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# Reaction Kinetics of Oxyphosphoranes with Model Compounds of Nucleosides

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Ester exchange reaction kinetics of oxyphosphoranes with several kinds of alcohols, the model compounds for nucleosides, has been investigated. Comparison of the reaction rates of oxyphosphorane (**1**) with alcohols indicated that the ester exchange rates of diols were much faster than that of monoalcohols. These results might provide a clue for the intrinsic difference between ribonucleotides and 2′-deoxyribonucleotides. © 1997 Academic Press

## INTRODUCTION

Ribonucleotides and 2′-deoxyribonucleotides showed great differences in chemical and biochemical properties, mainly because of the existence of the 2′-OH group in ribonucleotides. In the literature, phosphoranes had been proposed as the possible intermediates for the displacement reaction of nucleotides with water, alcohols, and other nucleophiles (*1–7*). In order to clarify the intrinsic different properties of ribonucleotides and 2′-deoxyribonucleotides, some simple alcohols were chosen as the model compounds for nucleosides and reacted with oxyphosphoranes. For example, ethylene glycol was chosen as the 2′,3′-diOH moiety of ribonucleosides, 1,3-propanediol as the 3′,5′-diOH moiety, 1,2,3-propanetriol as the 2′,3′,5′-triOH moiety, and ethanol, *n*-propanol as the 5′-OH moiety. Their structure and reactivity relationship could provide some understanding of the chemistry in life chemistry (*7*).

## RESULTS AND DISCUSSION

### *Reaction Kinetics of Oxyphosphorane* (**1**) *with Diols and Triol*

Oxyphosphorane (**1**) (*8*) dissolved in pyridine was reacted at room temperature with one molar equivalent of ethylene glycol to give a spirooxyphosphorane (**2**) in an almost quantitative yield (Scheme 1). The reaction proceeded so rapidly that **1** was consumed completely within 1 h. Ramirez *et al.* (*9*) obtained this spirooxyphosphorane from a three-step procedure in less than 50% yield.

Under the similar conditions, oxyphosphorane (**1**) was reacted with 1,3-propanediol within 5 h to afford a spirooxyphosphorane attached by a six-membered ring (1,3,2-dioxaphosphorinane ring) (**3**) in about 95% yield. The mass spectrum of **3**,



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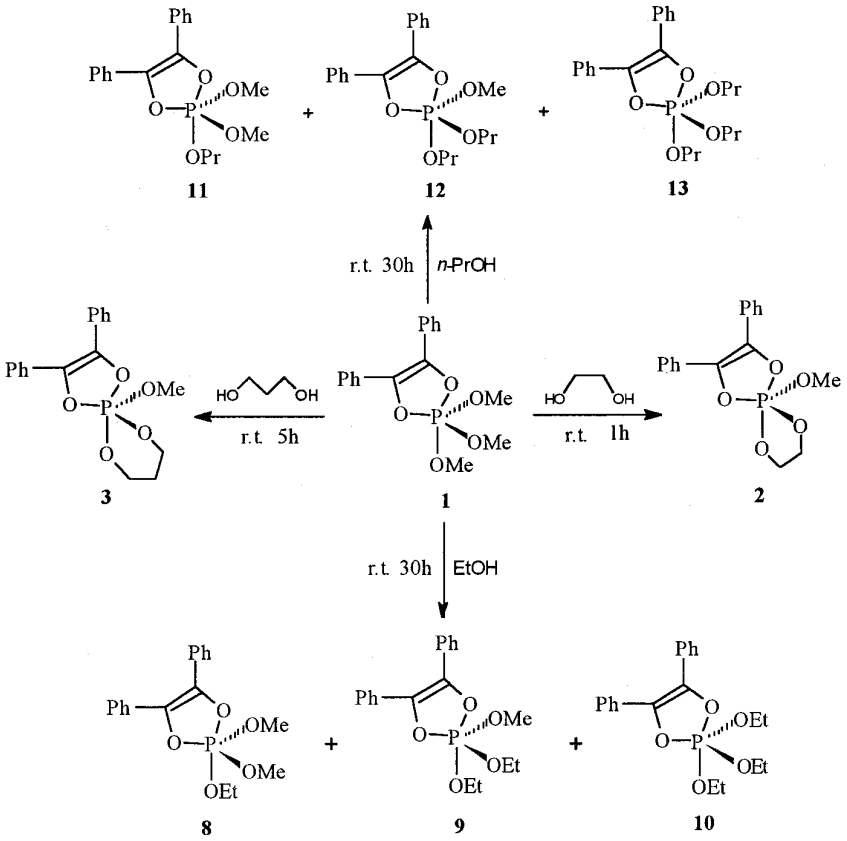



SCHEME 1. Reaction of oxyphosphorane (**1**) with ethylene glycol, 1,3-propanediol, ethanol and *n*-propanol (pyridine, 22°C).

which displayed a molecular ion peak at *m/z* 346, and its $^{31}$P NMR shift at −49.05 ppm, confirmed the structure.

The disappearance rate constants under different temperatuare for oxyphosphorane (**1**) as it was reacted with ethylene glycol and 1,3-propanediol respectively were calculated by means of $^{31}$P NMR spectra, and summarized in Table 1. At 0°C, the 1,2-diol reacted with **1** about 7.2 times faster than 1,3-diol. As the temperature raised to 22°C and 38°C, respectively, their absolute rate increased; however, the relative reactivities of 1,2-diol to 1,3-diol had decreased to 4.1 and 2.9, respectively. The difference of the activation energy Ea for the reaction of oxyphosphorane **1** with 1,2-diol and 1,3-diol was about 4.0.

When equal amounts of ethylene glycol and 1,3-propanediol were competed for the substrate **1**, after equilibrium, the product **2** was the major one in 92%, while **3** was the minor one in 8%. The ratio of **2** to **3** was about 12 : 1 (Scheme 2).

When 1,2,3-propanetriol was employed to proceed the ester exchange reaction,

TABLE 1
Thermodynamic Parameters for the Reaction of Oxyphosphorane (**1**) with Ethylene Glycol and 1,3-Propanediol[a]

| | $k \times 10^4$ | | | | | | |
|---|---|---|---|---|---|---|---|
| Alcohol | 0°C | 22°C | 38°C | Ea | ΔH | ΔS | ΔG |
| 1,2-diol | 9.78 | 31.2 | 65.5 | 8.46 | 7.87 | −43.3 | 20.6 |
| 1,3-diol | 1.35 | 7.55 | 22.6 | 12.5 | 11.9 | −32.5 | 21.5 |

[a] Unit of *k,* Ea (ΔH, ΔG), and ΔS is $M^{-1}.s^{-1}$, $kcal.mol^{-1}$ and $cal.deg^{-1}.mol^{-1}$, respectively.

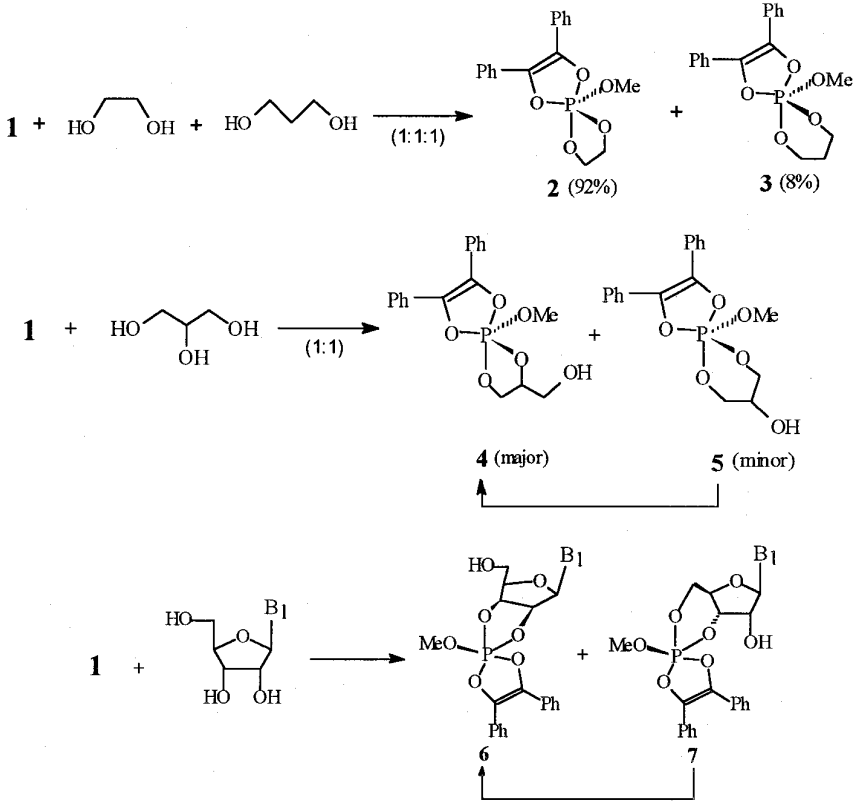
the $^{31}P$ NMR signals at −26.68 and −27.24 ppm for spirooxyphosphoranes with two five-membered rings (**4**) appeared first within 1 min. The signals at −49.33 and −50.04 ppm for spirooxyphosphoranes attached by six-membered rings (**5**) were emerged later. As the reaction was going on, the amounts of **4** increasd quickly. Meanwhile, **5** increased very slowly to reach the maximum within 25 min, then decreased gradually, and finally converted into **4**. The results were shown in Fig. 1, which were much similar than those when **1** was reacted with ribonucleosides (Scheme 2) (*10*). The structures of compounds **4** were determined by $^{31}P$, $^{13}C$ NMR spectral, and HRMS data. The $^{1}H$ NMR signals of **4** were serious overlapping, whereas the $^{13}C$ NMR spectrum has fairly good pattern to assign for the diastereomers **4a** and **4b** (Fig. 2).

*Reaction Kinetics of Oxyphosphorane* (**1**) *with Monoalcohols*

The nucleophilic substitution of oxyphosphorane (**1**) with a monohydroxyl compound such as ethanol proceeded much slower, compared to the 1,2-diol and 1,3-diol (Fig. 3). For example, at 22°C, within 1 h ethylene glycol reacted with **1** completely, while only about 4% of ethanol was reacted. It took 30 h to consume 60% of **1** when reacted with ethanol, and there were three products with the $^{31}P$ NMR signals at −49.47, −50.37, and −51.13 ppm. Their mass spectrum had three molecular ion peaks at *m/z* 348, 362, and 376, for the mono-, di-, and tri-ester exchanged products **8, 9,** and **10,** respectively (Scheme 1). The structure of **10** was confirmed by an authentic sample. The ratio of **8** to **9** to **10** was 10 : 5 : 1. When the exchanged alcohol was a larger molecule *n*-propanol, the substitution rate was expected to be slower than ethanol. Indeed, 30 h later, about 50% of the reactant **1** still remained. The $^{31}P$ NMR spectrum of the reaction mixture revealed three singlets at −49.50, −50.30, and −51.11 ppm in a ratio of 15 : 7 : 1, which were due to the mono-, di-, and tri-ester exchanged products **11, 12,** and **13** with molecular ion peaks at *m/z* 362, 390, and 418, respectively, observed in the EIMS.

*Reaction Kinetics of Other Oxyphosphoranes with 1,2-Diol*

It is obvious that the 1,2-diol is an unique reactant toward oxyphosphorane (**1**). Could it only be due to the formation of an extra five-membered ring? However,




SCHEME 2. Reaction regioselectivity of oxyphosphorane (**1**) toward ribonucleosides and their model compounds.

when oxyphosphorane (**14**) (*11*) with a saturated five-membered ring and electron-withdrawing groups (*p*-nitrophenyl) was reacted with ethylene glycol (Scheme 3), the reaction rate ($k = 4.25 \times 10^{-6}$ M$^{-1}$.s$^{-1}$) was 734 times slower than that of oxyphosphorane (**1**) with an unsaturated five-membered ring. Whereas the reaction rate ($4.91 \times 10^{-4}$ M$^{-1}$.s$^{-1}$) of oxyphosphorane (**16**) with an unsaturated five-membered ring attached by electron-donating groups (methyl) was only six times slower than that of oxyphosphorane (**1**). Hence, it is the double bonds, not the electron-withdrawing or electron-donating groups, of the five-membered rings in oxyphosphoranes, that play the key role during the ester exchange reaction of oxyphosphoranes. Since ribonucleotides have much higher reactivities than 2′-deoxyribonucleotides, it might be due to the participation of the 2′-OH in ribonucleotides. According to the literature, hydrolysis of RNA proceeds via cyclic oxyphosphorane transition states (*12–15*). Therefore from the results described above, it can be deduced that the sugar rings of nucleotides could be considered as the ''rigid double bonds.'' When ribonucleotides (**A**) are hydrolyzed, the oxyphosphoranes transition state with a five-membered ring (**B**) are formed, in which the sugar ring