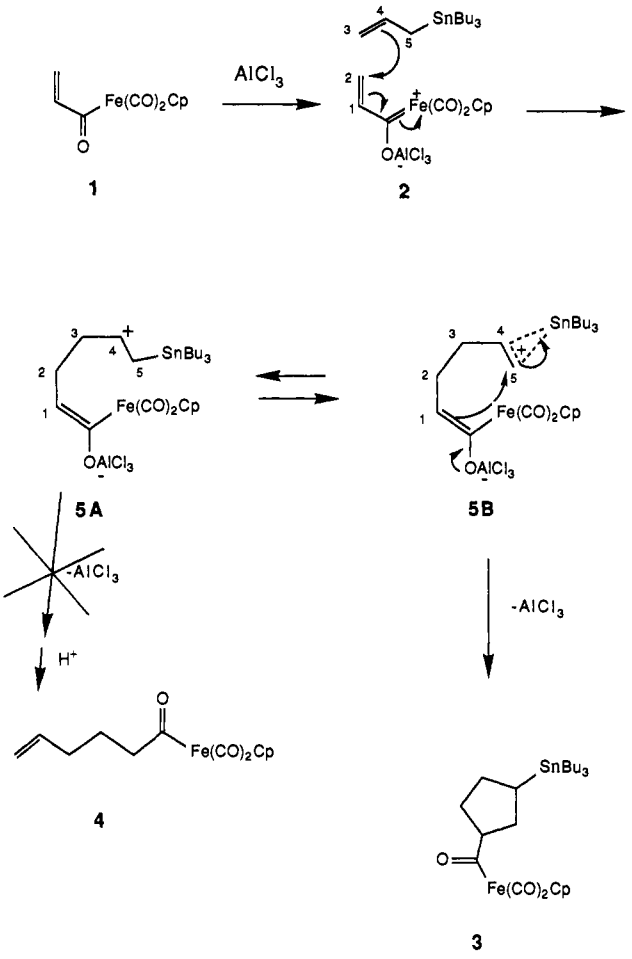
Scheme I



the analagous reaction with enones.[14] Interestingly, under identical conditions allyltrimethylsilane reacts with acryloyl complex **1** to give the 5-hexenoyl complex **4** exclusively. We believe this difference reflects lessened hyperconjugative stabilization of the β-carbocation **5** in the silicon case.[9] When methallyltributyltin reacts with **1** and $AlCl_3$, the only product isolated is the open-chain compound (entries 8, 14). Here, the intermediate carbocation **5B** is sterically destabilized and rapid destannylation occurs to give the open-chain compound. Alternatively, the intermediate carbocation more resembles **5A** (tertiary carbocation) and since in **5A** C-5 is not electrophilic, cyclization does not occur.

We are currently investigating this process with regard to mechanistic generalities and attempting to develop its synthetic potential for stereoselective five-membered ring construction.

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Supplementary Material Available: Spectral characterization of products and discussion of stereochemical assignments (4 pages). Ordering information is given on any current masthead page.

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(6) The stereochemistry of compound **4** (entries 1,2 of Table I) was assigned on the basis of ^{13}C-^{119}Sn coupling constants. The coupling constant between C_1 (74.2 ppm) and Sn was 42 Hz, which is more consistent with the cis orientation.[8]

(7) The coupling constant between the α-acyl carbon in this product and ^{119}Sn was 48 Hz. See: Kuivila, H. G.; Considine, J. L.; Sarma, R. H.; Mynott, R. J. *J. Organomet. Chem.* **1976**, *111*, 179-196.

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(15) **Note Added in Proof.** The reaction in entries 1 and 2 gives compound **3** in 64% yield (74% based on recovered starting material) with use of methylaluminum sesquichloride as catalyst.

Free Monomeric Metaphosphate in Protic Solution: Complete Racemization at Phosphorus in the *tert*-Butyl Alcoholysis of *p*-Nitrophenyl Phosphate

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The question of the intermediacy of monomeric metaphosphate in displacement reactions of phosphate monoesters has remained a controversial issue, despite efforts from many laboratories.[1] Several attempts have been made recently to obtain stereochemical information consistent with a dissociative pathway for the alcoholysis of [^{16}O,^{17}O,^{18}O]phosphate esters,[2-6] the most persuasive of which have demonstrated partial racemization at phosphorus in such displacement reactions in aprotic media. We now report the *complete* racemization at phosphorus in a simple phospho transfer reaction *in a protic solvent*, thus providing evidence for the intermediacy of a symmetrically solvated metaphosphate species in the solution reaction of a phosphate monoester.

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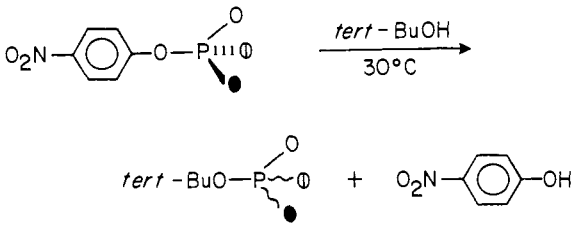
Scheme I



Despite the existence of much support for the intermediacy of metaphosphate[1] in, for example, the aqueous alcoholysis of phenyl phosphate monoanion, 2,4-dinitrophenyl phosphate dianion, or the zwitterionic form of an *N*-phosphoguanidine, we earlier showed[2] that all these reactions proceed with *inversion* of the configuration at phosphorus. Had a free metaphosphate intermediate been involved, we should, of course, have expected the product to have been racemic at the chiral phosphorus center. The mechanistic dilemma was resolved by suggesting that these reactions are constrained to preassociative pathways[2,7] in which the reversibly dissociating substrate only yields product in the presence of an acceptor nucleophile. This explanation was also used to accommodate the finding that the phospho group derived from a Conant–Swan fragmentation is also transferred (to a secondary alcohol) with inversion of the configuration at phosphorus.[3] In an effort to tip the balance in favor of metaphosphate, we followed the example of Ramirez and Maracek[8] and investigated the stereochemical course of the *tert*-butyl alcoholysis of phenyl phosphate dianion *in acetonitrile*.[4] These workers[8] had suggested that the formation of *tert*-butyl phosphate is diagnostic of metaphosphate formation, since direct nucleophilic attack by *tert*-butyl alcohol is sterically precluded. Concurrently, Cullis and Rous[5] reported the stereochemical course of the reaction of adenosine 5′-diphosphate with a primary alcohol in acetonitrile. In both of these reactions, substantial racemization was seen, though some 10% retention was observed in each case. At first sight, these experiments seemed to support the formation of a metaphosphate intermediate. However, the solvent acetonitrile is potentially nucleophilic, and the observed racemization could derive from a sequence of associative or preassociative displacements in which acetonitrile first attacks the substrate to form an acetonitrile–metaphosphate adduct[1] that then suffers multiple displacements by other acetonitrile molecules before being finally trapped by the acceptor alcohol. The small amount of overall retention observed in each of these reactions could derive from the occasional trapping of the first-formed acetonitrile adduct. These experiments do not therefore prove the intermediacy of metaphosphate. Cullis and Rous[6] have reported that phospho group transfer from a P^1,P^1-disubstituted pyrophosphorothioate to a primary alcohol proceeds with 30% inversion (and 70% racemization) *in dichloromethane*. This result, while consistent with a metaphosphate intermediate, does not indicate a completely free and symmetrically solvated species, and the authors suggested that a preassociation mechanism could also explain these data.

To resolve these concerns, and to discover whether the phosphorylation of *tert*-butyl alcohol indeed requires metaphosphate as an intermediate, we have now determined the stereochemical course of the solvolysis of the bis(tetra-*n*-butylammonium) salt of *p*-nitrophenyl (R_P)-[$^{16}O,^{17}O,^{18}O$]phosphate[9] (0.25 M) in neat *tert*-butyl alcohol at 30 °C (Scheme I). After about one half-life (220 min) the product *tert*-butyl phosphate and the remaining substrate *p*-nitrophenyl phosphate were isolated, and the absolute configuration at phosphorus was determined for each material, by the methods we have previously described.[2,4] The resulting

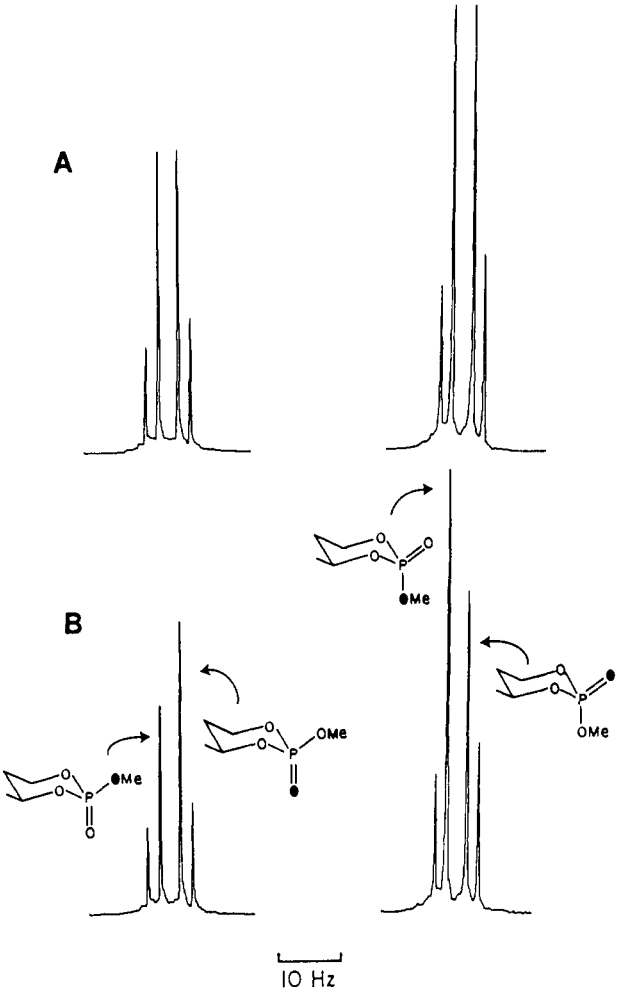


Figure 1. ^{31}P NMR spectra of the triesters from the in-line ring closure and methylation[2] of (A) 3-[$^{16}O,^{17}O,^{18}O$]phospho-(*S*)-butane-1,3-diol derived from *tert*-butyl [$^{16}O,^{17}O,^{18}O$]phosphate by phospho group transfer catalyzed by wheat germ acid phosphatase and of (B) 1-[$^{16}O,^{17}O,^{18}O$]phospho-(*S*)-butane-1,3-diol derived from recovered *p*-nitrophenyl [$^{16}O,^{17}O,^{18}O$]phosphate by phospho group transfer catalyzed by *E. coli* alkaline phosphatase. The spectra were taken on a Bruker WM-300 instrument at 121.5 MHz, Gaussian multiplication with Gaussian broadening, 0.05 Hz, and line broadening, −0.3 Hz. The downfield multiplets (syn isomers) are centered at 4.91 ppm, and the upfield multiplets (anti isomers) are centered at 5.88 ppm. The downfield signal in each quartet is from *un*labeled $^{16}O_2$ triester, and the upfield signal in each quartet is from doubly labeled $^{18}O_2$ triester. The singly labeled isotopomers that provide stereochemical information are illustrated. The product (in A) is clearly racemic, and the remaining substrate (in B) is 85% *R*.

^{31}P NMR spectra are shown in Figure 1, from which it is evident that *the phospho group has suffered complete racemization* upon transfer from *p*-nitrophenyl phosphate to *tert*-butyl alcohol. The NMR spectrum from the stereochemical analysis of the remaining substrate shows that this material is itself configurationally stable during the reaction. A control experiment confirmed that the product *tert*-butyl phosphate is also completely configurationally stable under the reaction conditions.[10]

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(9) *p*-Nitrophenyl (R_P)-[$^{16}O,^{17}O,^{18}O$]phosphate was synthesized by the route employed for 2,4-dinitrophenyl (R_P)-[$^{16}O,^{17}O,^{18}O$]phosphate[2] except that *p*-nitrophenol was used in place of lithium 2,4-dinitrophenolate.

(10) The bis(tetra-*n*-butylammonium) salt of bridge-labeled [^{18}O]-*tert*-butyl phosphate (65 ± 2% enriched) was incubated with *p*-nitrophenol (1 equiv) in unlabeled *tert*-butyl alcohol at 30 °C. After 48 h (that is, 13 times longer than the reaction time with *p*-nitrophenyl phosphate in the transfer experiment), *no* loss of isotopic label from the bridge position of *tert*-butyl phosphate could be detected by ^{13}C NMR. That the rate of label loss from bridge-labeled *tert*-butyl phosphate is a good measure of the rate of racemization of chiral *tert*-butyl [$^{16}O,^{17}O,^{18}O$]phosphate was shown by the equivalence of these rates for appropriately labeled samples of *tert*-butyl phosphate in decalin containing *tert*-butyl alcohol at 80 °C. We are grateful to a referee for pointing out the need for the control experiment in the presence of *p*-nitrophenol.

The results demonstrate the intermediacy of a completely free, symmetrically solvated monomeric metaphosphate intermediate in a phospho group transfer to a hindered nucleophile in a protic solvent and are consistent with the proposal that the formation of *tert*-butyl phosphate is, in such reactions, diagnostic of the metaphosphate intermediate.[11]

(11) **Note Added in Proof.** The results reported here are in gratifying agreement with those of Cullis and Nicholls (Cullis, P. M.; Nicholls, D. *J. Chem. Soc., Chem. Commun.* **1987**, in press) on the positional isotope exchange observed in adenosine 5′-[α,β-^{18}O]diphosphate trianion in neat *tert*-butyl alcohol.

Detailed Tautomeric Equilibrium of Aqueous D-Glucose. Observation of Six Tautomers by Ultrahigh Resolution Carbon-13 NMR

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The equilibrium tautomeric composition of aqueous reducing monosaccharides has been extensively studied for almost 150 years.[1] Each aldopentose or aldohexose exists as a mixture of at least six compounds: the aldehyde, the hydrated aldehyde (*gem*-diol), the two pyranoses, and the two furanoses.[2] However, the proportion of the *gem*-diol has not been reported for any unmodified aldopentose or aldohexose,[2] although the ^{13}C NMR signal of the *gem*-diol tautomer of D-[1-^{13}C]idose has been detected.[3]

The composition of aqueous D-glucose is the greatest challenge of the remaining gaps of knowledge about tautomeric equilibria. The reported proportions of β-D-glucofuranose and *aldehydo*-D-glucose are 0.14% (at 43 °C) and 0.002% (at 20 °C), respectively.[2] The *gem*-diol and α-furanose tautomers have not been detected. In this report we show that ultrahigh-resolution NMR methodology[4-9] yields resolved resonances for all six tautomers in ^{13}C NMR spectra of aqueous D-[1-^{13}C]glucose. We present equilibrium proportions as a function of temperature.

The sample was maintained at each temperature for at least 5 h prior to data acquisition, in order to establish tautomeric equilibrium.[1,10-14] Figure 1 shows the region of saturated C1 resonances in the ^{13}C NMR spectrum of 1.4 M D-[1-^{13}C]glucose[15] in H_2O (with 10% v/v dioxane-d_8 and 1% v/v dioxane), at 37 and 67 °C. The truncated peaks 3 and 4 are the resonances of β-D-glucopyranose and α-D-glucopyranose, respectively.[16] The peaks labeled with X are instrumental artifacts (see below). The peaks designated with C are the $^1J_{CC}$ satellites that arise from the

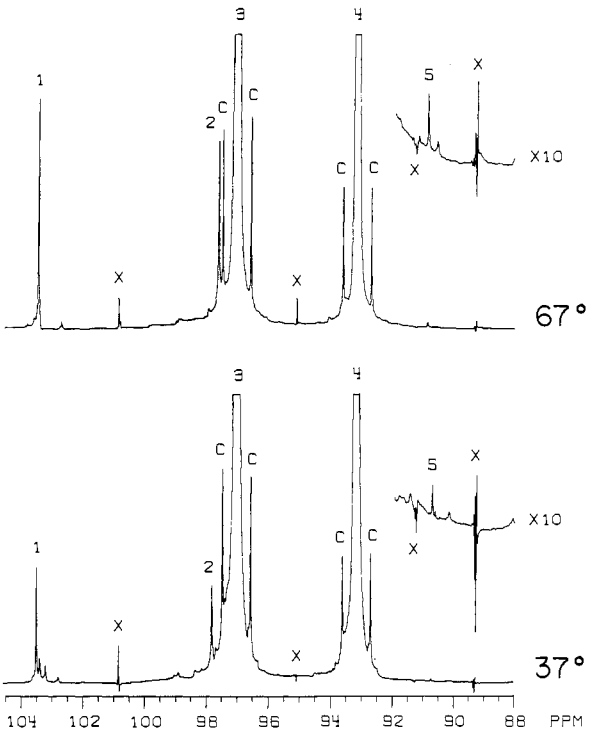

Figure 1. Region of the saturated anomeric carbons in the proton-decoupled ^{13}C NMR spectrum of 1.4 M D-[1-^{13}C]glucose in H_2O, with 10% v/v dioxane-d_8 and 1% v/v dioxane, recorded at 50.3 MHz and temperatures of 37 °C (pH 6.0) and 67 °C (pH 4.8), with an acquisition time of 3.28 s, a spectral width of ±10 000 Hz (quadrature detection), and 128K time-domain points. Homogeneity (Z_1 gradient only) was automatically adjusted prior to each batch of 200 scans. Each batch was automatically added to a double-precision (40-bit) data file which contained the sum of all prior batches. 140 and 376 batches were recorded at 37 and 67 °C, respectively. Each final time-domain spectrum was processed in the floating-point mode with 0.5-Hz digital broadening and Fourier transformation. Chemical shifts are expressed in parts per million from Me_4Si, but they were measured relative to internal dioxane, taken to have a chemical shift of 67.47 ppm at 37 °C. The β-pyranose resonance of the spectrum at 67 °C was aligned with the corresponding one in the spectrum at 37 °C. In each spectrum, the β-pyranose resonance is truncated at 0.8% of its full peak height.

pyranose tautomers of the 1.1% of molecules doubly ^{13}C labeled at C1 and C2. Spinning sidebands have been smeared out by spinner speed modulation.[17] We shall show that peaks 1, 2, and 5 arise from the β-D-glucofuranose, α-D-glucofuranose, and *gem*-diol tautomers, respectively. First, we rule out the possibility that these small peaks are artifacts or arise from impurities by noting that they exhibit large monotonic intensity increases as the temperature is raised. Peak 1 has already been assigned to the β-furanose tautomer.[18] Its chemical shift is consistent with those of anomeric carbons of furanoses with O1 trans to O2.[16] Peak 2 has a chemical shift consistent with a furanose ring which has O1 cis to O2,[16] and is therefore assigned to α-D-glucofuranose. We assign peak 5 to the *gem*-diol tautomer, because its chemical shift (90.66 ppm from Me_4Si at 37 °C) is almost identical with the values reported for the *gem*-diol tautomers of D-[1-^{13}C]-threose[13] and D-[1-^{13}C]idose.[3] Because peak 5 is extremely small relative to the resonances of the pyranose tautomers, it is particularly important to rule out the possibility that it is an artifact. Not only does the intensity of peak 5 increase with temperature but its line width also increases, a behavior consistent with an exchange contribution to the line width from *gem*-diol/aldehyde interconversion (see below).

Figure 2 shows the effect of temperature on the C1 resonance of the aldehyde tautomer. Because the resonance is very broad, each spectrum was processed with 10-Hz digital Lorentzian

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