and macrolide antibiotics will be reported in the future.

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Supplementary Material Available: Experimental procedures and spectroscopic data (NMR, IR, mass spectroscopy) (12 pages). Ordering information is given on any current masthead page.

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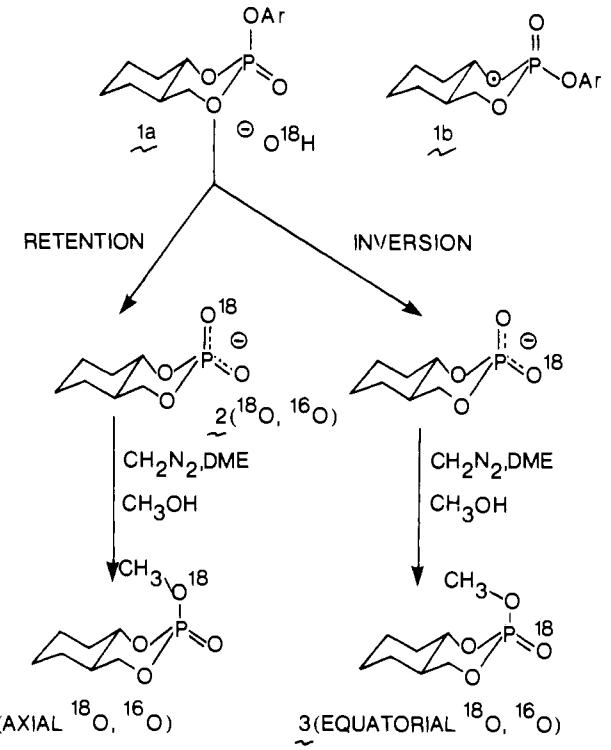
Isotopic Oxygen-18 Shifts in Phosphorus-31 NMR as a Probe of Stereochemistry of Hydrolysis in Phosphate Triesters

Sir:

Recent demonstration of an ^{18}O isotope shift in ^{31}P NMR chemical shifts has provided a convenient new probe for study of the stereochemistry of the hydrolysis of phosphate esters.[1-3] Previous work on the stereochemistry of nucleophilic displacement reactions in cyclic phosphate esters has been based upon the determination of the ratios of geometrical isomers that are formed.[4-6] Thus, we have previously established that the methoxide reaction of the 2,4-dinitrophenyl ester of 1,3,2-dioxaphosphorinane (**1**) proceeds with 100% inversion for the equatorial epimer and 83% inversion for the axial epimer[6a] (Scheme I). Product stereochemistry was determined by ^{31}P NMR analysis of the methyl esters of **1** since axial isomers of chair six-membered ring phosphorinanes resonate 4-6 ppm upfield from equatorial isomers.[5,6] This method, however, cannot be used for hydroxide or water attack on **1** since the product, cyclic diester **2**, has a prochiral phosphorus center. In this communication, we demonstrate a new, general technique for resolution of this problem by application of an ^{18}O isotope shift on the ^{31}P chemical shift of an ^{18}O isotopically substituted phosphate ester.

Scheme I



Base-catalyzed hydrolysis in $H_2{}^{18}O$/dioxane of the aryl dioxaphosphorinane **1** yielded the monooxygen-18 labeled cyclic diester **2**. The ^{18}O incorporation into the phosphate diester was determined by ^{31}P NMR analysis as shown in Figure 1A. In D_2O, the ^{31}P chemical shift of the $^{16}O,^{16}O$ cyclic diester (exocyclic oxygens only are designated) is -2.53 ppm. The $^{16}O,^{18}O$ cyclic diester is shifted 0.026 ppm upfield. This ^{18}O-induced upfield shift is expected from earlier studies.[1-3] Integration of the two signals confirms that ^{18}O hydroxide attack produces 100 ± 5% P-O aryl cleavage, based upon the calculated atom percent of ^{18}O in the hydroxide solution. No ^{18}O was incorporated into the 2,4-dinitrophenol product (analyzed via mass spectra) as expected for complete P-O aryl cleavage.

Reaction of the cyclic diester anion with diazomethane in methanol yields the axial methyl ester while reaction in water yields the equatorial ester. Epimers were identified by comparison with authentic methyl esters by GPC and ^{31}P NMR spectroscopy (axial methyl ester in $CDCl_3$, -5.96 ppm; equatorial methyl ester in $CDCl_3$, -3.97 ppm).[6] Verkade[9] has previously noted that the stereochemistry of methylation of phosphate anions by diazomethane is quite sensitive to the experimental conditions, although a 100% change in epimer distribution has not previously been observed.

The high-resolution ^{31}P NMR spectrum of the axial methyldioxaphosphorinanes produced by methylation of the cyclic diester product from the ^{18}O hydroxide catalyzed hydrolysis of the axial epimer of 2,4-dinitrophenyldioxaphosphorinane (**1**) is shown in Figure 1B. Signals at -5.833, -5.848, and -5.873 ppm integrate for 43.5, 10.3, and 46.3% of the total signal, respectively. Mass spectral analysis of this ^{18}O-enriched triester indicates 61 ± 5% $^{16}O,^{18}O$ methyl ester. No $^{18}O,^{18}O$ triester peak is seen in the mass spectrum. Addition of authentic $^{16}O,^{16}O$ methyl ester **3** to the NMR sample of Figure 1B increased the intensity of the downfield signal at -5.833 ppm and confirms that the two upfield signals at -5.848 and -5.873 ppm both represent $^{16}O,^{18}O$ stereoisomers **3**. NMR integration of the two upfield signals shows 56.6 ± 5% ^{18}O enrichment and is within experimental error of the mass spectral value.

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(7) Typical analysis of the stereochemistry of hydrolysis proceeded as follows: epimeric pairs of 2-(2,4-dinitrophenoxy)-2-oxo-*trans*-5,6-tetramethylene-1,3,2-dioxaphosphorinane (**1**) were prepared as previously described in ref 6. To a solution of 42 mg (0.12 mmol) of the axial 2,4-dinitrophenyl ester in 0.9 mL of dioxane is added 0.3 mL of 95% $H_2{}^{18}O$ and 19 mg (0.47 mmol) of NaOH. The mixture was tightly stoppered, stirred, and reacted at 60 °C for 14 h. The dioxane/$H_2{}^{18}O$ was recovered by sublimation. An aliquot of 4 mL of water was added to the residue. The solution was acidified to pH 2, and the 2,4-dinitrophenol was extracted three times with methylene chloride. The water was then removed from the diester, **2**, by sublimation.
(8) The ^{18}O-labeled diester (**2**) was dissolved in methanol and reacted with diazomethane in 1,2-dimethoxyethane as in ref 9. The solvent was removed on a rotary evaporator, and the methyl triester (**3**) was partitioned between 15 mL of chloroform and 5 mL of water. The chloroform layer was extracted with 10 mL of 10 mM EDTA in water. From this point, all glassware used had been soaked in concentrated nitric acid to remove metal ions. The chloroform was removed on a rotary evaporator. The residue was dissolved in $CDCl_3$ (Norell) and centrifuged. In the other preparation, the chloroform was dried with $MgSO_4$ then removed in vacuo. The residue was dissolved in 30% dioxane/70% D_2O containing 10 mM EDTA, and Chelex-100 was added. After the mixture stood for 30 min, the Chelex was centrifuged down and the solution pipetted into an NMR tube.
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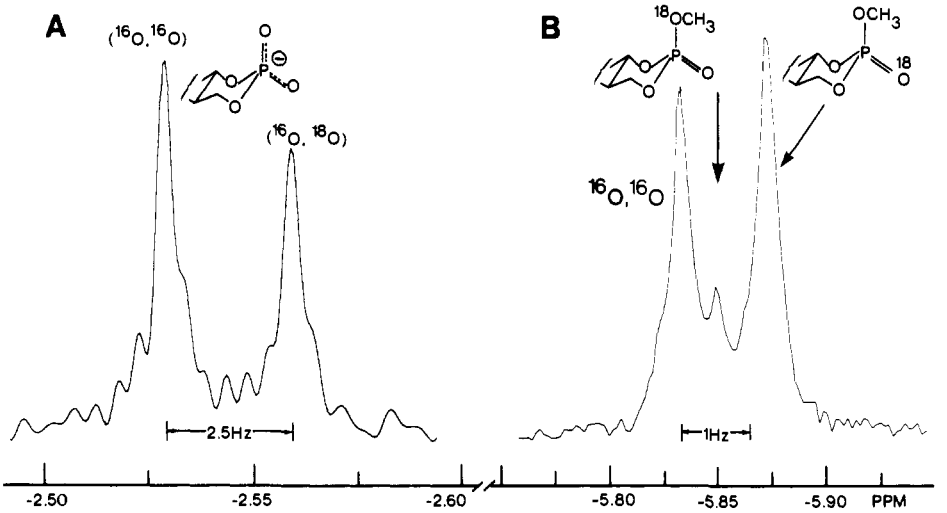

Figure 1. (A) 80.9-MHz ^{31}P NMR spectrum of 45% ^{18}O-enriched 1,3,2-dioxaphosphorinane diester (**2**) (^{18}O label in exocyclic oxygens). The upfield signal at -2.563 ppm represents the monooxygen-18 labeled diester. Spectral conditions on the Nicolet NTC-200 spectrometer: 444 scans, 1.7-s recycle time, 56° pulse width, 20% D_2O/H_2O solvent. (B) 32.4-MHz ^{31}P NMR spectrum of the axial epimer of 2-methoxy-1,3,2-dioxaphosphorinane (**3**). Total monooxygen-18 enrichment into the exocyclic oxygens is 61%. Spectral conditions on the Bruker WP-80 spectrometer: 6000 scans, 8-s recycle time, 67° pulse width, $CDCl_3$ solvent.

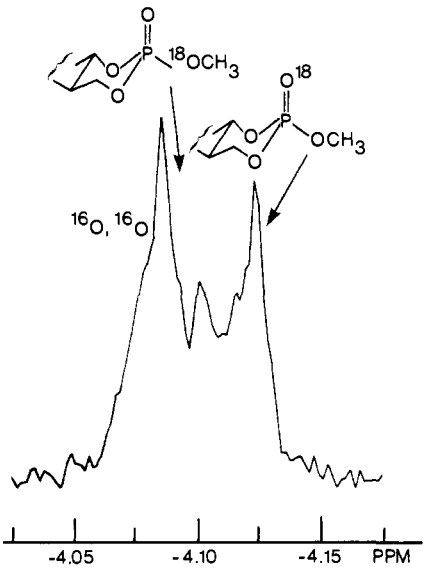

Figure 2. 32.4-MHz ^{31}P NMR spectrum of the equatorial epimer of 2-methoxy-1,3,2-dioxaphosphorinane (**3**). Total oxygen-18 enrichment into exocyclic oxygens is 59%, 4950 scans.

Cohn and Hu[10] have shown that a rough linear correlation exists between the magnitude of the ^{18}O isotope ^{31}P shift and the bond order between phosphorus and the isotopically substituted atom. In ADP and ATP, ^{18}O substitution on a single P–O bond produces a 0.0166-ppm upfield shift, and ^{18}O substitution on a P–O bond with half single-bond character and half double-bond character is 0.0285 ppm. Utilizing these two numbers and extrapolating to ^{18}O substitution on a full double bond yields a calculated ^{18}O isotope shift of 0.0404 ppm. As shown in Figure 1B, the shift between the two larger ^{31}P signals is 0.040 ppm and that between the downfield and middle signals is 0.015 ppm. The furthest upfield signal is thus associated with ^{18}O isotopic substitution into a full equatorial P=O bond and the middle signal ^{18}O substitution into a single bond. Hydroxide attack on the axial epimer of 2,4-dinitrophenyl ester (**1**) yields 82% inversion, assuming no epimerization occurs during the methylation reaction.

These assignments were confirmed by a similar study of the stereochemistry for ^{18}O hydroxide catalyzed hydrolysis of the equatorial epimer of the (*p*-methoxyphenoxy)dioxaphosphorinane **1**. Mass spectral analysis of the methyl triester indicates 59 ± 5% ^{18}O enrichment. The ^{31}P NMR spectrum of this equatorial triester sample is shown in Figure 2, and integration of the $^{16}O,^{18}O$ signals at -4.100 and -4.123 ppm indicates 51 ± 5% ^{18}O enrichment. The methyl triester ^{18}O signal distribution indicates that hydroxide attack proceeds with 59% inversion.

The stereochemistry for hydroxide attack in the *p*-methoxyphenoxy ester differs significantly from the stereochemistry for methoxide attack in methanol. Thus, the methoxide displacement proceeds with only 9% inversion,[6a] while 59% inversion is observed in the hydroxide reaction. In contrast, the 2,4-dinitrophenoxy triester yields 82–83% inversion for both hydroxide and methoxide displacement.[6a]

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A New Process for Sensitization of Ketone Photoreduction: Exploitation of Low-Lying Metal-to-Ketone Charge-Transfer Excited States

Sir:

Sensitizing organic reactions to longer wavelengths of light than absorbed by reactants is an important objective of photochemistry research.[1] We report a new mechanism for sensitizing the photoreduction of ketones by exploiting absorption that populates a low-lying metal-to-ketone charge-transfer excited state in complexes of the formula *fac*-$[XRe(CO)_3L_2]$ (X = Cl and L = 4-benzoylpyridine or X = I and L = 4-acetylpyridine). The process also depends on (i) electron-transfer quenching of the excited state and (ii) substitution lability of the Re-bound photoreduction products. Numerous examples[2-6] of photoredox processes via

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