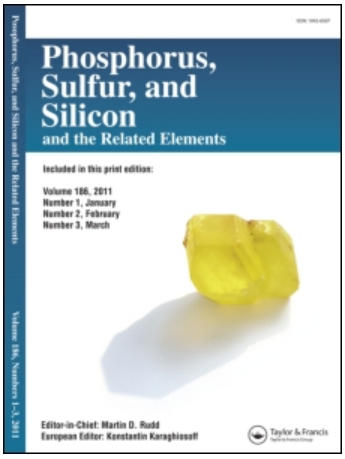

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Nan-Jing Zhang[a]; Xin Chen[a]; Yu-Fen Zhao[a]; Ru-Gang Zhong[b]
[a] Bioorganic Phosphorus Chemistry Lab, Department of Chemistry, Tsinghua University, Beijing, China [b] Department of Chemistry & Environmental Engineering, Beijing Polytechnic University, Beijing, China

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INVESTIGATIONS ON KINETICS AND MECHANISMS OF REACTIONS OF MONOCYCLIC OXYPHOSPHORANES WITH ETHYLENE GLYCOL

NAN-JING ZHANG[a], XIN CHEN[a], YU-FEN ZHAO[a] and RU-GANG ZHONG[b]

[a] *Bioorganic Phosphorus Chemistry Lab, Department of Chemistry, Tsinghua University, Beijing, 100084, China.* [b] *Department of Chemistry & Environmental Engineering, Beijing Polytechnic University, Beijing, 100022, China*

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The reaction of monocyclic oxyphosphorane compounds **1a, 1b, 1c** with ethylene glycol in pyridine was studied by ^{31}P NMR. The results showed that compound **1a** with an unsaturated five-membered ring reacts slightly faster than compound **1b** with a saturated ring attached by two trans p-nitro phenyl groups, which reacts 100 times faster than the cis compound **1c.** To interpret the mechanism, hexacoordinated intermediates **3** and **4** were proposed. The properties of **3b** and **3c,** as well as **1b** and **1c,** were investigated on the basis of PM3 calculations.. The calculations showed that there was about 2.9 kcal/mol difference between the active energy of the ester exchange reaction for compound **1b** and **1c,** which matched well with our experimental results and provided more support to the proposed mechanism.

Keywords: monocyclic oxyphosphorane; ethylene glycol; ester exchange reaction; PM3

Pentacoordinated oxyphosphoranes had been studied both as the structurally interesting compounds and as the intermediates during the phosphoryl transfer reaction.[1] In the enzymatic reaction involving cAMP and the hydrolysis reaction of RNA, the pentacoordinated phosphorus compound plays a significant role.[2,3] Our recent studies are focused on the pentacoordinated phosphorus compounds containing ribonucleosides residue, which were studied by the ester exchange reactions of monocyclic oxyphosphorane with ribonucleosides.[4] For the purpose of studying the ester exchange reactions, ethylene glycol was selected as a model compound of ribonucleosides. The reactions of ethylene glycol with different monocyclic oxyphosphoranes were studied and the preliminary kinetics was previously reported.[5] The present paper will give the further investigations on both

the kinetics and mechanisms of the reactions as well as the calculation support to our mechanism.

In order to study the pentaoxyphosphorane compounds **1a, 1b, 1c,** synthesized according to Ramirez's method[6,7], were reacted with ethylene glycol. In pyridine, compounds **1a-1c** were treated with equal molar ethylene glycol at room temperature to give the five-five membered spirooxyphosphorane **2a-2c** with the ^{31}P chemical shifts at about -24 ppm. **(Scheme 1).** The reactions were traced by ^{31}P NMR. The concentrations of compound **1a-1c** and their corresponding products **2a-2c** at each interval time were determined by the quantitative ^{31}P NMR. The result showed that **1a** and **1b** reacted with ethylene glycol much faster than compound **1c.** Compound **1a,** with two phenyl groups attached on an unsaturated five-membered ring, was the most reactive one. While compound **1b,** with two p-nitro-phenyl groups trans to each other attached on a saturated five-membered ring, showed a little slower rate. Compound **1c**, with two p-nitro phenyl groups cis to each other attached to a saturated five-membered ring, reacted 100 times slower than compound **1a. Figure 1** shows that within 40 min, compound **2a** was formed in 45% yield and **2b** in 25% yield, while **2c** was barely formed. The reactions were characterized as second order reactions and the rate constants are given in **Table I.**

The results showed that the relative position of the two p-nitro phenyl groups attached on the five-membered ring played a significant role in determining the reaction rates. Different from the regular organic reactions, the trans-isomer **1b** reacted approximately 100 times faster than the cis-isomer **1c.** In regular nucleophilic or electrophilic reactions, the trans- isomer often had a lower reactivity

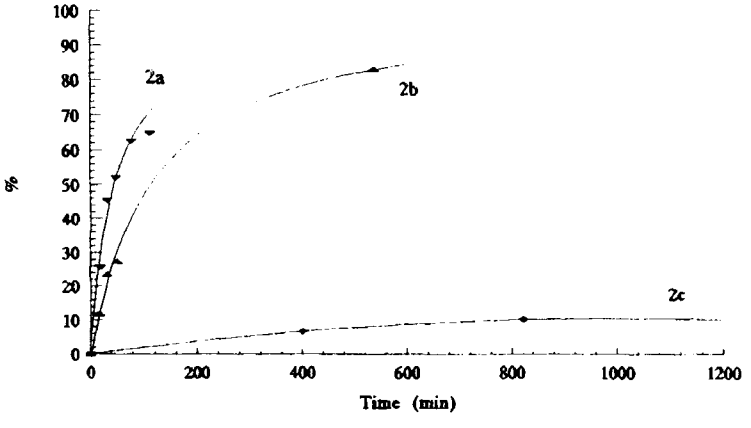
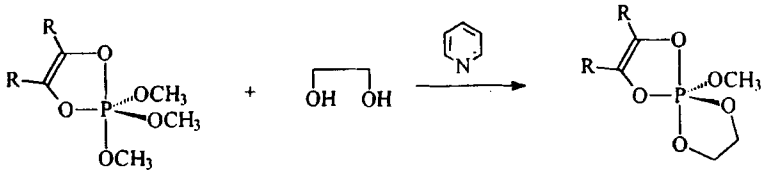
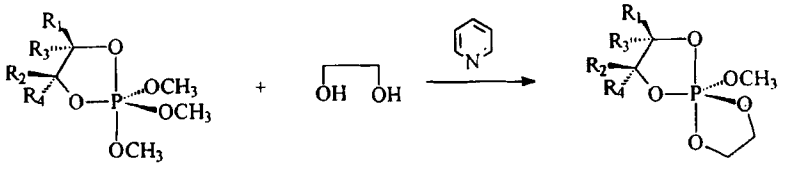


FIGURE 1 The percent contents of **2a, 2b, 2c** vs. time as 0.2 mmol oxyphosphorane **1a, 1b, 1c** and 0.2 mmol ethylene glycol reacted in 0.5 ml pyridine at 25°C respectively



1a R= R= Ph **2a**



1b R_1= R_4= p-$NO_2C_6H_4$- **1c** R_1= R_2= p-$NO_2C_6H_4$- **2b**
R_2= R_3= H R_3= R_4= H **2c**
trans- cis-

SCHEME 1

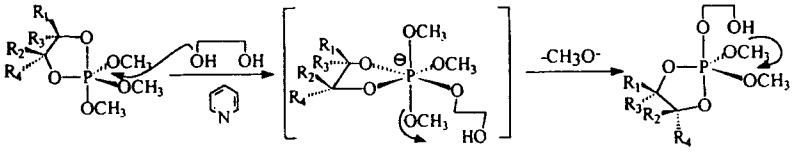
TABLE I The kinetic constants for the reaction of monocyclic phosphoranes **1a, 1b, 1c** with one molar equivalent of ethylene glycol in pyridine (25°C, 0.4 M)[a]

Compound	*1a*	*1b*	*1c*
k ($M^{-1} \cdot s^{-1}$)	5.37×10^{-4}	3.00×10^{-4}	4.17×10^{-6}

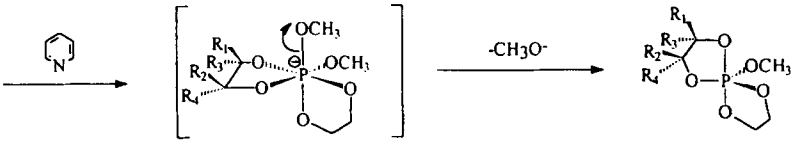
a.The values were obtained from the integration of ^{31}P NMR signals and only approximate (ca ± 5%)[8]

because of a greater steric effect on the attacking reagent. So, we proposed that the reactions proceeded via hexacoordinated transition states or intermediates **3** and **4 (Scheme 2),** and the rate difference might result from the relative energy (stability) of the hexacoordinated intermediate or transition state. The relative energy (stability) was related to the relative position of the phenyl or p-nitro phenyl group on the five-membered ring. When compound **1a** reacted with ethylene glycol, the phenyl group was nearly in the same plane with the five-membered ring. The hexacoordinated intermediates **3a** and **4a** were not too crowded and easy to form, hence compound **1a** reacted fastest. Compound **1b,** with two

p-nitro phenyl groups trans to each other, whose hexacoordinated intermediates **3b** and **4b** were not much crowded either, reacted at a similar rate. However, compound **1c,** with two p-nitro phenyl groups cis to each other, whose corresponding hexacoordinated intermediate **3c** and 4c were much more crowded and not easy to form, hence reacted much more slowly.



3a, 3b, 3c



4a, 4b, 4c

3a 4a: R_1=R_2=Ph, with a unsaturated ring
3b, 4b: R_1=R_4= p-NO_2Ph
R_2=R_3=H, trans- with a saturated ring

3c, 4c: R_1=R_2= p-NO_2Ph,
R3=R4= H, cis- with a saturated ring

SCHEME 2

In order to obtain a better insight into the properties of the proposed intermediates **3,** a set of PM3 semiempirical calculations on the intermediates **3b** and **3c,** as well as the original compounds **1b** and **1c,** were performed. The calculations were started by using the proposed intermediates concerning all the possible isomers. During the calculations, all the bond angles and torsion angles were fully optimized. The structures were built in Alchemy III and were used as the input value for the calculations with PM3 in MOPAC6.3. The calculations showed that the energy difference between **1b** and **1c** was about 6.4 kcal/mol ($\triangle E_1=E_{1c}-E_{1b}$=6.4 kcal/mol), and the difference between **3b** and **3c** about 9.3 kcal/mol ($\triangle E_3=E_{3c}-E_{3b}$=9.3 kcal/mol) **(Figure 2)**. Supposing that the difference between $\triangle E_1$ and $\triangle E_3$ is approximately the difference of their corresponding energy of activation, the calculated energy of activation difference $\triangle$Ea for compound **1b** and **1c** was about 2.9 kcal/mol. According to our experimental result, the ratio k_{1b}/k_{1c} of about 100 corresponded to an energy of activation difference of 2.3 kcal/mol, which very closely matched the calculated results of 2.9 kcal/mol.

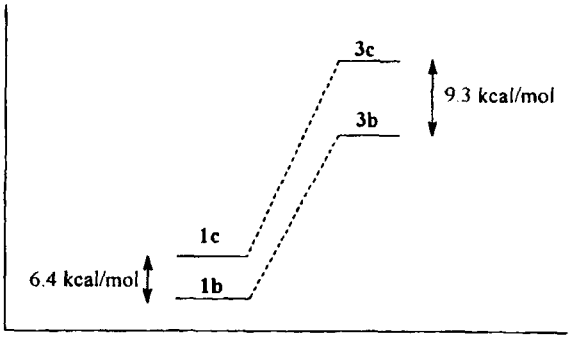


FIGURE 2 The relative energy for compound **1b, 1c** and proposed intermediates **3b, 3c** by the calculations with PM3

The resulting structures are depicted in Figure 3. The structures revealed that the attacking group (-2-hydroxyl ethoxy group) was favored over the position opposite to the P-O bond of the five-membered ring.

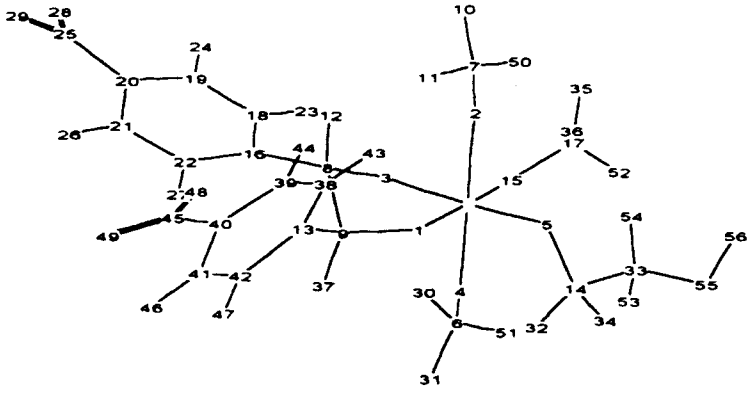
CONCLUSIONS

The ester exchange reactions of monocyclic oxyphosphoranes **1a, 1b, 1c** with ethylene glycol probably proceeded via hexacoordinated intermediates. The rate of the reaction was affected by the stability of the hexacoordinated intermediates. For compound **1a, 1b, 1c,** the lower rate constant for compound **1c** may result from the higher instability of the hexacoordinated **3c**. PM3 calculations gave more support to the proposed hexacoordinated mechanism.

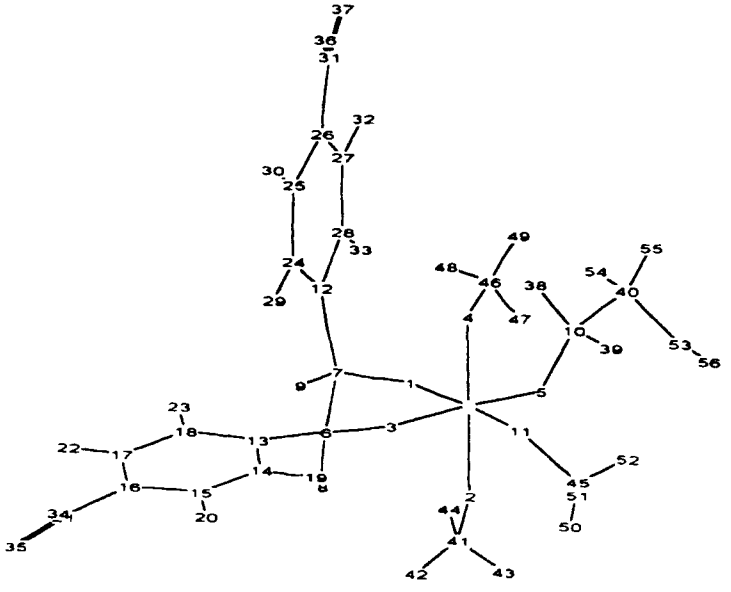
EXPERIMENTAL SECTION

All glassware were dried in an oven for at least 4hrs at 120°C before use. Air sensitive materials were transferred under nitrogen atmosphere. ^{31}P spectra were recorded at 25°C and chemical shifts for ^{31}P NMR spectra in ppm were referenced to 85% H_3PO_4 with negative shifts upfield on a Bruker AC200 FT-NMR spectrometer. The monocyclic oxyphosphoranes **1a, 1b, 1c** were prepared according to Ramirez's methods.[6,7]

General Procedure For The Ester Exchange Reactions Of Monocyclic Oxyphosporanes With Ethylene Glycol: In a 5 mm NMR sample tube, 0.2 mmol monocyclic oxyphosphoranes **1a, 1b, 1c** and 0.2 mmol ethylene glycol



3b



3c

FIGURE 3 PM3-optimized geometries for proposed intermediates **3b** and **3c**

were dissolved in 0.5 ml pyridine respectively. The concentrations of the starting material and products were calculated from the areas of the corresponding NMR peaks, assuming that all the oxyphosphoranes had approximately the same peak per unit concentration.

Calculation Of The Relative Energy Of Compound 1b, 1c, 3b, 3c By Using PM3: The original structure was built and the original geometry parameters were obtained from Alchemy III. These parameters were used for the semiempirical calculations with PM3 in MOPAC 6.3. These calculations were performed on a Pentinum-133 computer with full optimization to the geometry structures.

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