phosphite has dropped ~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 → σ^*) 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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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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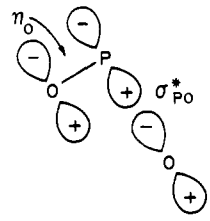
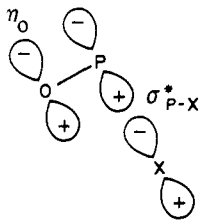
The stereoelectronic effect in the hydrolysis of phosphate esters is attributed to $n_O \leftrightarrow \sigma^*_{P-O}$ orbital mixing which will facilitate



P–O ester bond cleavage (or its formation).[1-7,10-14] Similar stereoelectronic interactions should facilitate P–X bond formation in nucleophilic displacement reactions by phosphite esters:

$$(RO)_3P: + X-Y \rightarrow (RO)_3P^+-X + Y^-$$

(In the previous calculations, a proton replaced the electrophile X–Y.) In this case $n_O \leftrightarrow \sigma^*$ orbital mixing is possible when a lone pair on the oxygen of the phosphite ester is app to the newly formed P–X bond (X = O or C)



As shown in this article, the relative reactivity of a series of trialkyl phosphites **1–4** with several different electrophiles provides support for this kinetic stereoelectronic effect.

Experimental Section

^1H and ^{31}P NMR spectra were recorded on a Bruker WP-80 spectrometer at 80 and 32.4 MHz, respectively, or ^1H NMR on a 60-MHz Varian T-60 spectrometer. Chemical shifts in parts per million for spectra are referenced to external 85% H_3PO_4. Infrared spectra were obtained on a Perkin-Elmer 727B spectrometer. Mass spectra were obtained on a Hewlett-Packard 5985 gas chromatograph mass spectrometer. Melting points were taken on a Thomas-Hoover apparatus and are uncorrected. Chemicals were generally of highest purity. All solvents were distilled before use and stored over 4-Å molecular sieves (Grace Chemical Co.).

Bicyclic Phosphite (1). 1-Methyl-4-phospha-3,5,8-trioxabicyclo-[2.2.2]octane (**1**) was prepared by the method of Verkade and Reynolds.[15a] To effect purification the crude product was sublimed three times at 50 °C (2 mm); mp 96.5–98 °C (lit.[15a] mp 97–98 °C after three sublimations); ^1H NMR ($CDCl_3$) δ 3.95 (d, J_{P-H} = 2 Hz, 6 H), 0.73 (s, 3 H); ^{31}P NMR ($CDCl_3$) δ 91.4 (lit.[15b] δ 91.5).

Triethyl Phosphite (2). (Aldrich) was distilled under argon atmosphere, bp 155.0–156.0 °C, and stored in a freezer with molecular sieves under argon atmosphere.

***trans*-2-(Hydroxymethyl)cyclohexanol** was prepared by the Prins reaction on cyclohexane:[16] bp 106–108 °C (1.3 mm) [(lit.[16]bp 101–103 °C (0.96 mm)].

(2β,4aα,8aβ)-Hexahydro-2-chloro-4*H*-1,3,2-benzodioxaphosphorin (7). Phosphorus trichloride (0.185 mol) in 40 mL of anhydrous ether was added dropwise to a solution of *trans*-2-(hydroxymethyl)cyclohexanol (0.185 mol) and dry triethylamine (0.369 mol) in 200 mL of anhydrous ether at 0 °C with stirring. After removal of the ammonium salts the product was vacuum distilled at 102 °C (2.2 mm); ^{31}P NMR ($CDCl_3$) δ 152.2.

Chair–Axial (OMe) Phosphite (3). [(2β,4aα,8aβ)-Hexahydro-2-methoxy-4*H*-1,3,2-benzodioxaphosphorin] was prepared by the general method of Verkade.[17,18] Equimolar quantities of trimethyl phosphite and *trans*-2-(hydroxymethyl)cyclohexanol were mixed and heated until methanol began to reflux. The mixture was then stirred at room temperature overnight. Methanol was removed by distillation at atmospheric pressure with oil bath temperatures up to 120 °C. The chair–axial (OMe) phosphite was obtained by distillation at 100–103 °C (3.3 mm) [lit.[19] bp 67–69 °C (0.25 mm)]: ^1H NMR ($CDCl_3$) δ 4.3–3.3 (m, 3 H), 3.5 (d, J = 12 Hz, $-OCH_3$), 2.1–0.9 (br, ring CH, 9 H); ^{31}P NMR ($CDCl_3$) δ 129.8 (lit.[19] δ 129.3).

Chair-pseudoequatorial (OMe) Phosphite (4). [(2α,4aα,8aβ)-Hexahydro-2-methoxy-4*H*-1,3,2-benzodioxaphosphorin] was prepared by the general method of Verkade et al.[17] To a stirred solution of (2β,4aα,8aβ)-hexahydro-2-chloro-4*H*-1,3,2-benzodioxaphosphorin (**7**) (8.10 g, 0.0416 mmol) in 50 mL of anhydrous ether maintained at 0 °C was added dropwise with stirring a solution containing 0.9 equiv of methanol (1.20 g, 0.0375 mol) and 1.0 equiv of triethylamine (4.21 g, 0.416 mol) in 35 mL of anhydrous ether. After removal of ammonium salts by filtration the product was concentrated and vacuum distilled at 62–64 °C (0.3 mm) [lit.[19] bp 67–69 °C (0.25 mm)]: ^1H NMR ($CDCl_3$) δ 4.2–3.4 (m, 3 H), 3.6 (d, J = 11 Hz, $-OCH_3$), 2.3–0.9 (br, ring CH, 9 H); ^{31}P NMR ($CDCl_3$): δ 133.5 (lit.[19] δ 132.0).

1-Methyl-4-phospha-3,5,8-trioxabicyclo[2.2.2]octane 4-Oxide (6). Bicyclic phosphite **1** was oxidized with 30% hydrogen peroxide by the method of Verkade and Reynolds.[15a] The product after crystallization from absolute ethanol melted at 245–248 °C (lit.[15a] mp after three sublimations 249–250 °C): ^1H NMR ($CDCl_3$) δ 4.50 (d, J = 6 Hz, 6 H), 0.90 (s, 3 H).

Benzenesulfenyl chloride was prepared by the method of Lecher et al.:[20] bp 62–63 °C (4 mm) [(lit.[20] bp 58–60 °C (3 mm)]; ^1H NMR ($CDCl_3$) δ 7.7–7.5 and 7.5–7.2 (m, Ar).

Ethyl benzenesulfenate was prepared from benzenesulfenyl chloride and ethanol[21] under an argon atmosphere: bp 58–59 °C (2 mm); ^1H NMR ($CDCl_3$) δ 7.27 (Ar, 5 H), 3.85 (q, J = 7 Hz, 2 H), 1.27 (t, J = 7 Hz, 3 H).

Diethyl peroxide was prepared by the method of Pryor and Huston:[22,23] bp 62–63 °C (lit.[22] bp 62–63 °C); ^1H NMR ($CDCl_3$) δ 4.02 (q, J = 7 Hz, 2 H), 1.20 (t, J = 7 Hz, 3 H).

Pentaethoxyphosphorane (8) was prepared by the method of Denney et al.[21a,24] Diethyl peroxide and triethyl phosphite were mixed and kept in the dark under an argon atmosphere for 1 month. The purity of the resulting pentaethoxyphosphorane was greater than 70%. Although the byproduct triethyl phosphate may be removed by extracting with propylene carbonate, the mixture of 70% pentaethoxyphosphorane and 30% triethyl phosphate was used for the exchange reaction because the phosphate was inert and contamination by the propylene carbonate could be avoided: ^{31}P NMR ($CDCl_3$) δ −68.9 (lit.[24] δ −69). ppm).

Attempted Formation of Bicyclic Phosphorane 5 by the Reaction of Ethyl Benzenesulfenate and 1. Ethyl benzenesulfenate (0.0619 g, 0.401 mmol) was mixed with the bicyclic phosphite **1** (0.0297 g, 0.200 mmol) in 0.5 mL of $CDCl_3$ in an NMR tube at room temperature. Several hours after mixing there was no change in the ^1H NMR spectrum. Upon heating the reaction at 50 °C overnight a small doublet appeared at 4.5 ppm due to the slow formation of the bicyclic phosphate, **6**. Further reaction for 3 days produced only a slight increase in the doublet at 4.5 ppm.

Although the above concentrations could not be achieved when hydrocarbons were used as the solvent due to the poor solubility of the bicyclic phosphite **1**, a saturated solution of **1** with 0.4 mmol of ethyl benzenesulfenate in 0.5 mL of pentane did not show any change in the ^{31}P NMR spectrum after several hours.

Attempted Formation of 5 by the Reaction of 1 with Diethyl Peroxide. When diethyl peroxide (0.0572 g, 0.584 mmol) was mixed with the bicyclic phosphite **1** (0.0864 g, 0.583 mmol) in 0.5 mL of $CDCl_3$, the only product appearing was the bicyclic phosphate **6** after 23 days. No phosphorane **5** was detected.

Pentaethoxyphosphorane [P(OEt)$_5$] (8). Reaction of triethyl phosphite (**2**) with ethyl benzenesulfenate is known to produce $P(OEt)_5$, even at −78 °C.[24] In contrast with the behavior of **1**, when **2** (65 μL, 0.38 mmol) was added to ethyl benzenesulfenate (0.117 g, 0.759 mmol) at room temperature in 0.5 mL of $CDCl_3$, a vigorous exothermic reaction ensued.

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This indicates a substantial difference in reactivity between **1** and **2**.

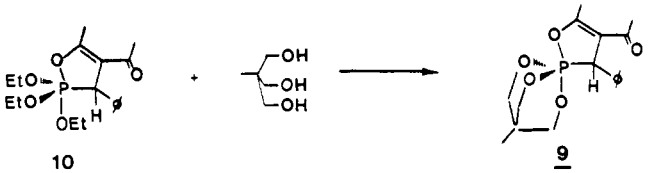
Formation of Bicyclic Phosphorane 5. When $P(OEt)_5$ was stirred overnight under an argon atmosphere in the dark with an equimolar amount of carefully powdered and dried 1,1,1-tris(hydroxymethyl)ethane (Aldrich Chemical Co., recrystallized from ethanol), and solid triol dissolved slowly and **5** formed (^{31}P δ −67.8). The reaction may be monitored by ^{31}P NMR as described in the next section. Unfortunately **5** decomposed upon attempted purification by vacuum distillation.

Equilibration of Chair–Axial (OMe) and Chair–Pseudoequatorial (OMe) Cyclic Phosphites 3 and 4. Each isomer (80 μL, 0.47 mmol) was dissolved in 0.3 mL of $CDCl_3$ and heated at 70 °C in a sealed NMR tube for 12 h and then kept at 35 °C for 7 h. The epimer **3** yielded 3.0% of **4** (97% of **3** remaining unchanged) based upon ^{31}P NMR integration. Most of **4** (99.0%) was converted to **3**, leaving only 1.0% of **4**. Based upon the ^{31}P NMR integration method, the equilibrium concentrations of axial (OMe) and pseudoequatorial (OMe) isomers at 35 °C are ca. 98% (**3**) and 2% (**4**), respectively. These results indicate that the chair–axial (OMe) isomer **3** is about 2.4 kcal/mol more stable than its epimer **4** at 35 °C in $CDCl_3$.

Kinetics of Formation of Phosphoranes in Michael Addition. All measurements were done on a Bruker WP-80 NMR spectrometer at 32.4 MHz (^{31}P). 3-Benzylidene-2,4-pentanedione (6.36 g, 33.8 mmol), purchased from Aldrich and purified by vacuum distillation [(bp 132–133 °C (1 mm)], was diluted to 25.0 mL with $CDCl_3$. Each phosphite (0.0677 mmol) was added to an aliquot of this solution (625 μL, 0.845 mmol) and formation of the corresponding phosphorane was followed by ^{31}P NMR at −28.9 ppm for triethyl phosphite, at −28.0 ppm (br) for the bicyclic phosphite, **1**, and at −26.8 or −28.2 ppm (because of the prochiral center at the benzylidene carbon) for both **3** and **4**. Although reasonable pseudo-first-order rate constants were obtained in this manner, the numbers are quite crude because of the formation of several side products, such as phosphonate (^{31}P δ 27) (especially in the case of the bicyclic phosphite), and because of the limitations of the NMR integration method.

The bicyclic phosphorane **9** could be independently prepared by heating a solution of bicyclic phosphite **1** (1.48 g, 0.01 mol) and 3-benzylidene-2,4-pentanedione (1.88 g, 0.01 mol) in 2 mL of 1-bromonaphthalene at 75 °C with stirring overnight. Trituration with pentane yielded a crude product which was further purified by recrystallization from benzene–hexane. This bicyclic phosphorane **9** decomposes at ca. 140 °C and is sensitive to moisture. Both ^{31}P and ^{1}H NMR spectra show broad signals at the expected chemical shifts. (This broadening in the NMR is under investigation, and is likely attributed to pseudorotation and/or chemical exchange effects.)[25-28] MS (20 eV): molecular ion at *m/e* 336.3 (1.14% base abundance).

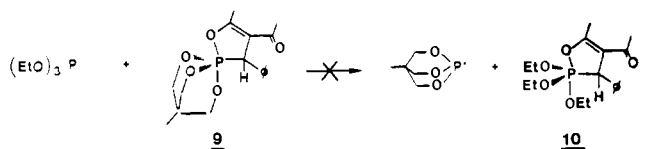
Ligand Exchange (10 → 9). To a solution of **10** (0.130 g, 0.367 mmol) in 0.3 mL of Me_2SO-d_6 was added an equimolar amount of 1,1,1-tris(hydroxymethyl)ethane. Within 5 h all starting phosphorane **10** (^{31}P δ −28.9) was converted into ca. 60% of the bicyclic phosphorane



10 **9**

9 (^{31}P δ −28.0) and ca. 40% of the corresponding phosphonate (^{31}P δ 25.2). This 0.9-ppm downfield shift upon bicyclic ring formation (ligand exchange) is consistent with our previous observation (**8** → **5**).

The bicyclic phosphorane **9** did *not* convert to **10** when equimolar amounts (0.18 M in $CDCl_3$) of **9** and triethyl phosphite **2** were mixed



9 **10**

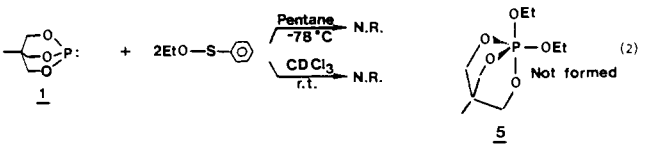
at room temperature and kept at 50 °C for 2 days, also suggesting (but not proving) that **9** is thermodynamically more stable than **10**. Unfortunately this assumes that the rate of retroaddition of **9** to yield bicyclic phosphite and 3-benzylidene-2,4-pentanedione is reasonably fast at 50 °C, which may not be true (see ref 27).

Results and Discussion

Pentaalkoxyphosphorane Formation. A common route for the preparation of pentaalkoxyphosphoranes has been the reaction of trialkyl phosphites either with diethyl peroxide or with the much more reactive alkyl benzenesulfenates. Thus, when triethyl phosphite **2** is allowed to react with 2 equiv of ethyl benzenesulfenate in pentane at −78 °C, a rapid reaction occurs with the production of pentaethoxyphosphorane (**8**) and diphenyl disulfide (eq 1).[24] Significantly, under the same or more forcing condition,

$$\underset{\mathbf{2}}{(EtO)_3P:} + 2EtOSPh \xrightarrow[-78\ ^\circ C]{\text{pentane}} \underset{\mathbf{8}}{P(OEt)_5} + PhSSPh \quad (1)$$

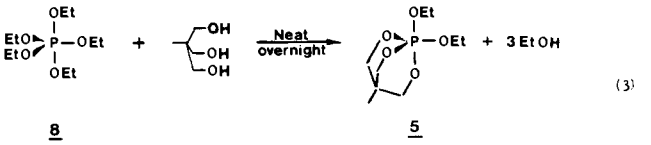
the bicyclic phosphite **1** (1-methyl-4-phospha-3,5,8-trioxabicyclo[2.2.2]octane) was resistant to the ordinarily highly reactive ethyl benzenesulfenate (eq 2). In contrast to the unreactivity



1 **5** (2)

of **1**, at room temperature triethyl phosphite reacts uncontrollably (explosively) with ethyl benzenesulfenate.

It may be shown that the lack of formation of **5** is due to a kinetic and *not* to a thermodynamic barrier. In fact **5** is thermodynamically more stable than pentaethoxyphosphorane **8**. As monitored by ^{31}P NMR , when pentaethoxyphosphorane is treated with an equimolar amount of carefully powdered and dried 1,1,1-tris(hydroxymethyl)ethane without any solvent, the acyclic phosphorane is completely converted to **5** (^{31}P chemical shift, −67.8 ppm) by ligand exchange. There is no reversal of the reaction in the presence of 3 equiv of ethanol (eq 3). Apparently there



8 **5** (3)

is a high kinetic barrier in the reaction of eq 2, but none in that of eq 1.

Although the detailed mechanism for the formation of pentaalkoxyphosphoranes via the alkyl benzenesulfenate reaction is not known, it is believed to proceed via a concerted biphilic insertion[24] or through a nucleophilic displacement to yield an initial phosphonium intermediate such as $(RO)_3P^+$–OR'.[24b] In either mechanism the phosphite reactivity will likely be governed at least partially by its nucleophilicity.[24] Attempts to detect radical or radical pairs as intermediates have not been successful. In the case of the related diethyl peroxide reaction with trivalent phosporus compounds, both biphilic and nucleophilic components to the reaction at phosphorus have also been noted.[29] Thus, for arylphospholens, electron-donating substituents accelerate the rate of reaction with diethyl peroxide, yielding a Hammett ρ value of -0.5 ± 0.2.[29a] Other triarylphosphine, diaryl phosphinite, and aryl phosphonites also show similar, negative ρ values.[29a] The reaction thus displays a small nucleophilic component at phosphorus, although the transition state does not have such a large charge development as in the Arbusov reaction with alkyl halides (ρ value of −1.1 to −1.2).[29c]

A stereoelectronic effect provides the most satisfying explanation for the poor nucleophilicity which we observe for the bicyclic phosphite.[1] Thus, in the case of triethyl phosphite, assuming free rotation about the P–O bonds, a maximum of *three* lone pair

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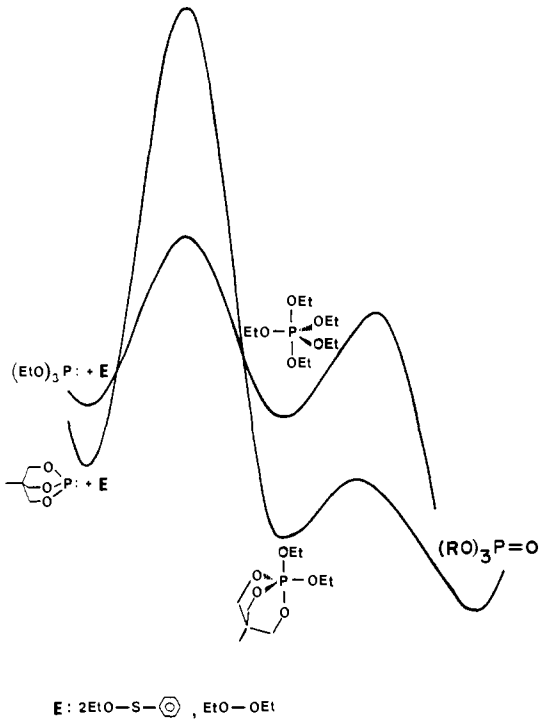
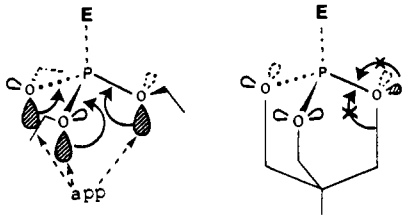


Figure 1. Qualitative energy diagram for formation of bicyclic and acyclic phosphoranes.

orbitals on oxygens are available (i.e., antiperiplanar) to the newly forming phosphorus–electrophile (P–E) bond ($n-\sigma^*_{P-E}$ stabilization). However, no comparable stabilization from the oxygen lone pairs is possible for the bicyclic phosphite **1** because of ring constraints (all lone pairs are locked gauche to the incipient P–E bond). Because $n-\sigma^*_{P-E}$ stabilization in the acyclic phosphite is much greater than the $\sigma_{O-C}-\sigma^*_{P-E}$ stabilization in the bicyclic phosphite,[1] the energy of the acyclic transition state can be stereoelectronically significantly stabilized compared with that of the *bicyclic* transition state. We regard this as the origin of the superior nucleophilicity for the acyclic phosphite compared with that of the bicyclic phosphite.



The phosphonium ion intermediate, or the transition state leading to it, will have a higher energy in the case of the bicyclic phosphite because of the unfavorable stereoelectronic effect previously described.[1] Instability of such phosphonium ion intermediates can also be seen from the resistance of the bicyclic phosphate **6** toward alkylation.[30,31] The reduced nucleophilicity of the bicyclic phosphite is even more remarkable when one consideres that steric effects would suggest that **1** ought to be more reactive than the acyclic phosphite. For example, the bicyclic amine quinuclidine (1-azabicyclo[2,2,2]octane) is much more reactive than the acyclic species triethylamine toward methyl iodide in nitromethane.[32] By steric analogy then, the bicyclic phosphite should be a better nucleophile than an acyclic phosphite.

Michael Addition and Phosphorane Formation. To eliminate ambiguity concerning the nature of the rate-determining step in the above reactions and to measure the rate of a direct nucleophilic

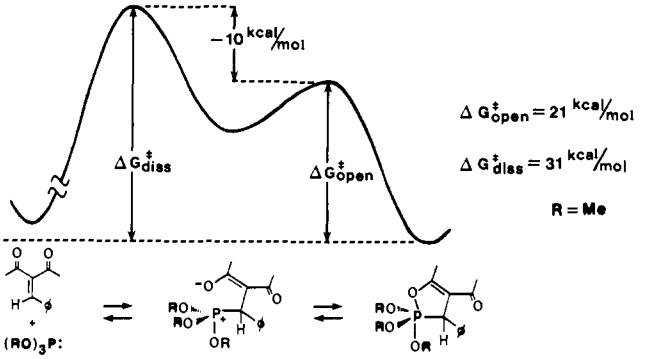
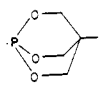
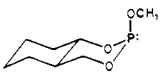
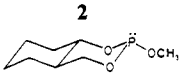


Figure 2. Activation parameters in Michael addition.

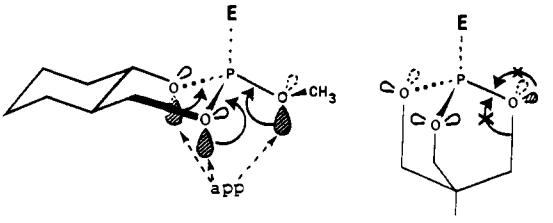
Table I. Relative Reactivity of Phosphites with 3-Benzylidene-2,4-pentanedione[a]

nucleophile	k, h^{-1} M^{-1}	relative reactivity
 **1**	0.04	1
 **3**	5	125
$:P(OCH_3CH_3)_3$ **2**	10	250
 **4**	30	750

[a] Solvent, $CDCl_3$; [phosphite], 0.106 M; [diketone], 1.33 M.

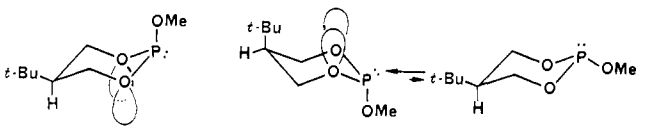
step, we felt that the best system was a cycloaddition to an α,β-unsaturated ketone to form a phosphorane. For example, trialkyl phosphites react readily with 3-benzylidene-2,4-pentadione to form cyclic alkyloxyphosphoranes.[25-28,33,34] This reaction consists of two steps, the first a nucleophilic Michael addition by the phosphite, followed by a second intramolecular cyclization. The rate of the closure has previously been shown to be rapid compared with the initial nucleophilic attack step. This was conclusively established with trimethyl phosphite as the nucleophile, by determination of the activation parameters shown in Figure 2.[27,28]

Thus, in this system we can clearly check the effect of orbital orientation at the nucleophilic attack stage. Rate-constant determinations for this reaction were carried out by following the formation of the phosphoranes by ^{31}P NMR, and the results are shown in Table I. Although these rate constants are quite crude because of formation of side products and because of the limitations of the NMR integration method, the order and approximate magnitude of the relative reactivity are as indicated. As expected from the stereoelectronic effect, the nucleophile having the largest number of lone pairs on oxygen which are app to the incipient P–C bond possesses the highest reactivity, *and the bicyclic phosphite without any app lone pairs reacts slowest.*



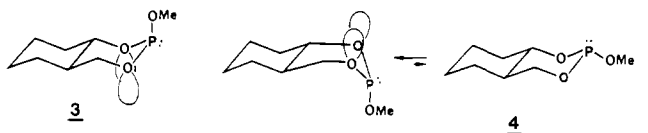
(30) Verkade, J. G. *Bioinorg. Chem.* **1974**, *3*, 165.
(31) Verkade, J. G. *Phosphorus Sulfur* **1976**, *2*, 251.
(32) Brown, H. C.; Eldred, N. R. *J. Am. Chem. Soc.* **1949**, *71*, 445.
(33) Ramirez, F.; Madan, O. P.; Heller, S. R. *J. Am. Chem. Soc.* **1965**, *87*, 731.
(34) Ramirez, F.; Pilot, J. F.; Madan, O. P.; Smith, C. P. *J. Am. Chem. Soc.* **1968**, *90*, 1275.

As shown in Table I, the most rigid bicyclic phosphite **1** reacts much more slowly than the others because the lone pairs on the ring oxygens are synclinal to the newly forming bond, so that n–σ^* mixing is minimal. (Additionally, ring strain likely increases upon nucleophilic addition.) This slower rate for the bicyclic phosphite is not due to a thermodynamic barrier. As in our previous system, the bicyclic phosphorane appears to be thermodynamically more stable than the acyclic counterpart (see Experimental Section on ligand exchange). This exchange reaction is not as clean as the previous system (**8** → **5**), because of decomposition of the initial bicyclic phosphorane **9** in Me_2SO. Although the chair–pseudo-equatorial (OMe) phosphite **4** having a pseudoaxial lone pair on phosphorus did react faster than the corresponding epimer **3** (equatorial lone pair) as expected from the stereoelectronic effect, the reactivity difference was not as great as might have been expected based on rigid axial and equatorial chair conformations. As we have encountered in a phosphate ester hydrolysis study, the decalin-type system still has some conformational flexibility.[35] Bentrude and Hargis studied the conformations of isomeric six-membered cyclic phosphites.[36] A phosphite ring (*cis*-5-*tert*-butyl-2-methoxy-1,3,2-dioxaphosphorinane) with an equatorial phosphorus lone pair orbital was shown to be the more stable isomer by about 1.4 kcal/mol at 25 °C; NMR analysis indicated it to be a chair conformer with the *tert*-butyl group equatorial and the methoxy group axial. The predominate conformer of the trans isomer is surprisingly the chair form with both substituents axial. This is, of course, due to a stereoelectronic influence in the ground state (the anomeric effect).



axial, cis isomer equatorial, trans isomer

Although our phosphites are more rigid than those of Bentrude and Hargis, we still face a conformational flexibility problem. The chair–axial (OMe) isomer (equatorial lone pair) **3** is about 2.4 kcal/mol more stable than its epimer **4** at 35 °C in $CDCl_3$ (see Experimental Section). In our case the stability difference between the respective isomers is greater than in the monocyclic phosphites. This may be due to reduced conformational freedom in the less stable isomer **4** which, unlike Bentrude and Hargis's trans isomer, cannot assume a chair conformation with the methoxy group axial. The predominate conformers in our system seem to be a chair–chair form for the axial (OMe) isomer **3**, and a chair–twist-boat form for its epimer **4** (hence, our referral to the pseudoequatorial orientation of methoxyl for **4**).



3 **4**

Ab initio calculations support the idea that nucleophilicity is greatest in conformations in which lone pair orbitals on adjacent oxygen atoms are antiperiplanar to a newly forming bond.[1] In rigid systems calculations suggest that the stereoelectronic effect at the transition state (kinetic anomeric effect) should in principle be far larger than for the ground state (equilibrium anomeric effect). In less rigid systems such as the phosphorinanes, where lone pair electrons on the ring oxygens tend to be app to the electronegative methoxy group and not to the incipient phosphorus–electrophile bond, reaction can still proceed via the stereoelectronically favored orientation by conformational adjustment. In this case, a thermodynamically unfavorable conformation will be the reactive species, as shown in Figure 3. Unfortunately, this phenomena will always present a problem in interpreting rate accelerations attributable to the stereoelectronic effect unless ΔG or $\Delta G_2^{\ddagger}$ (conformational change) is greater than $\Delta G_1^{\ddagger}$, which is unlikely, or $\Delta G_3^{\ddagger}$ is greater than $\Delta G_1^{\ddagger}$, which is also unlikely since the stereoelectronic effect is enhanced at the transition state,[1] such that, $\Delta G_1^{\ddagger} - \Delta G_3^{\ddagger}$, $\gg \Delta G$, and thus, $\Delta G_1^{\ddagger} \gg \Delta G_3^{\ddagger}$. The stereoelectronic effect on the reactivity of conformational isomers of such mobile systems are, therefore, expected to be considerably smaller and much more difficult to observe. This is why the greatest reactivity decrease occurs in very rigid systems, such as **1**.

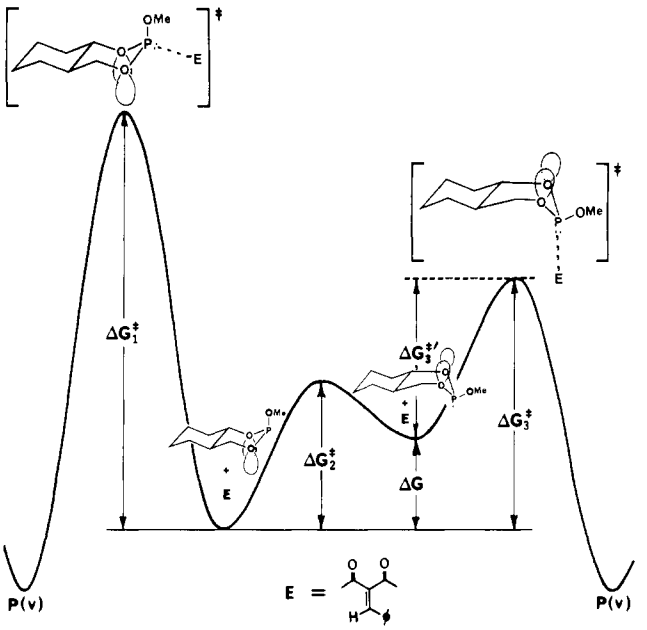


Figure 3. Qualitative energy diagram for a nucleophilic reaction of different conformers.

In conclusion, the search for support of the stereoelectronic effect at phosphorus has often been frustrated by conformational flexibility of the reactants.[1-9] In this paper we have found rate differentials in reactions of phosphites which provide evidence in support of the stereoelectronic effect. In each of the reactions discussed, alternative explanations for these kinetic effects may be offered[31,37] (and indeed could be partially correct!). However, it is in this *growing body* of evidence[8] that we continue to find strong support for the stereoelectronic effect.

Acknowledgment. The support of this research by NSF and the U.S. Army Research Office (to D.G.G.) is gratefully acknowledged.

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(36) Bentrude, W. G.; Hargis, J. H. *J. Am. Chem. Soc.* **1970**, *92*, 7136.
(37) (a) We are aware of the fact that bond angle and hybridization changes (such as in five-membered vs. six-membered ring phosphites) also affect the phosphite reactivity. (b) Turabi, M. S. Ph.D. Thesis, Rutgers University, 1978. (c) Denney, D. B.; Wagner F. A., Jr. *Phosphorus* **1973**, *3*, 27.