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EXPERIMENTAL TESTS OF THE STEREOELECTRONIC EFFECT AT PHOSPHORUS: MICHAELIS-ARBUSOV REACTIVITY OF PHOSPHITE ESTERS.

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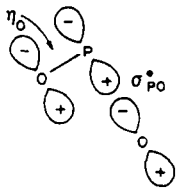
Abstract - Whereas triethyl phosphite readily reacts with benzoyl chloride to yield the Michaelis-Arbusov product, diethyl benzoyl phosphonate, 1-methyl-4-phospha-3,5,8-trioxabicyclo[2.2.2]octane, 1, is essentially unreactive, even at a higher temperature. The bicyclic phosphite 1 also reacts slower than the triethyl phosphite 2 in an oxidation with t-butyl hydroperoxide. These results are interpreted in terms of the stereoelectronic effect.

INTRODUCTION

Stereoelectronic effects have been suggested to significantly influence the rates, products, and stereochemistry of reactions of organophosphorus compounds.[1-10] In contrast to the large body of experimental and theoretical work supporting the role of orbital orientation (the stereoelectronic effect) in carbon chemistry,[4b,11-14] no direct experimental evidence yet exists to support this hypothesis in the reactions of organophosphorus compounds.

Our ab initio molecular orbital calculations[2-7] 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 (app) 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]

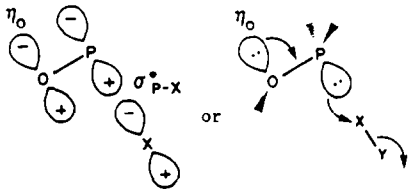
The stereoelectronic effect in the hydrolysis of phosphate esters is attributed to n_O <--> σ^*_{P-O} orbital mixing (n_O, oxygen lone pair; σ^*_{P-O}, P-O antibonding orbital)



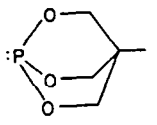
which will facilitate P-O ester bond cleavage (or its formation).[2-10,13] Similar stereoelectronic interactions should facilitate P-X bond formation in nucleophilic displacement reactions by phosphite esters:

$$(RO)_3P: + X\text{-}Y \longrightarrow (RO)_3P^+\text{-}X + Y^-$$

In this case n_O <--> σ^* 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):



The poor nucleophilicity for the bicyclic phosphite 1 is consistent[1,2] with the inability of oxygen lone pairs on the ring constrained system to be oriented app to the σ^* orbital. Here, we want to provide experimental support for this stereoelectronic effect. Additional reactions of phosphites 1 and 2 with various electrophiles are considered.



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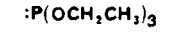


2

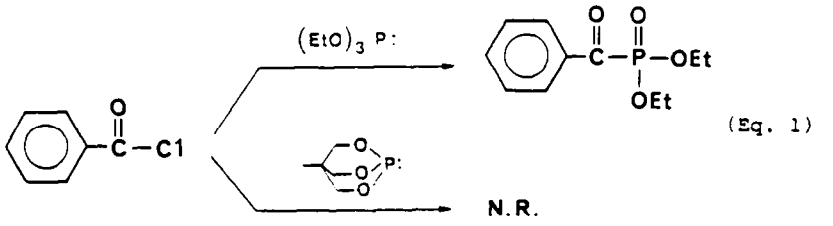
RESULTS AND DISCUSSION

Bicyclic phosphite 1 has been shown to not react with the electrophiles ethyl benzenesulfenate and diethyl peroxide, in contrast to triethyl phosphite which readily formed pentaethoxyphosphorane.[1]

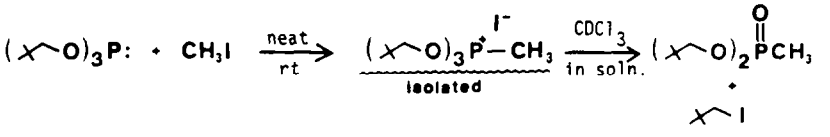
A similar nucleophilicity difference between 1 and triethyl phosphite was observed in the Michaelis-Arbusov reaction. Thus, a solution of 1.94 M in both triethyl phosphite and benzoyl chloride in dry dioxane at 31°C readily produced the Michaelis-Arbusov product with a half life for the reaction of ca. 4 min. However, the bicyclic phosphite 1, under identical concentrations in a sealed NMR tube, was recovered unreacted after 3 months at 31°C (Eq. 1). This represents at least a 10^5-fold lower reactivity for the bicyclic phosphite 1. In order to make this comparison, however, we must establish if the rate-determining step is the same for both phosphite reactions. In the normal Michaelis-Arbusov reaction the first step has been shown to be the rate-determining step by a quantitative study of the following reaction.[16,17a]

$$(EtO)_3P: + EtI \longrightarrow (EtO)_2\overset{O}{\overset{\|}{P}}Et + EtI$$

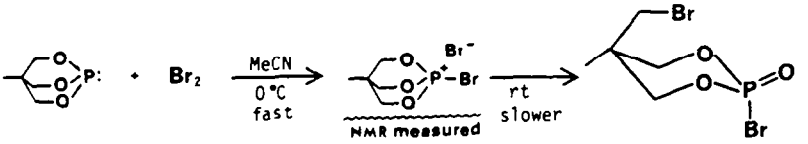
The rate of product formation was followed by infrared spectroscopy and the study showed: (a) ethyl iodide was not consumed during the reaction; (b) the rate was proportional to [EtI]; (c) the rate was not enhanced by increasing $[I^-]$; and (d) the reaction was much faster in acetonitrile (dielectric constant (25°C), D = 36.2) than in benzene (D = 2.27). Although these results are uniquely consistent with a rate-limiting first step, this conclusion should not be used for bulkier phosphites. In some cases, in fact, the Michaelis-Arbusov intermediate has been isolated as a crystalline product[18,19] (Eq. 2). Also when electrophiles are highly

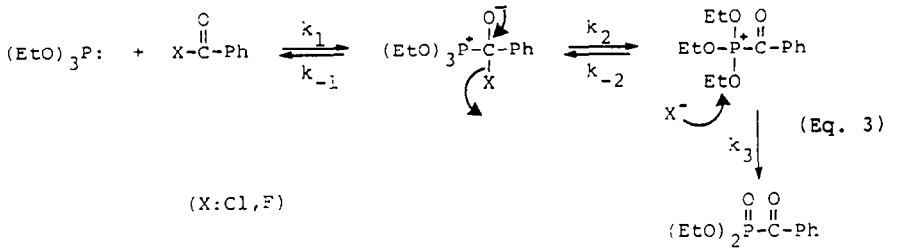


(Eq. 1)



(Eq. 2)



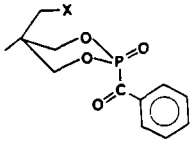


(Eq. 3)

reactive, this generalization does not seem to hold. For example, when triethyl phosphite was treated with benzoyl halide, the first step did not seem to be the rate-determining step (Eq. 3). Only when the first step is the rate-determining step, is the reaction faster with X = F, since chloride is the better leaving group (k_2 step) and the better nucleophile (k_3 step) than fluoride. Although triethyl phosphite (1.94 M) reacted completely with benzoyl chloride (1.94 M) at rt in dioxane within one hour, 90% of triethyl phosphite was found unchanged when benzoyl fluoride (1.94 M) was used as the electrophile under the identical conditions within 90 h. Therefore, in equation (1), the nucleophilic attack (first step) is not the rate-determining step for the triethyl phosphite. The first step must be even faster than the overall reaction rate. In contrast, the slow reaction rate of the bicyclic phosphite seems to be due to rate-determining nucleophilic attack. Although trineopentyl phosphite reacted with methyl iodide at room temperature (Eq. 2),[18] the bicyclic phosphite did not react with boiling methyl iodide.[20] The failure of the reaction must again be due to the poor nucleophilicity of the bicyclic phosphite. If a Michaelis-Arbusov phosphonium ion intermediate of the bicyclic phosphite and methyl iodide had been formed, it would have decomposed as quickly as the intermediate of trineopentyl phosphite and methyl iodide, because the methylene carbons of the bicyclic intermediate should not be sterically more crowded than that of the neopentyl groups. The following relative reactivity for several phosphites in the Michaelis-Arbusov reaction can best be explained by the stereoelectronic effect since the bicyclic phosphite 1 does not have any oxygen lone pairs app to the P-electrophile bond.

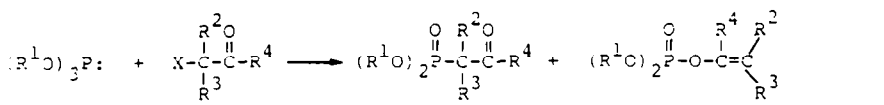
$$(EtO)_3P: > (Neopentyl\text{-}O)_3P: >> H_3CC(H_2CO)_3P:$$

It should be noted that the lack of reactivity of the bicyclic phosphite 1 with benzoyl chloride could alternatively be attributed to an unfavorable thermodynamics of reaction. The inability to observe any product in the reaction could suggest that the Arbusov product,



is thermodynamically unstable relative to starting materials. Although we cannot definitively eliminate this possibility, this result would be without precedence. The formation of the very strong P=O double bond provides a major driving force for reaction of many organophosphorus compounds, and should push the Arbusov reaction of 1 to completion (assuming it could overcome the kinetic barrier for the reaction). In fact, Michaelis-Arbusov reaction of $H_2C{=}CRCH_2X$ with 1 proceeds in the presence of Ni catalysts.[21]

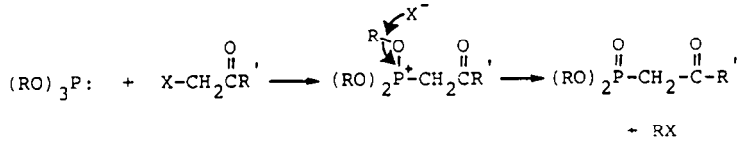
Similar results were observed in the Perkow reaction in the work of Denney and Wagner[22] Trialkyl phosphites react with α-halocarbonyl compounds to give either an α-ketophosphonate or a vinyl phosphate or a mixture of both (the Perkow Reaction, Eq. 4).[17b] The mechanism of this reaction has intrigued



(Eq. 4)

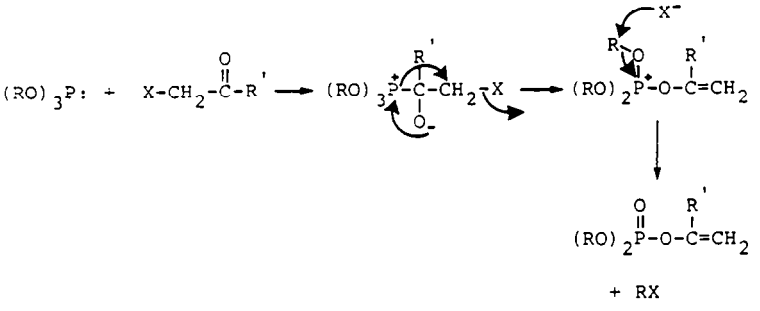
investigators for over 20 years and is still not completely resolved, mainly because of four possible sites for nucleophilic attack (attack at the α-carbon, on halogen, carbonyl carbon, or carbonyl oxygen). It seems highly likely that formation of the keto-phosphonate product occurs via nucleophilic attack on the α-carbon which is strictly analogous to the mechanistic pathway of the Michaelis-Arbusov reaction.

The concept of rate-determining nucleophilic addition to carbonyl carbon is also supported by the work of Denney et al. who studied the reaction of a series of acyclic and cyclic phosphites with chloral, CCl_3CHO, and α,α,α-trichloroacetophenone, Cl_3CCOPh.[22] Rates for the Perkow reaction were in the following order which is identical to the order observed for reactions of the same phosphites with dibenzoyl peroxide and alkyl

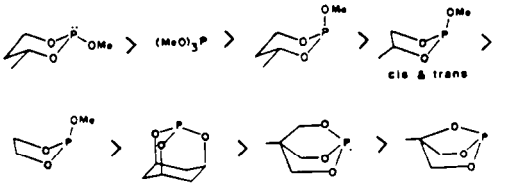


Attack on halogen as a route to vinyl phosphate is untenable, and the consensus of current opinion favors attack on the carbonyl group as the operative mechanism for the Perkow reaction.[17b]

halides. (The time to consume 50% of the carbonyl group differs from less than 2 min (fastest) to no detectable reaction within a month (slowest).)[22]



Unlike the reaction between triethyl phosphite and benzoyl halide (Eq. 3), the rate-determining step of the Perkow reaction is likely to be the first nucleophilic attack step because the halogen reactivity order is the reverse for the reaction of Eq. 3 (Cl > Br > I for the Perkow reaction), and the C_α-X bond does not seem to be broken. Additionally, kinetic studies by Borowitz et al.[23] suggest X^- does not attack R in the rate-determining step.



The reaction with chloral was stereospecific and occurred with retention of configuration at phosphorus which is expected for carbonyl attack by phosphorus.[22]

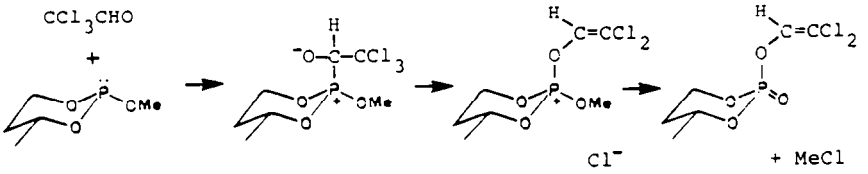
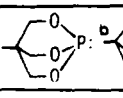
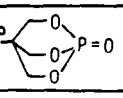
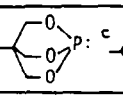
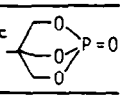


Table I

Oxidation of Phosphites with t-Butyl Hydroperoxide

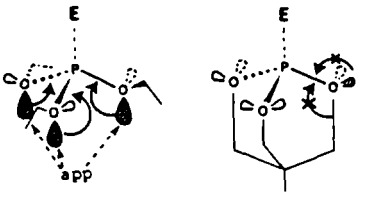
Scanning Time[a]	% Starting Phosphite and Product Phosphates					
t (min)	$(EtO)_3P$:[b]	$(EtO)_3P{=}O$				
2-8	9	91	75	25	38	62
10-18			54	46	10	90
20-28			26	74	1	99
60-68			6	94		

[a] Time after initiation of the reaction for ^{31}P NMR spectral scanning of the reaction products.
[b] in pure dioxane
[c] in 50% aqueous solution (pH 7 and 9)

The relative order of reactivity for the phosphites in the Perkow and Arbusov reactions is thus consistent with the stereoelectronic effect.[2] Those phosphites such as 1 and related bicyclic phosphites in the Perkow series study do not possess any oxygen lone pairs app to the phosphite-electrophile bond and are the least reactive. As shown in Denny's Perkow reaction study, it appears that bond angle and hybridization changes (such as in five-membered vs. six-membered ring phosphites) also affect the phosphite reactivity.[22]

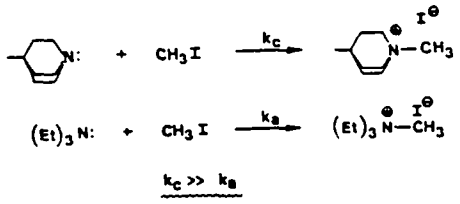
Interestingly, this order of reactivity also holds for oxygen transfer reactions (oxidation of phosphites).[22,24] As shown in Table I, the bicyclic phosphite 1 is oxidized slower than the acyclic triethyl phosphite when t-butyl hydroperoxide is used as the oxidizing agent, and there is no oxygen transfer to bicyclic phosphite 1 when pyridine N-oxide is used (see also Denney et al.[22,24]). There is some evidence that oxygen transfer from N-oxides proceeds via a free radical mechanism.[24] In fact, triethyl phosphite reacted more slowly with 4-nitropyridine oxide than pyridine N-oxide.

A stereoelectronic effect provides the most satisfying explanation for this poor nucleophilicity of the bicyclic phosphite.[1,2] Thus, in the case of triethyl phosphite, assuming free rotation about the P-O bonds, a maximum of <u>three</u> lone-pair orbitals on oxygens are available (antiperiplanar) to the newly forming phosphorus-electrophile (P-E) bond ($n\text{-}\sigma^*_{P\text{-}E}$ 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 $n\text{-}\sigma^*_{P\text{-}E}$ stabilization in the acyclic phosphite is much greater than the $\sigma_{O\text{-}C}\text{-}\sigma^*_{P\text{-}E}$ stabilization in the bicyclic phosphite,[2] the energy of the <u>acyclic</u> transition state can be stereoelectronically significantly stabilized compared with that of the <u>bicyclic</u> 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 stereo-

electronic effect previously described.[1,2] The reduced nuclophilicity of the bicyclic phosphite is even more remarkable considering that steric effects would suggest that 1 ought to be more reactive than the acyclic phosphite. For example, the bicyclic amine quinuclidine is more reactive (k_c/k_a=60) than the acyclic species, triethylamine, towards methyl iodide in nitromethane.[25] By steric analogy then, the bicyclic phosphite should



be a better nucleophile than an acyclic phosphite.

In summary, the clearest explanation for the kinetic barrier for formation of the Michaelis-Arbusov product from 1 and the slower reactivity of 1 toward t-butyl hydroperoxide is provided by the stereoelectronic effect. More generally (as discussed in reference 2) the stereoelectronic effect provides a likely explanation for a significant portion of the enhanced reactivity of nucleophiles with unshared electrons α to the nucleophilic atom (the α-effect).[25-29] As also pointed out by Verkade and Hudson[30-33] and in ref 1 the unusually poor nucleophilicity of 1 compared to acyclic phosphites suggests that orbital interactions such as the stereoelectronic effect[2] (or lone-pair-lone-pair interactions[30-33]) are responsible for the great differences in α-effect nucleophilicity between acyclic and bicyclic phosphites.

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 ^1H NMR spectra are referenced to internal Me_4Si and for ^{31}P NMR spectra are referenced to external 85% H_3PO_4. Melting points were taken on a Thomas-Hoover apparatus and are uncorrected.

Chemicals were generally of highest purity. Solvents were distilled before use and stored over 4 Å molecular sieves (Grace Chemical Co.).

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.

Bicyclic phosphite, 1 (1-methyl-4-phospha-3,5,8-trioxabicyclo[2.2.2]octane) was prepared as previously described.[1]

Michaelis-Arbusov Reactions. The reactions were followed by ^{31}P NMR on a Bruker WP-80 spectrometer at 32.4 MHz. In all cases 0.680 mmol of benzoyl halide (1.94 M) was mixed with an equimolar amount of the phosphite in 0.35 mL of carefully dried dioxane (dried over metallic sodium and kept in a refrigerator under argon atmosphere with molecular sieves). Benzoyl halides were also purified by distillation and kept under an argon atmosphere.

Benzoyl Chloride Arbusov Reaction with Triethyl Phosphite. The formation of diethyl benzoylphosphonate was followed by NMR at δ ^{31}P - 1.8 ppm at 31°C. The reaction was very fast: the half life was about 4 minutes and within 1 h all the triethyl phosphite was completely converted to diethyl benzoylphosphonate.

Benzoyl Chloride Arbusov Reaction with Bicyclic Phosphite, 1. Identical concentrations of benzoyl chloride and bicyclic phosphite 1 were kept in a sealed NMR tube under argon atmosphere in a 31°C bath. Within three months there was no detectable amount (S/N limit ±2%) of any reaction product other than the starting material, bicyclic phosphite 1.

Benzoyl Fluoride Arbusov Reaction with Triethyl Phosphite. The identical concentration of triethyl phosphite reacted with benzoyl fluoride much more slowly than with benzoyl chloride. Within 90 h, over 90% of the triethyl phosphite remained unreacted. The only detectable products were 2% diethyl phosphite ($\delta^{31}P$ 6.4 ppm) and 7% triethyl phosphate ($\delta^{31}P$ - 1.1 ppm).

Oxidation of Phosphites with t-Butyl Hydroperoxide. The reactions were followed by ^{31}P NMR on a Bruker WP-80 spectrometer at

32.4 MHz. To a solution of 11.6 μL (0.068 mmol) of triethylphosphite in 0.4 mL of dioxane (0.17 M) was added 12.0 μL (0.084 mmol) of 70% t-butyl hydroperoxide and then the formation of triethyl phosphate was monitored by ^{31}P NMR at 31°C. Results are shown in Table 1.

To a solution of 0.0100 g (0.068 mmol) of bicyclic phosphite 1 in 0.4 mL of dioxane was added 12.0 μL of 70% t-butyl hydroperoxide and the reaction was followed as described above.

A solution of 0.0100 g (0.068 mmol) of bicyclic phosphite in 0.2 mL of dioxane was mixed with 0.2 mL of 0.5 M pH 9 tris-buffer in D_2O. To this was then added 12.0 μL (0.084 mmol) of 70% t-butyl hydroperoxide and the reaction was followed as above. When 0.5 M pH 7 tris-buffer was used in place of pH 9 buffer, identical results were obtained.

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