acyclic" **9** has dropped to about its lowest energy and the HOMO for "bicyclic" and "acyclic" phosphite conformations has risen correspondingly. Thus, by 3–4 Å, major mixing of the HOMO and LUMO will occur. Significantly in the ground-state protonated phosphite, the LUMO of the "acyclic" **9** conformation is *higher* energy than that of the "bicyclic" **8** conformation. By 3–4 Å, the LUMO of the "acyclic"

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(25) DePuy, C. H.; Della, E. W.; Filley, J.; Grabowski, J. J.; Bierbaum, V. M. *J. Am. Chem. Soc.* **1983**, *105*, 2481.

(26) Grekov, A. P.; Veselov, V. Ya. *Russ. Chem. Rev.* (*Engl. Transl.*) **1978**, *47*, 631.

(27) Fina, N. J.; Edwards, J. O. *Int. J. Chem. Kinet.* **1973**, *5*, 1.

(28) Filippini, F.; Hudson, R. F. *J. Chem. Soc., Chem. Commun.* **1972**, 522. Hudson, R. F.; Filippini, F. *Ibid.* **1972**, *726*.

(29) Klopman, G.; Evans, R. C. *Tetrahedron* 1978, *34*, 269.

(30) Heaton, M. M. *J. Am. Chem. Soc.* **1978**, *100*, 2004.

(31) We are aware of equilibrium α-effects[32] as well. However, these are generally small (<100, α-effects measured by rate constant ratio, $k_{NH_2NH_2}/k_{glycylglycine}$).

(32) Dixon. J. E.; Bruice, T. C. *J. Am. Chem. Soc.* **1971**, *93*, 3248.

(33) Levine, I. N. "Quantum Chemistry", 2nd ed; Allyn and Bacon: Boston, 1974; p 106.

phosphite has dropped $\sim$2 eV below the LUMO of the "bicyclic" phosphite, and thus oxygen lone pair orbitals which are app to the antibonding P–H orbital can more effectively mix in this LUMO. This supports the HOMO/LUMO ($n \rightarrow \sigma^*$) mixing interpretation for the stereoelectronic effect and the α-effect.

It should be stressed that the total and HOMO/LUMO orbital energies for the partially protonated phosphites are strongly dependent on the scale factors chosen (see Figure 6A,B). The STO-3G minimal basis set with standard scale factors did not provide enough flexibility to allow convergence in the SCF procedure. This is quite reasonable since during protonation of the phosphite a large amount of charge transfer occurs. At infinite separation of proton and neutral phosphite no electron density is permitted on the proton. As the proton moves closer, electron density from the phosphite (particularly from the phosphorus *and* oxygen lone pair orbitals) moves onto the hydrogen. To permit this the 1s orbital on hydrogen must be allowed to become less diffuse and thus the hydrogen scale factor must increase with decreasing P–H bond distance. At the stationary point for the protonated phosphite nearly one electron (Table II) has transferred from the phosphite to the proton 1s orbital (the hydrogen has only a small positive charge). Obviously the same *optimized* scale factor for this cannot be used for unprotonated, protonated, and partially protonated structures. By 3–4 Å (again the "transition-state" distance) most of the charge transfer has occurred. Only at shorter P–H distances (<3 Å) are standard scale factors permissible. Using standard scale factors and the STO-3G basis set at a P–H distance of 3 Å the acyclic phosphite is 12 kcal/mol more stable than the bicyclic phosphite (Figure 6B). When optimized scale factors are used for the higher energy structure, this energy difference increases to 25 kcal/mol.

Finally, completing the picture for proton transfer, at longer P–H bond distances the energy difference between conformations **9** and **8** again decreases and as discussed previously at infinite separation of the phosphite and proton, the relative energies of the two conformations reverses.

Experimental support for these ideas is provided in the accompanying paper.

Acknowledgment. Support of this work by NSF (CHE 8205353), NIH (GM 17575), and DoD (FED CHEM 83 K0098) is greatly appreciated. The generous allocation of computing time by the UIC Computer Center and the help of Shigeyuki Urano (UIC) with the implementation of GAUSSIAN 80 is also appreciated.

Experimental Tests of the Stereoelectronic Effect at Phosphorus: Nucleophilic Reactivity of Phosphite Esters

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Received January 9, 1984. Revised Manuscript Received June 8, 1984

Abstract: Triethyl phosphite rapidly reacts with ethyl benzenesulfenate or diethyl peroxide to yield pentaethoxyphosphorane. In contrast, 1-methyl-4-phosha-3,5,8-trioxabicyclo[2.2.2]octane (**1**) fails to react with either electrophile to yield the expected bicyclic phosphorane **5**. The poor reactivity of the bicyclic phosphite **1** is due to a kinetic rather than a thermodynamic barrier because **5** is formed smoothly from an equimolar mixture of $P(OEt)_5$ and the triol 1,1,1-tris(hydroxymethyl)ethane. This result is interpreted in terms of the stereoelectronic effect. The order of nucleophilic reactivity of trialkyl phosphites with 3-benzylidene-2,4-pentanedione is also shown to be consistent with the stereoelectronic effect. The bicyclic phosphite **1** reacted 750 times slower than the pseudoequatorial 2-methoxy ester of hexahydrobenzo-1,3,2-dioxaphosphorinane in a Michael addition reaction with 3-benzylidene-2,4-pentanedione.

Stereoelectronic effects have been suggested to significantly influence the rates, products, and stereochemistry of reactions of organophosphorus compounds.[1-11] In contrast to the large body of experimental and theoretical work supporting the role of orbital orientation (the stereoelectronic effect) in carbon chemistry,[12-14] no direct experimental evidence has previously existed to support this hypothesis in the reactions of organophosphorus compounds.

As described in the preceding article and in others in this series,[1-7] our ab initio molecular orbital calculations have suggested that the orientation of lone pairs on directly bonded oxygen or nitrogen atoms can significantly affect the reactivity of organophosphorus compounds. In phosphate esters this stereoelectronic effect involves activation of a P–O ester bond by antiperiplanar (app) interaction with oxygen or nitrogen electron lone pairs. Calculations have suggested that orientation of a lone pair antiperiplanar to a scissile bond can lower the energy of a transition state by as much as 11 kcal/mol relative to a corresponding transition state without this app lone pair.[4,7] Unfortunately, attempts to experimentally confirm this effect have been frustrated by conformational flexibility in the relatively unconstrained phosphate ester systems earlier studied.[9]

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(1) Taira, K.; Gorenstein, D. G. *J. Am. Chem. Soc.*, preceding paper in this issue.

(2) Gorenstein, D. G.; Findlay, J. B.; Luxon, B. A.; Kar, D. *J. Am. Chem. Soc.* **1977**, *99*, 3473.

(3) Gorenstein, D. G.; Luxon, B. A.; Findlay, J. B.; Momii, R. *J. Am. Chem. Soc.* **1977**, *99*, 4170.

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(5) Gorenstein, D. G.; Luxon, B. A.; Goldfield, E. M. *J. Am. Chem. Soc.* **1980**, *102*, 1757.

(6) Gorenstein, D. G.; Rowell, R.; Taira, K. In "Phosphorus Chemistry"; American Chemical Society: Washington, DC, 1981; ACS Symp. Ser. No. 171, p 69.

(7) Gorenstein, D. G.; Luxon, B. A.; Findlay, J. B. *J. Am. Chem. Soc.* **1979**, *101*, 5869.

(8) Gorenstein, D. G.; Taira, K. *J. Am. Chem. Soc.* **1982**, *104*, 6130. Taira, K.; Fanni, T.; Gorenstein, D. G. *J. Am. Chem. Soc.* **1984**, *106*, 1521.

(9) Gorenstein, D. G.; Rowell, R.; Findlay, J. *J. Am. Chem. Soc.* **1980**, *102*, 50.

(10) Lehn, J. M.; Wipff, G. *J. Chem. Soc., Chem. Commun.* **1975**, 800.

(11) (a) Lehn, J. M.; Wipff, G. *J. Am. Chem. Soc.* **1974**, *96*, 4048. (b) *Ibid.* **1976**, *98*, 7498. (c) *Helv. Chim. Acta* **1978**, *61*, 1274.

(12) (a) Radom, L.; Hehre, W. J.; Pople, J. A. *J. Am. Chem. Soc.* **1972**, *94*, 2371. (b) Jeffrey, G. A.; Pople, J. A.; Radom, C. *Carbohydr. Res.* **1972**, *25*, 117. (c) Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4540. (d) Anh, N. T.; Eisenstein, O. *Tetrahedron Lett.* **1976**, 155.

(13) Kirby, A. J. "The Anomeric Effect and Related Stereoelectronic Effects at Oxygen"; Springer-Verlag: Berlin, 1983; pp 1–149.

(14) Deslongchamps, P.; Taillerfer, R. J. *Can. J. Chem.* **1975**, *53*, 3029 and references cited therein.