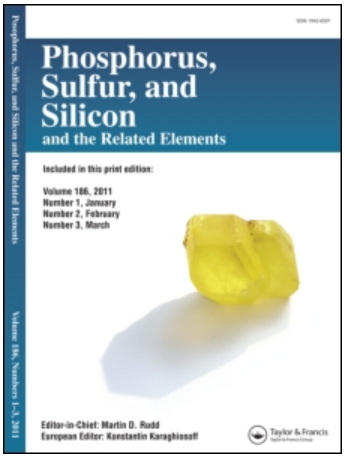

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STEREOCHEMISTRY OF THE REACTION OF GLUCOPYRANOSYL IMINES WITH PHOSPHITES AND THE MOLECULAR STRUCTURES OF THE PRODUCTS

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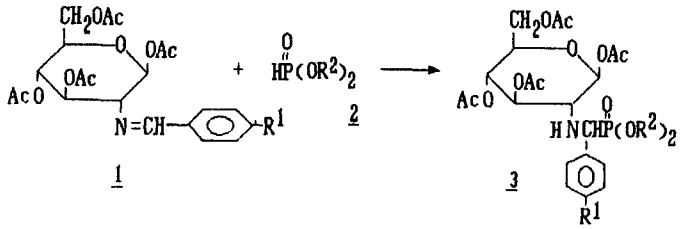
The stereochemistry of the reaction of *N*-[*p*-methyl(or methoxy)benzylidene]-2-amino-2-deoxy-1,3,4,6-tetra-O-acetyl-β-D-glucopyranose and phosphites is discussed. The configurations of the products are determined by X-ray diffraction analysis. It is found that the content of R-isomers increases as the size of alkyl groups of phosphites increases. This is probably due to the difference of steric hindrance of C_1—AcO and C_4—AcO of the glucopyranosyl group to the attack of the phosphite on the imine.

Key words: Stereochemistry; glucopyranosyl imine; phosphite; configuration.

INTRODUCTION

The anticancer properties of α-aminophosphonate derivatives have been previously reported.[1] In order to search for novel anticancer drugs, a series of O,O-dialkyl α-(2-deoxy-1,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)amino-*p*-methyl(or methoxy)phenylmethylphosphonates **3** were synthesized[2] by the addition reactions of phosphites **2** and imines **1**, which were produced from 2-amino-2-deoxy-glucopyranose and aryl aldehydes (Scheme I).



3a: R^1 =OCH_3, R^2=CH_3; **3b**: R^1=OCH_3, R^2=Et;
3c: R^1 =OCH_3, R^2=Pr^n; **3d**: R^1=CH_3, R^2=Pr^i;
3e: R^1 =CH_3, R^2=CH_3; **3f**: R^1=CH_3, R^2=Et;
3g: R^1 =CH_3, R^2=Pr^n; **3h**: R^1=CH_3, R^2=Pr^i;

SCHEME I

In this paper, the stereochemistry of the addition reactions of imines **1** with phosphites **2** and the molecular structures of the products are discussed.

RESULTS AND DISCUSSION

The configurations of the five chiral carbon atoms of the glucose unit are known, but the newly formed chiral carbon atom from the addition reaction might have two configurations. Thus, there may be a mixture of diastereoisomers for compounds **3**. In the ^{1}H NMR spectra of compounds **3**, two diastereoisomers were clearly observed, because each of C_1—H and C_2—H of glucopyranosyl group gave two sets of signals (Table I). The isomer with the chemical shift of C_2—H at higher field and C_1—H at lower field is assigned configuration A. The isomer with the chemical shift of C_2—H at lower field and C_1—H at higher field is B. According to the integration ratios given in the ^{1}H NMR spectra, it is found that the content of the isomers A is larger than B in the compounds **3**, and increases with the increase of the size of R^2 groups of the phosphites **2** (Table II).

When the imines **1** react with the phosphites **2**, there are two possible addition modes (Scheme II). First, the phosphorus atom may attack the carbon atom from the back of the imine (mode a). Second, the phosphorus atom may attack the carbon atom from the front of the imine (mode b). If the reaction takes place according to mode a, the configuration of the chiral carbon atom formed by the

TABLE I

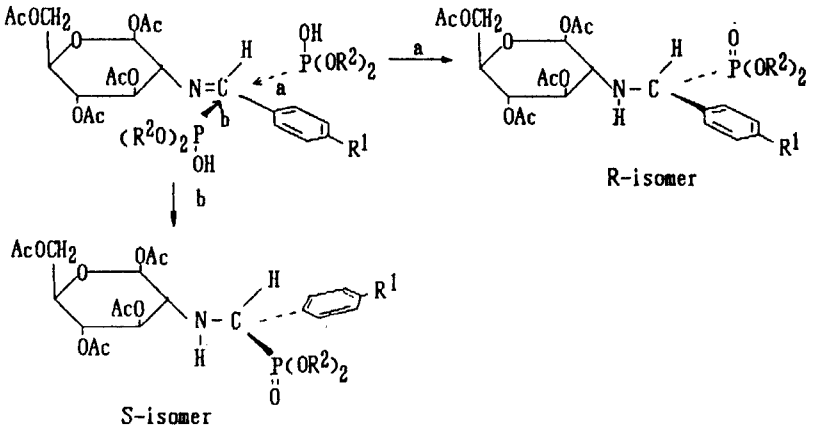
200 MHz ^{1}H NMR data of compounds **3a-h**

Compounds	3a		3b		3c		3d	
Isomers	A	B	A	B	A	B	A	B
C_1-H(ppm)	5.55(d)	5.42(d)	5.52(d)	5.45(d)	5.50(d)	5.42(d)	5.46(d)	5.41(d)
C_2-H(ppm)	2.78(t)	2.98(t)	2.77(t)	2.95(t)	2.75(t)	3.0(t)	2.73(t)	2.99(t)
Compounds	3e		3f		3g		3h	
Isomers	A	B	A	B	A	B	A	B
C_1-H(ppm)	5.51(d)	5.39(d)	5.50(d)	5.40(d)	5.46(d)	5.36(d)	5.46(d)	5.39(d)
C_2-H(ppm)	2.75(t)	2.95(t)	2.80(t)	3.0(t)	2.70(t)	2.95(t)	2.77(t)	2.98(t)

TABLE II

The ratio of isomers A and B of compounds **3**

Compounds	3a	3b	3c	3d	3e	3f	3g	3h
R^1	OCH_3	OCH_3	OCH_3	OCH_3	CH_3	CH_3	CH_3	CH_3
R^2	CH_3	Et	Pr^n	Pr^i	CH_3	Et	Pr^n	Pr^i
Isomer A:B	2:1	2.29:1	3:1	5.25:1	2:1	2.86:1	3:1	6.65:1



SCHEME II

reaction is R. For mode b, the configuration of the chiral carbon atom formed by the reaction is S.

Based on a spacefilling model, if the addition reaction takes place according to mode a, there is little steric hindrance to the attack of the phosphite, because the AcO group attached to C_1 of the glucopyranosyl group is located at the trans-position with respect to the nitrogen atom. However, when the addition reaction proceeds according to mode b, the AcO group attached to C_4 of the glucopyranosyl group provides steric hindrance to the attack of the phosphite, since it is located at the cis-position with respect to the nitrogen atom. Therefore, the reaction according to mode a is easier than mode b, and the content of the product of mode a is greater than that of mode b. In other words, the R-isomer exceeds the S-isomer in the product. It can be concluded that the product is a mixture of diastereoisomers in which isomer A is of R configuration and B is of S.

With the increase of the size of R^2 groups of the phosphites **2**, the steric hindrance of the AcO group attached to C_4 of the glucopyranosyl group to the attack of the phosphites **2** from the front of the imines **1** increases, making mode b of the reaction more difficult, and causing the content of the S-isomer to be reduced. Meanwhile, because the steric hindrance of the AcO group attached to C_1 of the glucopyranosyl group to the attack of the phosphites **2** from the back of the imines **1** is very little, the content of the R-isomer increases. Based on the above facts, it can be further concluded that the isomers A are of R-configuration and B are of S.

In order to prove further the molecular structures of the compounds **3** and the above conclusion, a mixture of the diastereoisomers of **3h** was recrystallized from acetone—petroleum ether to give a colorless solid **3h′**, the ^{31}P NMR spectrum of which showed a single signal at δ = 22.07, confirming that **3h′** is a pure isomer [$[\alpha]_D^{15}$ + 20.0° (C 0.17, acetone)]. In the ^1H NMR spectrum of **3h′**, C_1—H and C_2—H of the glucopyranosyl group gave a set of signals at δ = 5.46 and 2.77, respectively, proving that **3h′** not only is a pure isomer but also is the main isomer of **3h**. Also, a colorless solid **3d′** [$[\alpha]_D^{15}$ + 12.80° (C 0.50, acetone)] was obtained by recrystallization of **3d** (^{31}P NMR: 22.22 and 22.61) from the mixture of acetone and petroleum ether, with its ^{31}P NMR spectrum at δ = 22.21 and ^1H NMR

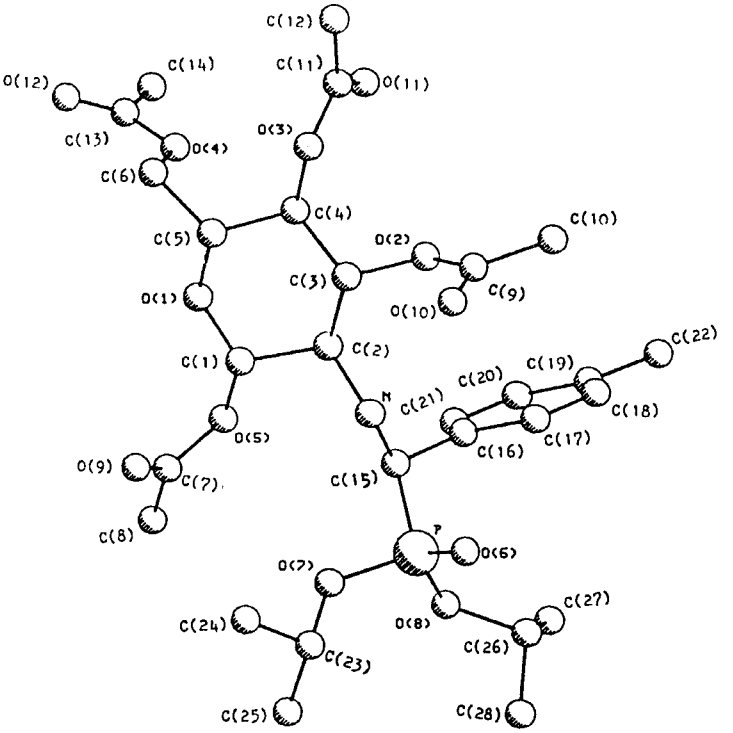


FIGURE 1 The molecular structure of **3h'**.

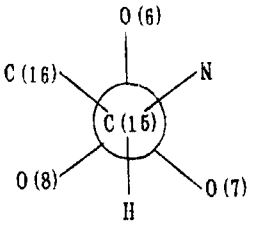


FIGURE 2 Newman projection of **3h'** from C(15) to P.

spectrum (C_1—H: 5.46 (*d*), C_2—H: 2.73 (*t*)) confirming that **3d'** is pure and the main isomer of **3d**.

A single crystal of **3h'** was cultured from the mixture of acetone and petroleum ether. The result of X-ray diffraction analysis proves the molecular structure of **3h'** (Figure 1). The crystal is monoclinic, space group $P2_1$, a = 10.158 (1), b = 9.069 (1), c = 18.147 (3) Å, β = 90.72 (1)°, V = 1671.6 Å^3, Mr = 617.61, Z = 2, Dx = 1.23 g/cm^3, μ = 2.16 cm^{-1}, F (000) = 660, R = 0.071, Rw = 0.073. The Newman projection from the chiral carbon atom C(15) to P atom (Figure 2) shows that the configuration of the chiral carbon atom C(15) formed by the reaction is R. It is obviously consistent with the previous conclusion.

EXPERIMENTAL

All ^1H NMR and ^{31}P NMR spectra were recorded with a Bruker AC-P 200 spectrometer. TMS was used as an internal standard for ^1H NMR, and 85% H_3PO_4 was used as an external standard for ^{31}P NMR.

ACKNOWLEDGEMENTS

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