Communication

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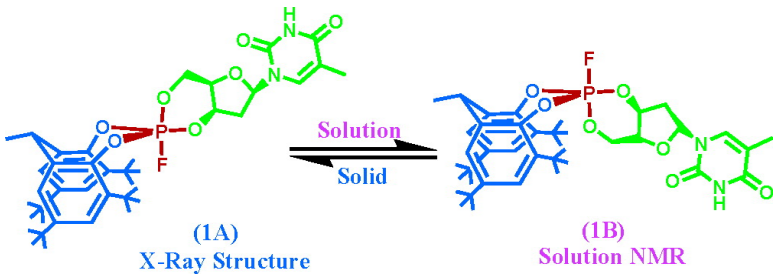

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Biologically Relevant Phosphoranes: Structural Characterization of a Nucleotidyl Phosphorane[1]

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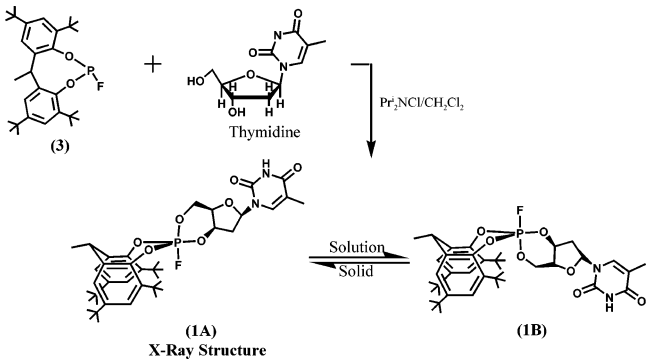
Pentacoordinate phosphorus is considered as an intermediate or transition state in the formation or hydrolysis of biologically relevant phosphorus compounds, for example, DNA, RNA, and c-AMP.[2] It is of interest to configure stable phosphoranes that more closely model proposed enzyme active site transition states than exist at the present time. Efforts to obtain solid-state structural information on pentacoordinate phosphorus containing nucleosides have not been successful despite studies[3−11] that have extended over the past 30 or so years. Most of these studies focused on solution NMR measurements and, in many cases, were performed on reaction mixtures without product isolation. However, phosphoranes containing the amino acids, valine and isoleucine, have been structurally characterized.[12]

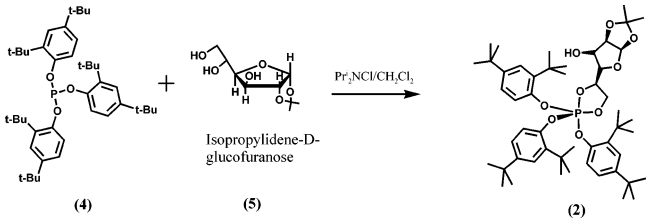
We surmised that the principal reason that the studies were unsuccessful was due to the fact that the phosphoranes are very sensitive to moisture, especially in the presence of the ribose system as it is most often water soluble or hydrophilic. Further, the ribose-based phosphoranes usually form powders from low polar solvents that are necessary to keep the phosphoranes stable. In the case of nucleosides, solubility is limited to highly polar solvents, such as pyridine, dimethylformamide, or dimethyl sulfoxide, which are not a good choice for the sensitive phosphoranes. To overcome these problems, we selected two systems, one cyclic and one acyclic, that would improve solubility, stability, and crystallizability. This strategy provided the first crystalline samples of biorelevant phosphoranes that were stable enough to be handled freely in ambient conditions. In this communication, we report the synthesis and first crystal structures of biorelevant nucleoside and carbohydrate-based phosphoranes, **1** and **2**, respectively.

The nucleotidyl phosphorane **1** was synthesized in 90% yield by reacting 2,2′-ethylidenebis(4,6-di-*tert*-butylphenyl)fluorophosphite **3** with thymidine in the presence of *N*-chlorodiisopropylamine in dichloromethane (Scheme 1). The carbohydrate-based phosphorane **2** was synthesized by reacting tris(2,4-di-*tert*-butylphenyl)-phosphite **4** with 1,2-*O*-isopropylidene-α-D-glucofuranose **5** in the presence of *N*-chlorodiisopropylamine in dichloromethane solution

Scheme 1



Scheme 2



(Scheme 2). The carbohydrate-based phosphorane **2** is freely soluble in hexane and, hence, posed a problem in crystallization. However, direct crystallization from the oil that formed in the synthesis was successful in providing reasonable crystals for X-ray analysis and pure enough samples for NMR studies. Both of these phosphoranes are very stable to water in low polar solvents. They undergo hydrolysis in solution on prolonged exposure and decompose fairly quickly in high polar solvents, such as acetonitrile.

Phosphorane **1** may be considered as a model transition state in the hydrolysis of a structural part of DNA. The geometry of pentacoordinated phosphorane **1** is trigonal bipyramidal (Figure 1) as is pentacoordinated phosphorane **2**.

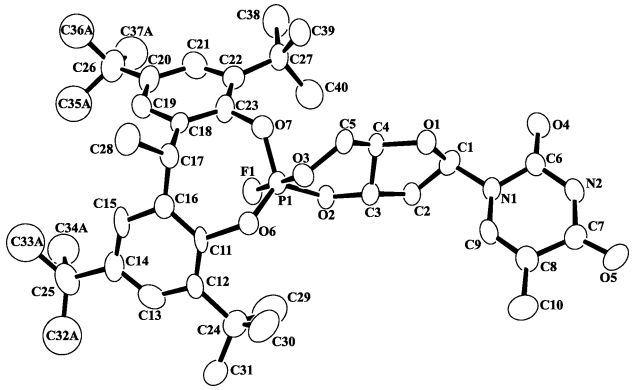


Figure 1. ORTEP[13] diagram of **1** (at 50% probability level with hydrogen atoms omitted for clarity). Only one set of the disordered *tert*-butyl group atoms is shown (with suffix "A").

The X-ray structure of phosphorane **1** shows that the eight-membered ring has an anti-conformation and occupies diequatorial positions similar to earlier observations.[14] The six-membered ribose ring occupies axial−equatorial sites as expected. NMR studies show that **1** exhibits isomerism (Scheme 1). The NMR data of **1** show that there is only one isomer in solution which is different from that found in the solid state. There are two protons from the ribose moiety with high shielding of more than 1.5 ppm. Such shielding can arise only if two of the ribose protons are in the shielding region of the aromatic ring. This leads to the structure with the primary alkoxy group placed in the axial position that is sandwiched between the aromatic rings. Similar shielding has been observed earlier,

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resulting in more than 1 ppm upfield shift for protons.[14d,15] This leaves the secondary alkoxy group to occupy the equatorial position.

The P−F coupling for an equatorial bond in a tetraoxyphosphorane was observed to be 922.5 Hz.[16] In phosphorane **1**, the values were far lower (in the order of 767 Hz), confirming the axial placement. Since the sandwiched axial position is used by the alkoxy group, the fluorine atom must be in the other axial position. In the solid state, as seen from the X-ray structure, the groups at the axial positions have interchanged.

The five-membered glucose ring in **2** occupies axial−equatorial sites as expected. In phosphorane **2**, in contrast to **1**, the bulkier secondary alkoxy group occupies the axial position, while the less bulky primary alkoxy group occupies the equatorial position. This suggests that the energy difference should be small. The proton NMR spectrum of phosphorane **2** does not show any difference between axial and equatorial aryloxy groups. This suggests that the molecule should undergo a fluxional process, possibly by a Berry pseudorotation process, which allows all of the groups to be equilibrated to give averaged signals.[17,18]

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Supporting Information Available: Experimental procedures, characterization data, crystallographic data (Table S1), ORTEP diagram for **2** (Figure S1), and the CIF files for both structures **1** and **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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