Scheme II

a: R=H   b: R = Me
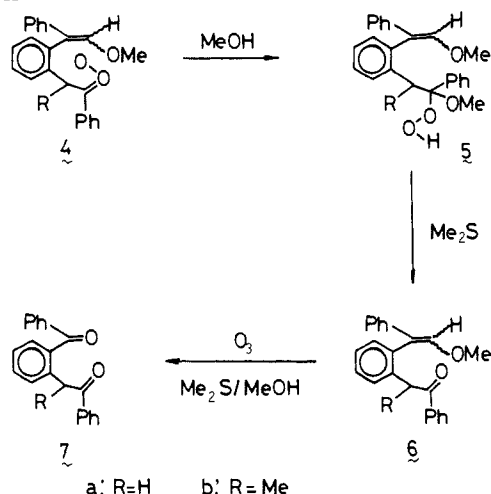
1a in carbon tetrachloride was not significantly perturbed by the presence of dimethyl sulfide or dimethyl sulfoxide which are well-known scavangers of carbonyl oxides.[1b,e]

From our preliminary work, it appears that, in favorable cases such as the intermediate **4**, the intramolecular oxygen transfer can be a highly efficient process. This is in marked contrast to the generally accepted view that carbonyl oxides are poor reagents for the epoxidation of electron-rich olefins.[1b,c] On the other hand, intermolecular oxygen transfer from nucleophilic carbonyl oxides is very slow and hence a variety of other processes including dimerization[6] and rearrangement[10] tend to predominate as, for example, in the ozonolysis of 1,1-diphenyl-2-methoxyethylene and 1-phenyl-2-methoxyethylene.[11]

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Structural Consequence of a Hydrophobic Environment on Phosphorus Dioxy Monoanions and the Potential Application to Structural Changes in Nucleic Acids

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As part of our research[1] on ionic interactions with phosphates we have begun to use $H_2PO_2^-$, phosphinate ion, to investigate structural changes in the $>PO_2^-$ group as a result of change in local environment.[2] The experimental probe is the one-bond P–H coupling constant, $^1J_{PH}$. One-bond C–H couplings are dependent primarily upon percent s character in the C–H bond and this determines the magnitude of the coupling constant.[3] The same principle appears dominant in $^1J_{PH}$. An increase or decrease in $^1J_{PH}$ in $H_2PO_2^-$ indicates more or less s character in the P–H bonds, caused by a smaller or larger O–P–O angle, respectively.

We have found previously that small metal cations increase $^1J_{PH}$ in $H_2PO_2^-$; guanidinium ions and large metal ions such as Ba^{2+} cause small changes in $^1J_{PH}$ whereas $^1J_{PH}$ increases substantially with metal cations with small ionic radii.[2] Therefore, we concluded that the effects are due to O–P–O angle contraction as would be

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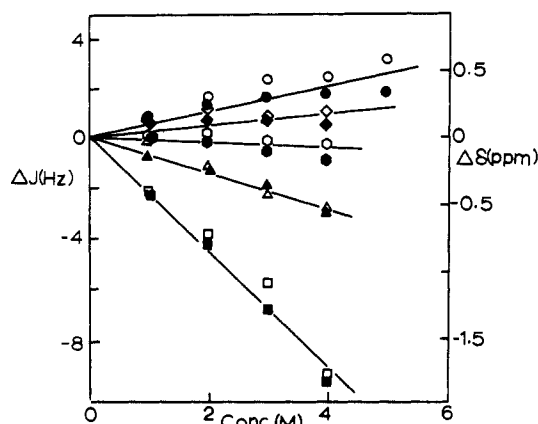
Figure 1. Correlations in change in coupling constant and change in chemical shift with the concentration of ammonium chlorides: O = NH_4Cl; ◊ = CH_3NH_3Cl; O = $(CH_3)_2NH_2Cl$; ▲ = $(CH_3)_3NHCl$; □ = $(CH_3)_4NCl$. The closed figures represent data for chemical shifts and the open figures represent data for coupling constants.
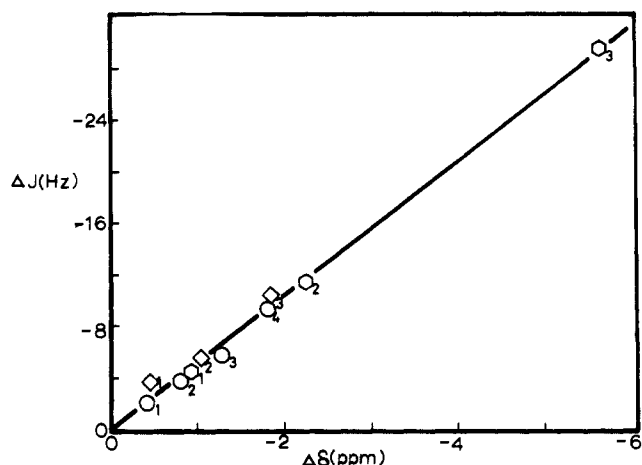
Figure 2. Correlation of chemical shift with coupling constant for tetraalkylammonium chlorides: O = $(CH_3)_4NCl$; ◊ = $(C_2H_5)_4NCl$; O = $(n\text{-}C_4H_9)_4NCl$. The subscripts represent the concentrations of tetraalkylammonium chlorides for each data point.

expected from chelation. For complete association, $\Delta J = 14$ Hz for Li^+, 18 Hz for Mg^{2+}, and 26 Hz for Zn^{2+} but only 4.5 Hz for Ba^{2+} and no significant change for guanidinium ion which can associate to $H_2PO_2^-$ with no effect on bond angle.[2,4,5] In this paper we report results which appear to reflect the structural changes in $H_2PO_2^-$ as the environment becomes hydrophobic.

Samples were prepared by adding a weighed amount of ammonium salt to about 1 mL of D_2O plus 0.2 mL of stock $H_2PO_2^-$ (0.2 M) which had been prepared by neutralizing reagent grade H_2PO_2H with tetramethylammonium hydroxide. The sample was brought to a volume of 2 mL and the pH was taken to ensure that the solution was near pH 7.0. ^{31}P NMR spectra were taken on a Varian XL-200 spectrometer. The frequencies were obtained from the printout of the stored digital data. Couplings should be accurate to 0.1 Hz. With no added ammonium salts, $H_2PO_2^-$ (0.022 M) gives $^1J_{PH} = 518.4$ Hz.

After observing a decrease in $^1J_{PH}$ on addition of tetramethylammonium chloride to aqueous solutions of $H_2PO_2^-$,[2] we investigated the effect of substitution of methyl groups by hydrogens with the results shown in Figure 1. The fanlike distribution of data demonstrates a progressive change in both coupling constants and chemical shifts which are correlated for each ammonium chloride. The more methylated ammonium ions decrease the coupling constant and shield the ^{31}P nucleus; $^+NH_4$ causes increases in the coupling constant and deshielding.[1]

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We have shown that equilibrium constants are about 0.2 M^{-1} for association of phosphate monoanions with monocations; so all these results represent partial association ranging from approximately 20% association at 1 M to 50% association at 5 M. In addition, it must be kept in mind that ion exchange is fast so the data represent time averages for all states of $H_2PO_2^-$.[1,2]

Figure 2 displays data for three tetraalkylammonium chlorides. There is a straight line correlation of ΔJ and $\Delta \delta$ for $(CH_3)_4N^+$, $(C_2H_5)_4N^+$, and $(C_4H_9)_4N^+$ solutions. In all cases decreases in chemical shifts and coupling constants are observed; the largest effects are observed with 3 M tetra-*n*-butylammonium chloride: $\Delta J = -29.4$ Hz and $\Delta \delta = -5.6$ ppm.

Since the more hydrophobic ammonium ions cause the largest decreases in $^1J_{PH}$, we propose that $^1J_{PH}$ decreases because of aggregation of the hydrophobic ions near $H_2PO_2^-$, thereby displacing water from the solvation shell and causing a large decrease in dielectric constant in the environment surrounding the $H_2PO_2^-$ ions. The low dielectric constant will cause greater electrostatic repulsion between the two oxygen atoms in $H_2PO_2^-$ leading to a widening of the O–P–O bond angle. Since a larger bond angle demands more s character at phosphorus for the P–O bonds, there must be less s character at phosphorus in the P–H bonds and this will cause the observed decreases in coupling constants. The reverse effect with small metal ions[2] is consistent with this origin of the changes in coupling constants.

^{31}P chemical shifts have been related to structure in phosphates: bond angle effects are thought to control ^{31}P chemical shifts.[6,7] Figures 1 and 2 show that there is direct correlation between decreased coupling constant and increased shielding. Some of the chemical shifts (Figure 2) are quite large. The decreased coupling constants are associated with larger O–P–O bond angles and larger bond angles are expected to cause deshielding.[6,7] Consequently, the increased shielding observed here must be due to increased electron density at phosphorus; this would be expected from increased electrostatic repulsion between the two oxygen atoms because this effect will force electrons toward the phosphorus atom. Therefore, it seems clear that there can be cases where bond angle effects are less significant than effects involving redistribution of electron density. This is also true for metal ions; those metal ions which appear to have small effects on the PO_2^- bond angle[2] cause deshielding of the ^{31}P nucleus.[1]

Possible Application to Nucleic Acid Structure. $H_2PO_2^-$ is structurally similar to the phosphate monoanion groups in nucleic acids. Previously, discussions of nucleic acid structure have focused on conformational changes.[8] Our results in this and the previous[2] paper indicate that there should be significant structural changes in nucleic acids if the phosphate monoanion groups change environment from association with metal cations[2] to a hydrophobic protein environment.[9] This could have important functional consequences for genetic expression, for enzymes which act on nucleic acids, and particularly for DNA structural changes including supercoiling and the A, B, and Z helices. These electrostatic effects can be large and could easily drive the observed structural changes.[10,11]

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Highly Diastereoselective Alkylation onto 4-Acetoxy-2-azetidinones Employing Tin(II) Enolates of C4-Chiral 3-Acyl-1,3-thiazolidine-2-thiones

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In the field of carbapenem syntheses, the carbon–carbon bond-formation methods at the 4-position of 2-azetidinones have been intriguing and the various fascinating reactions have been reported.[5] However, there is no report on a facile and efficient method for the chiral alkylation at the 4-position of achiral 2-azetidinones (e.g., 4-acetoxy-2-azetidinone (3)). We now report a new efficient methodology for the preparation of chiral 2-azetidinone intermediates applicable to the total synthesis of (+)-thienamycin and (−)-1-β-methylcarbapenem[6] based on the highly diastereoselective aldol-type reaction employing C4-chiral 3-acyl-1,3-thiazolidine-2-thiones[7,8] and 4-acetoxy-2-azetidinones.

To tin(II) enolate 2a,[9] prepared from 3-acetyl-4(*S*)-ethyl-1,3-thiazolidine-2-thione (1a) was added a THF solution of 4-acetoxy-2-azetidinone (3) at −40 °C. After being stirred at 0 °C for 1 h, the reaction mixture was subjected to the usual workup to afford a yellow mixture of 6a and 7a in a 95:5 ratio (HPLC analysis[7a]). The major product 6a was readily isolated in 82% yield by silica gel column chromatography (Scheme I). Other similar chiral alkylations of 3 by the tin(II) enolates of 1b–d gave, with high diastereoselectivity in the range of 90:10–98:2 ratios, the corresponding 4-alkylated 2-azetidinones 6b–d in 75–85% yields.[10]

Absolute configurations of the major products 6a and 6b were confirmed by their chemical conversion to the known compound 17 [[α]^{20}_D + 41.4° (c 0.86, benzene), lit.[11] [α]^{20}_D + 43.2° (c 0.37,

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