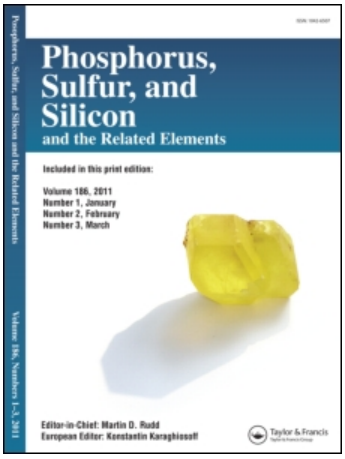

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DIASTEREOISOMERS FROM IODINE-INDUCED CYCLIZATION REACTION OF PHOSPHONATE

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DIASTEREOISOMERS FROM IODINE-INDUCED CYCLIZATION REACTION OF PHOSPHONATE

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Two products were isolated from the iodine-induced cyclization reaction of di-*n*-propyl-4-pentenyl-phosphonate, 1. One of them has previously been proven to be 2-*n*-propyloxy-2-oxo-6-(iodomethyl)-1,2-oxaphosphorinane, 2. The second product, 3, has the same molecular weight and mass spectral fragmentation patterns as 2. The results of one- and two-dimensional ^{1}H, ^{13}C, and ^{31}P multinuclear magnetic resonance spectroscopies indicate that 2 and 3 are the alkoxyl-*axial* and alkoxyl-*equatorial* diastereoisomers, respectively, of 2-*n*-propyloxy-2-oxo-6-(iodomethyl)-1, 2-oxaphosphorinane. The nuclear magnetic resonance spectroscopic parameters such as the ^{1}H, ^{13}C, and ^{31}P chemical shifts and the homo-(^{1}H—^{1}H) and hetero-(^{1}H—^{13}C, ^{1}H—^{31}P, and ^{13}C—^{31}P)coupling constants of 2, and 3 are documented in this report.

Key words: 2D-NMR, diastereoisomers, MS, 2-n-propyloxy-2-oxo-6-(iodomethyl)-1,2-oxaphosphorinane.

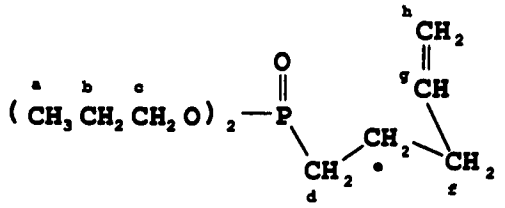
INTRODUCTION

The iodine-induced cyclization of unsaturated carboxylic acids was discovered early of this century.[1] Since then, the halolactonization reaction has been used extensively for regioselective and stereoselective control in organic synthesis.[2,3]

We have recently employed the iodine-induced cyclization reaction of O,O-dialkyl-4-pentenyl-phosphonates 1 as an alternative of producing the cyclic phosphonates.[4–7] The results show that two diastereoisomers of 2-*n*-propyloxy-2-oxo-6-(iodomethyl)-1,2-oxaphosphorinane (2 and 3 in Scheme I) are formed. The phosphorus atom is the new chiral center produced during the ring formation. The major product (2), previously isolated and identified by Zhao and coworkers,[4–7] is the alkoxyl-*axial* of the diastereoisomer and the minor product (3) is proven to be the alkoxyl-*equatorial* of 2-*n*-propyloxy-2-oxo-6(iodomethyl)-1,2-oxaphosphorinane by mass spectrometry and by one-dimensional (1-D) and various two-dimensional (2-D) ^{1}H, ^{13}C, and ^{31}P multinuclear magnetic resonance spectroscopies.

RESULTS AND DISCUSSION

Mass spectrometry: In order to test whether 2 and 3 are diastereoisomers, mixtures with different proportions of Samples A and B were analyzed by MS (Table I).



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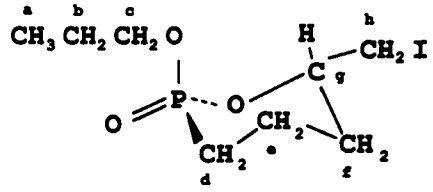
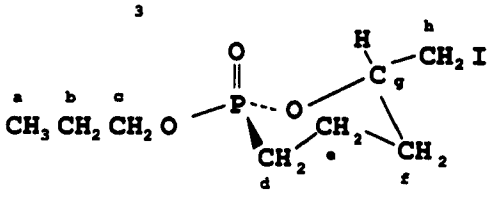


2, $CH_3CH_2CH_2O$- ***axial***



3, $CH_3CH_2CH_2O$ - ***equatorial***

SCHEME I
Molecular Structures of Compounds 1, 2, 3.

The $(M + H)^+$ ion for both samples is 319. In addition, there are three major fragments, 191, 277, and 149 in both Samples C and D, which most likely correspond to $(M - I)^+$, $(M - CH_3CH{=}CH_2 + H)^+$, and $(M - CH_3CH{=}CH_2 - I)^+$ ions (Scheme II). In addition, the relative intensity of these three fragments and $(M + H)^+$ in Samples C and D are the same. It is interesting to note that the m/z 277 peak may originate from the glycerol matrix. To verify if there is fragmentation at

TABLE I
Major ions of samples in MS

Fragment	Calcd. mass	Obsd. m/z	Relative intensity in sample C (%)	Relative intensity in sample D (%)
FAB – MS				
$(M + H)^+$	319	319	97	90
$(M\text{-}42 + H)^+$	277	277	24	25
$(M\text{-}I + H)^+$	191	191	16	15
$(M\text{-}42 - I)^+$	149	149	100	100
CI – MS (compound **2** only)				
M^+	318	318		
$(M\text{-}42)^+$	276	276		
$(M\text{-}I)^+$	190	190		
$(M\text{-}42 - I)^+$	149	149		

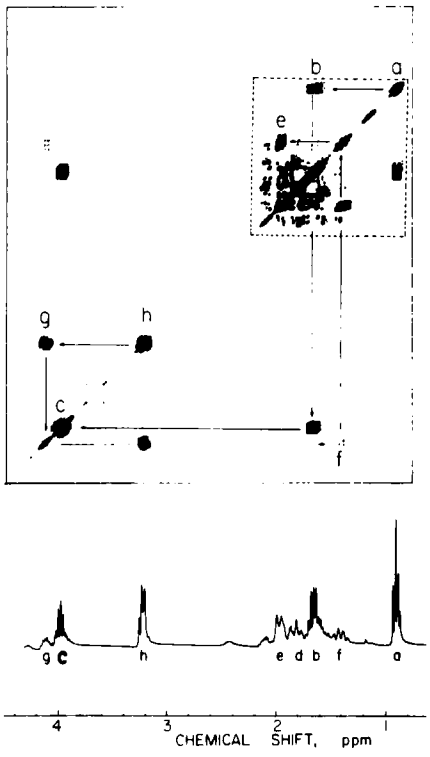
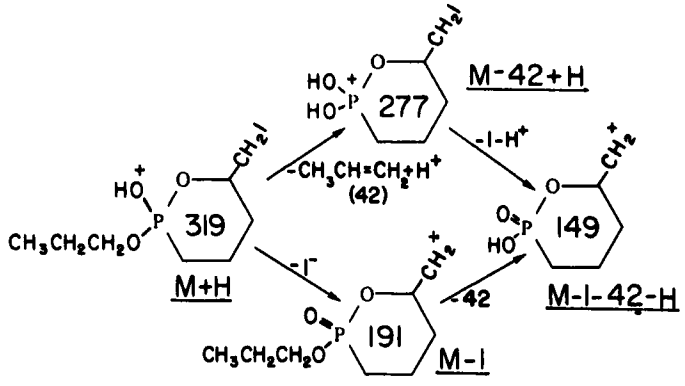


FIGURE 1 A contour plot of 2-D phase sensitive COSY of sample A. 1-D spectrum contains an 8 K data file covers a spectral window of 1300 Hz., which results in digital resolution of .32 Hz/pt. 16 scans were accumulated. The 2-D phase sensitive COSY spectrum has an 1K × 1K data matrix cover 1300 × 1300 Hz. The digital resolution is 2.56 Hz/pt. 256 t1's data were taken, then zero-filled to 1K. 96 scans for each t1 were accumulated. The coupling connectivities of major component (compound **2**) are illustrated by solid lines through the off-diagonal peaks.

m/z 277, the 2 was run by chemical ionization MS. The four fragments peak, i.e., 318, 276, 190, and 149, were observed. This additional evidence indicates the peak at 277 is contributed by $(M - CH_3CH{=}CH_2 + H)^+$ FAB—MS.

The NMR: Compound 2 is the major component (>95%) of sample A (see experimental section). Its 1-D and 2-D COSY ^1H NMR spectra are shown in Figure 1. Signals from the groups a, b, and c (Scheme I) can be identified immediately by their coupling connectivities (Figure 1). In addition, peaks h, g, and f can also be assigned by 2-D COSY in (Figure 1). Although resonances of b, d, e, and f are clustered in a small region, however, the identities of these signals can still be assigned by 2-D COSY. It has been clearly shown that f (1.44 ppm) is coupled to e (2.14 ppm) and e is coupled to d (1.88 ppm). In addition, the detail pattern can be seen by 2-D TPPI COSY, the connection between off-diagonal to diagonal peaks can then be identified. Therefore, the assignments of all proton resonances can be done and their chemical shift values are listed in Table II.

The ^1H NMR peaks originating from 3 can be distinguished by making a comparison between the ^1H NMR spectra of samples A and B. This is because the signals from compound 2 can readily be identified due to their known chemical shift values.



SCHEME II
The Fragmentation of Compounds **2** and **3** in Positive Ion FAB–MS.

The 1-D proton-coupled, decoupled, and 2-D ^{1}H—^{13}C HETCOR spectra of sample B are shown in Figure 2. Although the peaks from 2 are more intense due to the greater abundance (73%*), the weaker peaks from the minor species (3, 27%*) can also be seen (Figure 2). Thus, the ^{13}C NMR signals of both 2 and 3 can be determined by ^{1}H—^{13}C HETCOR and 1-D proton coupled NMR spectroscopy (Figures 2A and C). Namely, the identities of ^{13}C resonances can be determined by the known proton resonances in the same group through HETCOR (Figure 2C). In addition, the ^{13}C—^{1}H coupling pattern can be verified in Figure 2A. The chemical shift values has been recorded and also collected in Table II. It is interesting to note that the ^{13}C NMR chemical shift values for 2 and 3 are similar. Only g carbon shows pronounced differences in chemical shift (up to 2.4 ppm), which could be due to the P=O effect.This information again strongly suggests that compounds 2 and 3 are stereoisomers with phosphorus as the chiral center. The proposed structures of two dastereoisomers are illustrated in Scheme I, where

TABLE II
The multiNMR data (chemical shifts and coupling constants) of compounds **2**, **3**, as well as **1**

Compounds **2** and **3**						
	Chemical shifts (ppm)					
	^{1}H*		^{13}C*		^{31}P**	
Groups	**2**	**3**	**2**	**3**	**2**	**3**
			(JC-P, Hz)			
P					22.2	25.0
a	0.95	0.95	9.9	9.8		
b	1.70	1.70	23.6(5.7)	23.7(4.4)		
c	3.97	4.03	66.2(6.6)	67.7(7.1)		
	4.00	4.06				
d	1.88	1.82	21.8(129.1)	22.0(128.7)		
e	2.14	2.35	20.9(7.4)	19.0(6.9)		
f	1.44	1.62	31.2(6.1)	31.4(5.5)		
g	4.16	4.29	80.1(7.1)	77.7(4.8)		
h	3.22	3.27	7.3(8.5)	8.2(7.8)		

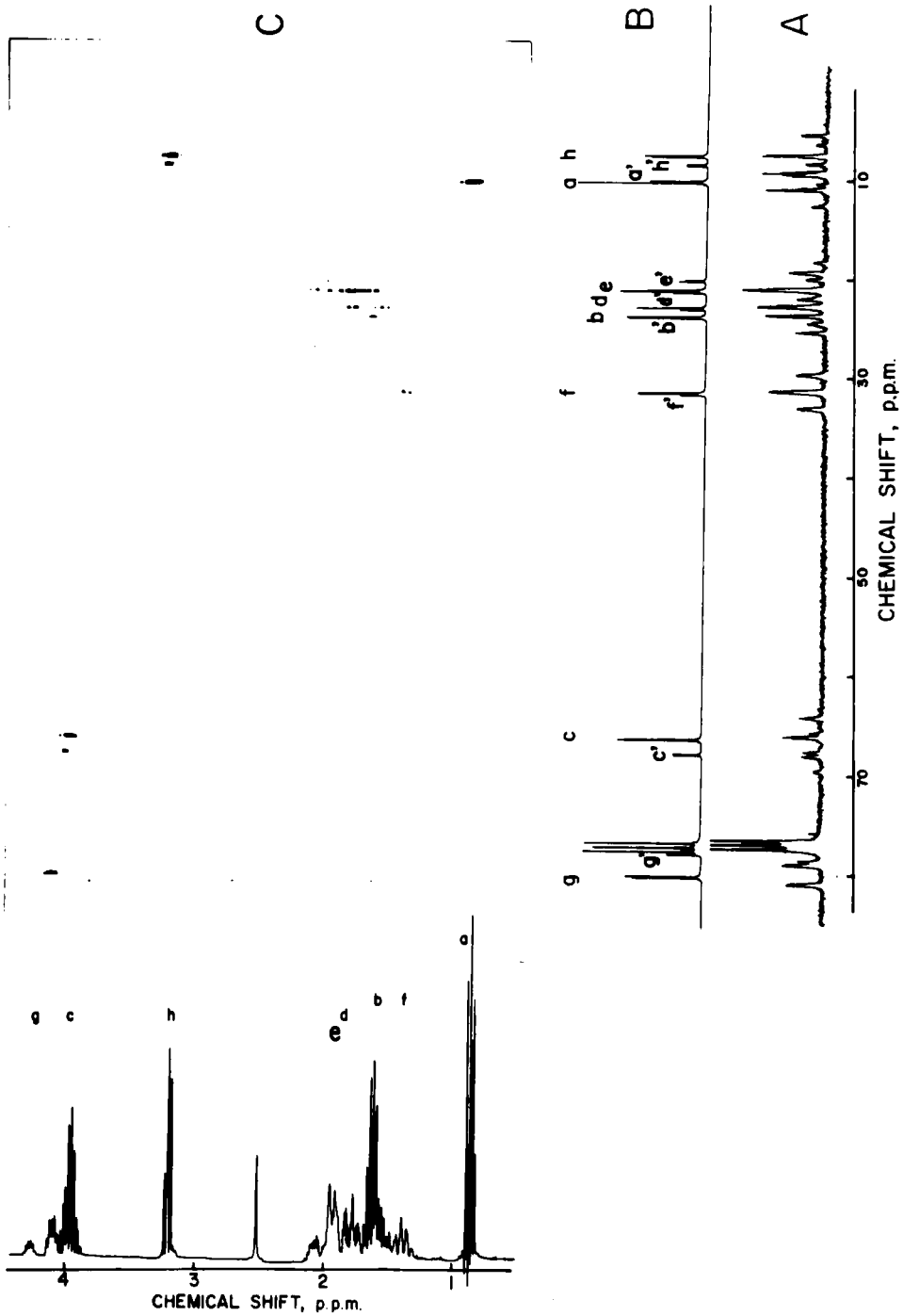


FIGURE 2 A contour plot of the ^{1}H—^{13}C chemical shift correlated 2-D NMR spectrum of sample B (2 and 3). 2A: ^{1}H coupled ^{13}C NMR. 32 K data set covered width of 7000 Hz. 256 scans were accumulated. 2B: The same as A, except ^{1}H decoupled. 2C: ^{1}H—^{13}C chemical shift correlated 2-D NMR spectrum. The data point matrix is 512 (for ^{1}H) × 2K (for ^{13}C).

R is the propyl group which can be *axial* or *equatorial* and the CH_2I group is in the less crowded equatorial position.[11,12]

There are clearly two ^{31}P signals (22.2 ppm and 25.0 ppm) in the spectrum of sample B. It is interesting to note that the hetereo coupling patterns of phosphorus nuclei to protons (c, d, e, and f) are very similar in both compounds. This also indicates the similarity in structure of 2 and 3. In general, the equatorial P=O leads to about a 3 to 5 ppm upfield shift,[13-16] which was consistent with the assignments of the diastereomers of the cyclic phosphate triesters labelled by ^{18}O.[17] Thus, 2 is most likely the alkoxyl-*axial* form and 3 is the alkoxyl-*equatorial* form of 2-(*n*-propyloxy)-2-oxo-6-(iodomethyl)-1,2-oxaphosphorinane.

CONCLUSION

The iodine-induced cyclization of di-*n*-propyl-4-pentenylphosphonate is stereoselective and gives the major product 2 with the *axial* propyloxyl group, while the minor one is 3, with the *equatorial* propyloxy group (deduced from the NMR study). Furthermore, the relative composition of these two diastereoisomers in samples A and B can be determined as 95:5 and 73:27, respectively, by comparing the area of ^{31}P and/or ^{13}C NMR signals.

EXPERIMENTAL

Preparation of the 2(n-propyloxy)-2-oxo-6-(iodomethyl)-1,2-oxaphosphorinane (2 and 3). A mixture of 1 (1.66 g; 7.08 mmol.) and iodine (3.24 g; 12.75 mmol.) was dissolved in 3.5 ml of $CHCl_3$. After stirred for 10 minutes, the homogeneous solution was allowed to settle for 74 hours at 10°C. The solvent was removed and the residue was passed through a 60–100 mesh silica gel column eluted with $CHCl_3$. The excess iodine was eluted out first. After removing $CHCl_3$ from the subsequent fractions, a viscous, yellow liquid was obtained. This crude product was rechromatographed on a 260 mesh silica gel column eluted with $CHCl_3/C_6H_{12}$ (4:1 by volume). Each collection tube was analyzed by ^{31}P NMR on a JEOL FX-100 spectrometer at 40 MH_z with 85% H_3PO_4 as an external reference. The first six fractions (10 ml per fraction) of the product peaks (80 mg., sample A) from chromatography were pooled and concentrated and were reported previously.[4-7] The major component of this fraction (>95%) designated as 2, has a phosphorus signal at 22.2 ppm. The minor component (<5%) designated as 3, has a ^{31}P NMR resonance at 25.0 ppm. However, the remaining four fractions of the product peaks (100 mg., sample B) also exhibited ^{31}P NMR resonances at 22.2 and 25.0 ppm. Thus, it was assumed (and later proved, see RESULT) that sample B also contained 2 and 3, but in different proportions (73% of 2 and 27% of 3, calculated by the integration of the area under the ^{31}P NMR signals).

Mass Spectrometry. Two different ionization methods were used to analyze the reaction products in this report. Positive ion fast atom bombardment (FAB) mass spectra were taken from a KYKY Zhp5A double focussing mass spectrometer (MS) (Scientific Instrument Factory, Beijing, China) equipped with a KYQ fast atom gun. The Argon atom beam was operated at the energy of 7 keV and gun loop current of 1.0 mA. Glycerol was used as a matrix for FAB analysis. Two mixed samples, sample C (a mixture of 95% of A and 5% of B) and sample D (a mixture of 68% of A and 32% of B), were used for the FAB-MS study.

Compound 2 has also been observed by a AEI-50 MS with chemical ionization method.

Multinuclear Magnetic Resonance Spectroscopy (NMR). There NMR samples were made by dissolving 10 mg. of 1, samples A and B in 0.4 ml 99.8% $CDCL_3$. All NMR spectra were obtained on a Bruker WM-300 spectrometer equipped with an ASPECT 3000 microcomputer. The ^1H, ^{31}P, and ^{13}C NMR spectra were obtained at operating frequencies of 300.13, 121.47, and 75.5 MH_z, respectively. A BVT-1000 temperature controller was used to maintain the probe temperature at 25°C.

The following NMR spectra were obtained: 1-D single and double-resonance spectra for ^1H, ^{13}C, and ^{31}P,2-D homonuclear J-resolved (2-D JRES) spectra[8] (for ^1H only), 2-D homonuclear phase sensitive

chemical shift correlated (2-D TPPI COSY) spectra[9] (for ^1H only), and 2-D heteronuclear chemical shift correlated spectra (HETCOR)[10] (for ^1H—^{13}C).

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