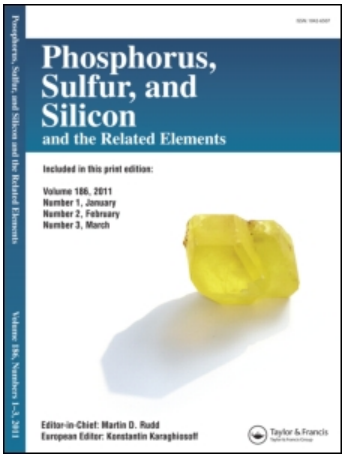

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FURTHER INVESTIGATION ON IODOCYCLIZATION OF UNSATURATED PHOSPHONATES AND CARBOXYLIC COMPOUNDS

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FURTHER INVESTIGATION ON IODOCYCLIZATION OF UNSATURATED PHOSPHONATES AND CARBOXYLIC COMPOUNDS

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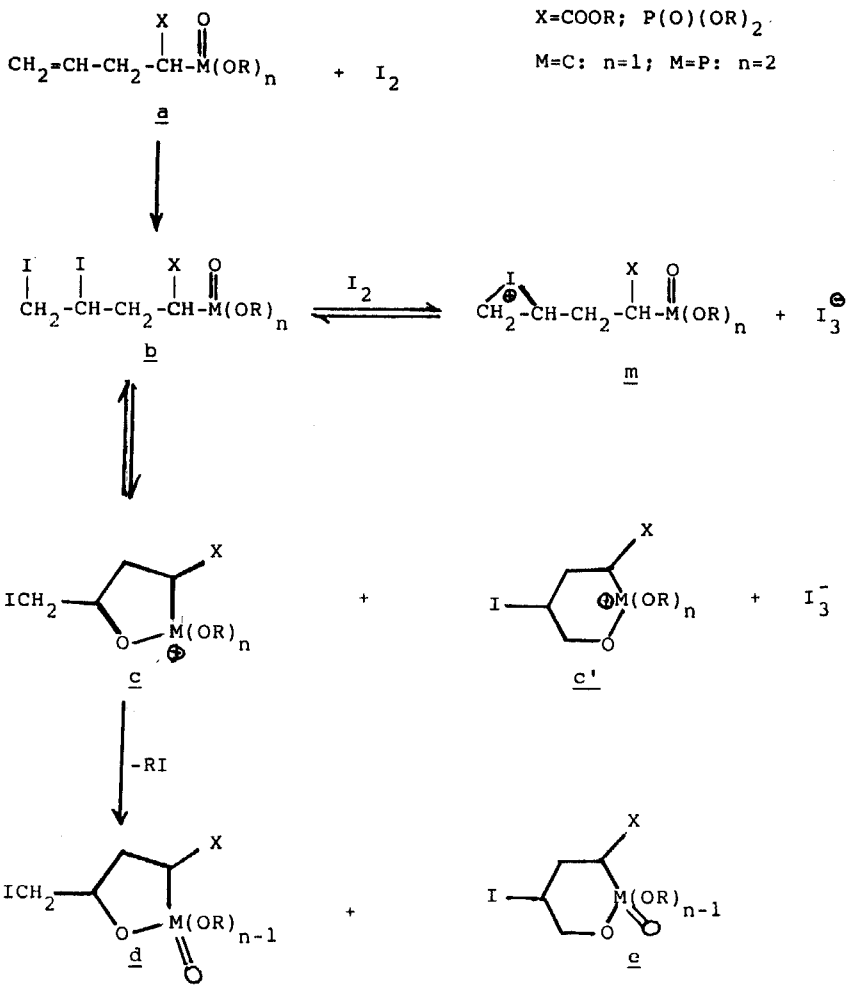
Six δ,γ-unsaturated compounds (1a–6a) were synthesized and treated with two equivalents of iodine. It was found that the α-carboxylic group and the α-phosphoryl group could act as stabilization groups to the positive ion intermediates in the iodocyclization reaction. The mechanism of this neighbouring groups' effect is discussed.

Key words: Iodocyclization; α-phosphoryl group stabilized intermediates; α-carboxylic group stabilized phosphonium ion intermediates; unsaturated phosphonates.

I. INTRODUCTION

The iodocyclization of unsaturated carboxylic acids and esters has been studied extensively for the purpose of stereocontrol in organic synthesis.[1] Although a general mechanism including a carbonium ion intermediate has been proposed by Amaral,[2] this supposed intermediate has not been observed because there were no accessible techniques to analyze the complicated reaction mixture. On the other hand, Zhao and co-workers have reported the observation of phosphonium ions and diiodo-compounds as the intermediates in iodocyclization of organo-phosphorus compounds,[3–5] and a detailed mechanism was proposed. It was thought that this mechanism might be generalized to all the systems dealing with the iodocyclization of unsaturated compounds (Scheme I). Indeed, when the reaction of 4-pentenoic acid and iodine was followed by the FAB-MS, the diiodo-adduct[3] existed as one of the intermediates, but the carbonium ion might have too short a life time to be picked up at the same time. According to the literature,[6] both hydroxyl and carboxyl group could compete to iodocyclization reaction due to the same order of the nucleophilicity. In this paper, a carboxyl or a phosphoryl group was introduced to an unsaturated carboxylic ester or amide (Table I) for the purpose of cyclization competition study.



SCHEME I. A general mechanism.

II. RESULTS AND DISCUSSION

The Comparable Nucleophiles, Carboxyl and Phosphonyl Group

When one molecule of unsaturated compound (a) was treated with two equivalents of iodine, it afforded one molecule of cyclization product and one molecule of alkyl iodide at the same time (see Scheme I). Hence the total reaction rate could be represented by the liberation speed of alkyl iodide (Equation 1):

$$\frac{dp}{dt} = \frac{d[\mathrm{RI}]}{dt} = \mathrm{Kobs} * [A] * [I_2] \tag{1}$$

where Kobs is the reaction rate constant observed.

TABLE I

Iodolactonization of 1a to 6a

Compd	X	$M(O)(OR)_n$	Product	Yield (%)
1a	H	$COOCH_3$	1d	86
2a	$COOCH_3$	$COOCH_3$	2d	81
3a	H	$P(O)(OEt)_2$	3e + 3d	57
4a	$P(O)(OEt)_2$	$COOCH_3$	4d[a]	90
5a	H	$CONEt_2$	1d	94
6a	$P(O)(OEt)_2$	$CONEt_2$	6c[b]	90

a: the $COOCH_3$ cyclized product.

b: the $CONEt_2$ cyclized product.

TABLE II

Kinetic data

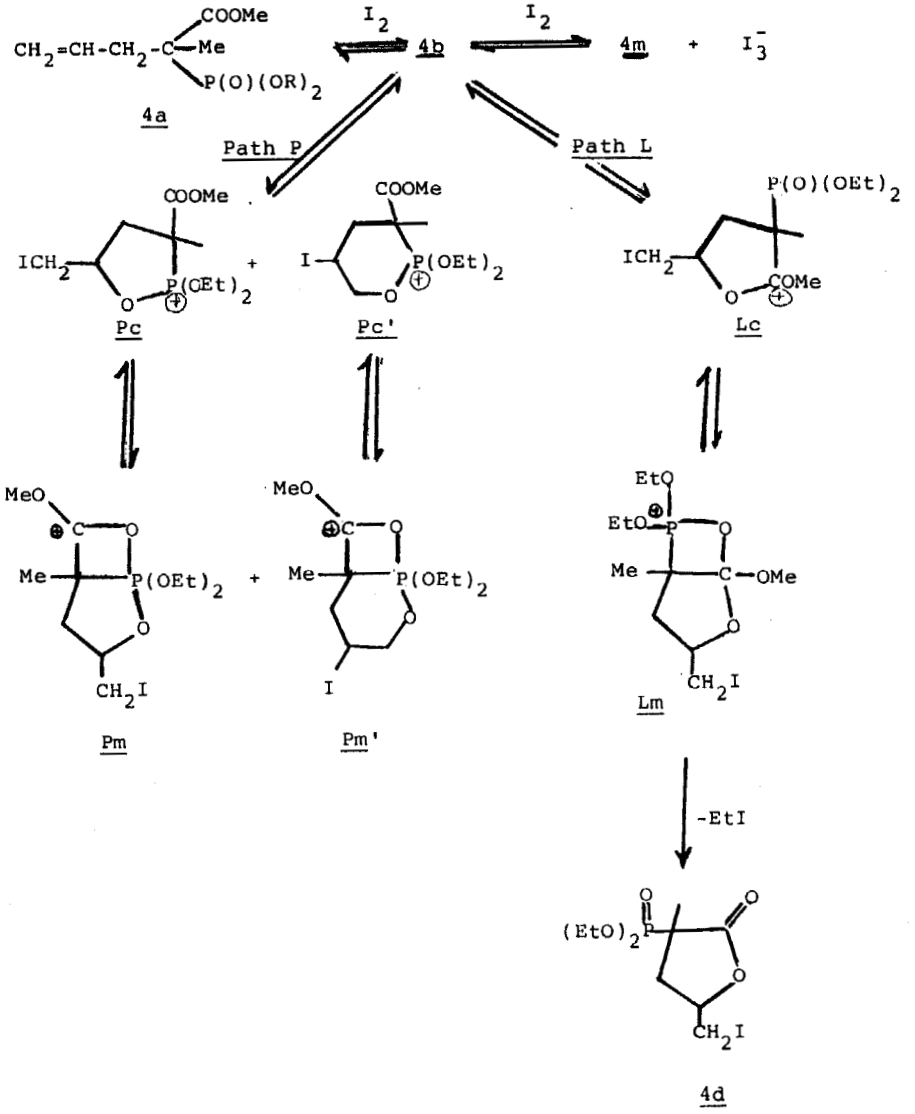
Compound	Condition	kobs (h^{-1}. mol^{-1}. l^{+1}.)
1a	55 °C, benzene	0.303
2a	55 °C, benzene	0.701
3a	55 °C, benzene	0.259
4a	55 °C, benzene	0.688

Investigation by Gas Chromatography (G. C.)† showed that an extra α-carboxyl group would accelerate the iodocyclization. For example, when 2a was compared with 1a, the presence of an α-carboxyl group did double the kobs (Table II). It seems that only the statistics effect the double of the rate in the biscarboxyl compound 2a, but it is interesting to note that the analogous compounds 3a and 1a, 4a and 2a showed comparable kobs. Since among the three steps involved in the lactonization reaction, the nucleophilic substitution reaction is the rate-limiting step, the relative kobs could reflect the relative nucleophilicity. Thus the close kobs values for 3a and 1a, 4a and 2a imply that there is no substantial difference between the carboxyl and phosphoryl group regarding to the nucleophilicity.

† The G. C. section will be reported in another paper.

Thermodynamically Controlled Products

As discussed above, it seems that as bi-nucleophile 4a reacted with iodine, there are to be expected at least two types of cyclization products, namely the lactone and the cyclic phosphonates. However, the lactone 4d is found to be the only type of product. This result suggests that thermodynamically the lactone is the more stable one for all possible cyclized structures. As one can see, the iodocyclization of the parent compound 3a, which has no α-carboxyl group, did give ring-closed compound 3d and 3e. Why has the introduction of an α-carboxyl group in 4a suppressed the formation of the cyclic phosphonates? If the α-carboxyl group could



SCHEME II. A proposed mechanism for 4a + I_2.

act as a sterically hindered or an electronically deactivating group to the phosphoryl group, why was in the same molecule the cyclization of a carboxyl group not disturbed by the phosphoryl group within the same range? It seems that the structural effect on the cyclization should be taken into account from a different point of view.

The Effect of α-Phosphoryl Group

When an α-phosphoryl group was introduced in 1a to give 4a, the compound after treatment with iodine yielded only the lactone type products, cis and trans 2-methyl-2-diethyl-phosphoryl-4-iodomethyl 1,4-butanolide (4d′ and 4d″) (Scheme II). As discussed above, the suppression of the nucleophilic substitution of the phosphoryl oxygen by the existence of an α-carboxyl group cannot be simply explained by the perturbation effect. The similar reaction path for 1a and 4a might indicate that the α-phosphoryl group played an important stabilization role in the lactone formation, while the α-carboxyl group played relatively less role of stabilization effect on the formation of the cyclic phosphonate.

In order to evaluate these two paths, the model compound 3a was tested at first by the ^{31}P-NMR technique. It was found that besides the starting material 3a (31.3 ppm) and the products—cyclic phosphonates (3d at 46.0 ppm, 3e at 21.0 ppm), which were isolated and charactered, there were three peaks at 66.0, 40.0 and 29.9 ppm (Figure 1). As the reaction proceeded, these peaks disappeared (as shown in Figure 2), which indicated that these three peaks are intermediates. The peak at 29.9 ppm is very close to the starting material at 31.3 ppm, which means that there is not much change at the phosphorus, according to the literature,[3] it is the diiodo-adduct 3b. The peaks at 40.0 ppm and 66 ppm could be the six-membered and five-membered phosphonium ions, respectively, which has been proved before. These assignments can also be compared with the general rule that the phosphonium ion is 20 ppm downfield relative to the phosphonate.[7]

Based on these results, it might be suggested that when 4a is treated with iodine, two cyclic phosphonium ions (Pc and Pc′) and a cyclic carbonium ion (Lc) should form for reaction Path P and Path L (Scheme II). Indeed, when the reaction mixture

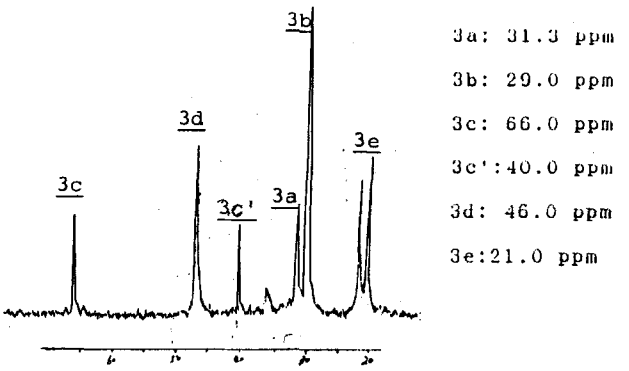


FIGURE 1 ^{31}P-NMR of 3a + I_2 (4 hr).

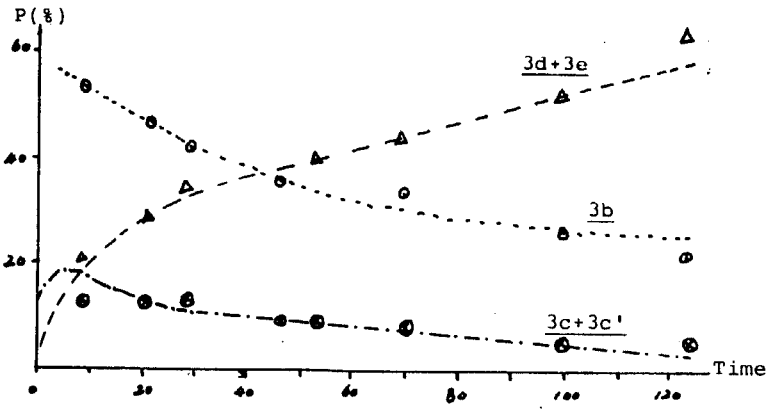


FIGURE 2 The reaction coordination of 3a + I_2.

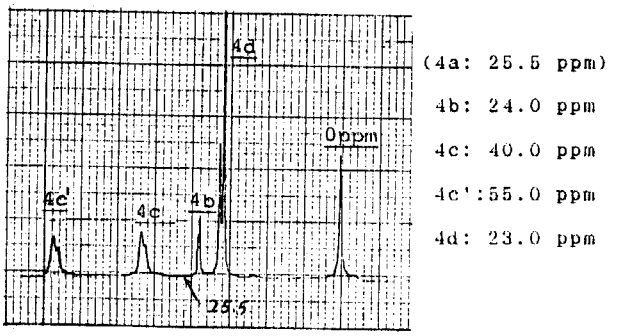


FIGURE 3 ^{31}P-NMR of 4a + I_2 (20 min).

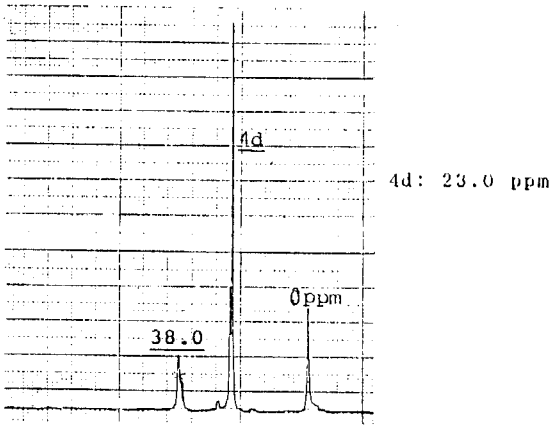


FIGURE 4 ^{31}P-NMR of 4a + I_2 (1 hr).

of 4a and two equivalents of iodine was investigated by ^{31}P-NMR, it was observed that when the starting material (4a at 25.5 ppm) was consumed completely, there were four peaks present (Figure 3): 23.0 ppm for the product (4d), 24.0 ppm for diiodo-adduct (4b), 55.0 ppm and 40.0 ppm for two unknown compounds. These two peaks disappeared when the reaction was completed (Figure 4), so they could be intermediates. Since they were similar to those of cyclic phosphonium ions 3c (66.0 ppm) and 3c′ (40.0 ppm) (Figure 1) in the reaction of 3a with iodine, they could be cyclic phosphonium ions. The broad peaks might indicated the rapidly resonancing species 4c (40 ppm) and 4c′ (55.0 ppm).

The results of the tracing experiment, shown in Figure 3, indicate that Path P competed with Path L at the beginning of the reaction. However, the greater thermodynamic stability of Lm drove the equilibrium to Path L. So the lactone product 4d was isolated as the major compounds as shown in Figure 4.

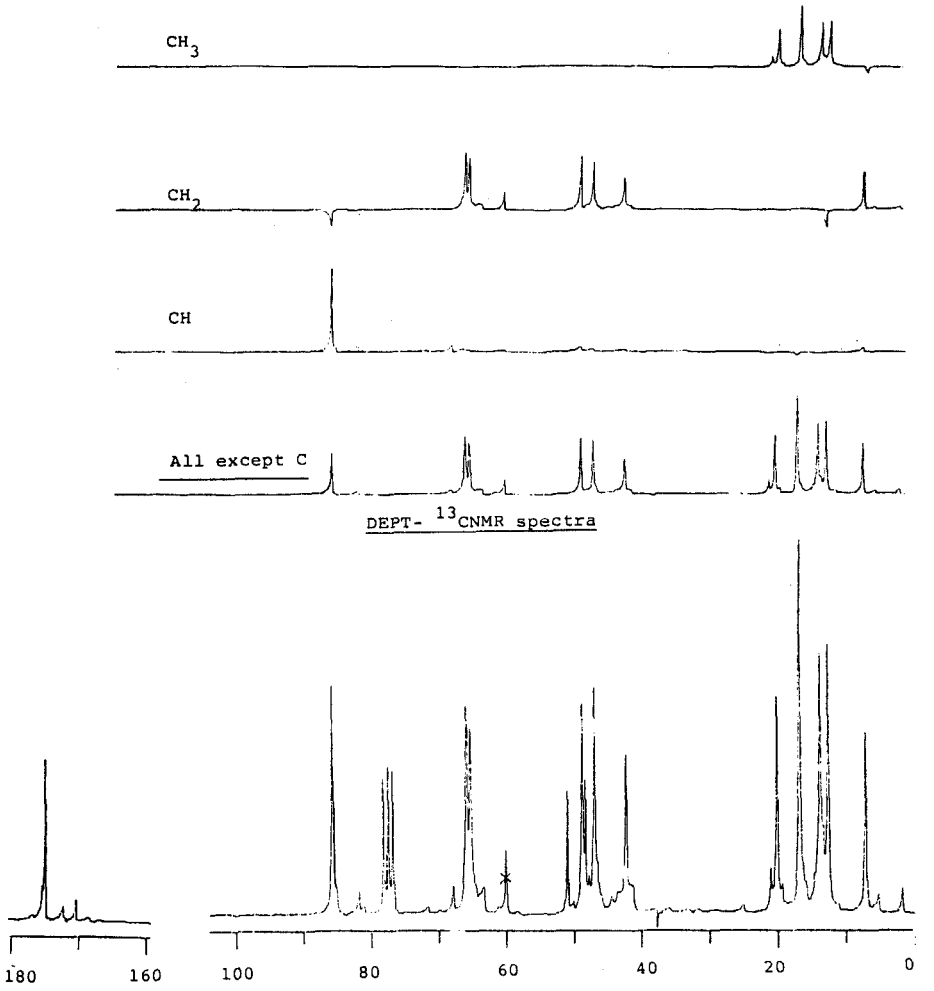


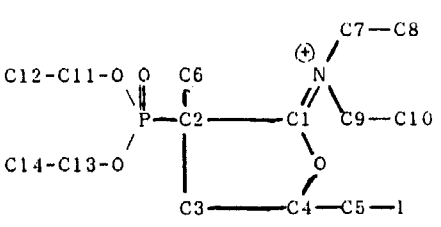
FIGURE 5 ^{13}C-NMR of 6c.

Stabilization of the Positive Ion by Phosphoryl or Carboxyl Group

From the above discussion, it seems that the phosphoryl group is an extraordinary stabilization group for the carbonium ion. In order to extend and prove this novel property, the model compounds 5a and 6a were prepared and their iodocyclization reaction were tested. It was found that when *N,N*-diethyl 4-pentenamide (5a) was treated with iodine in a THF/water (4:1) mixed solvent, the lactone (1d) was formed quantitatively. This result was consistent with the reported system.[8] But when the α-phosphoryl unsaturated amide (6a) was tested under the same condition, the corresponding lactone was not detected. Alternatively, a very stable positive ion species 6c was formed. This peculiar ion gave the m/z at 432, which is the base peak shown on the positive ion FAB-MS. And the negative counter ion is I_3^-. H-NMR showed that not only the *N*-ethyl group but also two diethyl groups on the phosphorus still existed in the molecule. In addition, the ^{31}P-NMR chemical shift at 21.0 ppm close to 6a (27.6 ppm) indicated that the phosphoryl group did not cyclize. This shows that the amide is a better cyclization group than the carboxyl group, which in turn is a more favourable cyclization group than a phosphoryl group[9] as discussed above. The ADEPT-^{13}C-NMR spectra of 6c (Figure 5) showed that there is one carbonyl group at 174.8; one carbon with no hydrogen on it at 49.4 (d); one CH at 85.2; six methylen groups and four methyl groups. This indicated for the cation of 6c the structure is as shown in Scheme III.

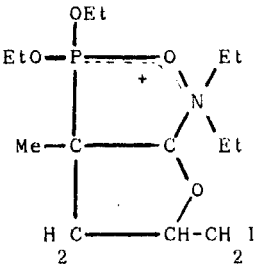
It is interesting to note that the cation (6c) was not hydrolyzed by water, which indicates that it is a very stable species. Since 5c could be hydrolyzed easily to form 1d, the stability of 6c might be due to the presence of the extra phosphoryl group, which may stabilize the positive charge on the nitrogen as shown in Scheme IV.

Similarly when 2a was treated with three eq. of iodine, in the FAB-MS spectrum



C1: 174.8
C2: 49.40 (J= 145 Hz)
C3: 42.0; C4: 85.2
C5: 7.0; C6:19.8
C7: 46.6; C8:12.4
C9: 48.5; C10: 13.6
C11: 65.0
C12,C14:16.6
C13: 65.5

SCHEME III. The structure of the cation in 6c.



SCHEME IV. The stabilization effect of phosphoryl group.

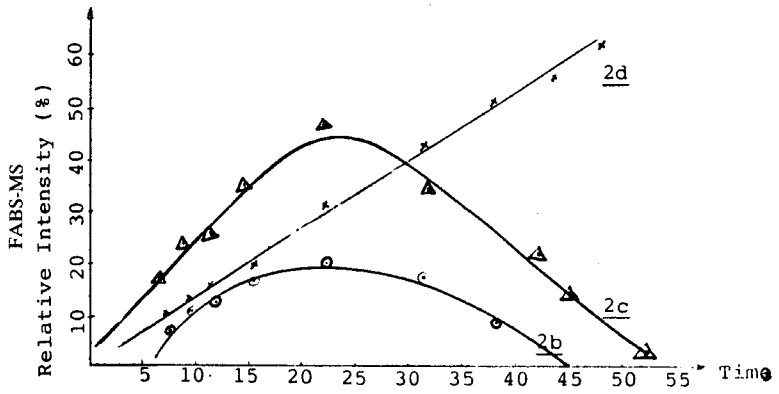


FIGURE 6 The reaction coordination of 2a + $3I_2$.

two intermediates were observed, one being diiodo-adduct 2b giving a peak at m/z 455, the other one could be the intermediate cation with m/z at 327, which still existed in a relative intensity of 13% when 2b was completely consumed (see Figure 6).

The reaction profile shown in Figure 6 indicated that the cyclic carbonium ion (2c) was a much more stable species than the diiodo-compound (2b). After isolating 2c through a flash silica-gel column chromatography at $-5°C$, the high-resolution positive ion FAB-MS of 2c gave an elemental composition of $C_{10}H_{16}O_4I$ with accurate mass at 327.0140. The counter ion of the cation was shown by negative ion FAB-MS to be mainly I_3^-. Based on these results, it is very likely that the α-carboxyl group had also played some stabilization role on the intermediate cation (2c). This role might be due to the presence of the oxygen atoms to disperse the positive charge.

III. CONCLUSION

The α-carboxyl as well as the α-phosphoryl group could serve as the novel positively charged ion stabilizing groups in the iodocyclization reaction. This phenomena has no precedent in the literature. It might play an important role in other related reactions.

EXPERIMENTAL

NMR spectra were taken on JEOL FX-100 NMR Spectrometer with TMS (^1H), $CDCl_3$ (^{13}C) and 85% aqueous solution of Phosphoric Acid (^{31}P) as standards. ADEPT-^{13}C-NMR was taken on Varian XL-300 FT NMR Spectrometer, the positive ion and negative ion, FAB-MS data were obtained on KYKY ZHP-5 Double Focussing Mass Spectrometer (Scientific Instrument Factory, Beijing, China). High-resolution FAB-MS were measured on ZAB-HS Spectrometer (VG Company, England). Elemental analysis was performed by the Analytic Laboratory, Institute of Chemistry, Academia Sinica, Beijing, China.

Synthesis of α-allyl methyl malonate (2a),[10] 4-pentenoic methyl ester (1a)[11] and diethyl 3-buten-1-ylphosphonate (3a)[12] was done as described in the literature.

Synthesis of α-allyl-α-diethyl phosphoryl-3-butenoic methyl ester (4a). To a solution of 0.66 g (80%)

of NaH in 20 ml of absolute THF, 3.7 g (0.017 mol) of α-diethyl phosphoryl-3-propanoic methyl ester in 10 ml THF was added with stirring at room temperature. The mixture was stirred overnight. After the solvent was removed, the residue was mixed with 10 ml water, extracted with ethyl acetate and dried with anhydrous magnesium sulfate, then filtered and the filtrate distilled under reduced pressure. Yield: 3.1 g (69%), b.p. 120–122°C/3 mmHg.

^{1}H-NMR δ: 1.2 (m, 9H); 2.5 (m, 2H); 3.5 (s, 3H); 4.0 (m, 4H); 5.17–5.78 (m, 3H)
^{31}P-NMR δ: 26.0 (s)
Elemental Analysis for $C_{11}H_{21}O_5P$: (fw. 264)
Calcd: C 50.00% H 7.95%
Found: 50.33% 8.12%

Synthesis of N,N-diethyl-4-pentenamide (5a). A pentenoic acid (10 mmol) was mixed with triethyl amine (11 mmol) and carbone tetrachloride (30 ml). The mixture was cooled to 0°C and diethyl phosphite (10 mmol) was added with stirring. After the addition it was stirred for 6 hr at 0°C. Then the solvent was removed at <30°C. The residue was mixed with 40 ml of ethyl acetate and washed with aqueous citric acid solution and aqueous potassium bicarbonate solution. The solution was dried with anhydrous magnesium sulfate. The crude product was purified by chromatography through a silica-gel column, 0.775 g of colorless oil was obtained. Yield: 50%.

^{1}H-NMR: 1.3 (m, 6H); 2.2–3.4 (m, 8H); 5–6 (m, 3H)
MS: 155 (m+)
Elemental Analysis for $C_9H_{17}NO$: (fw. 155)
Calcd: C 69.68% H 10.97% N 9.03%
Found: 69.33% 11.07% 8.81%

Synthesis of N,N-diethyl, α-diethyl phosphoryl-3-butenamide. Triethyl phosphite (9.0 ml, 0.05 mol) and 10.5 g *N,N*-diethyl (0.05 mol) bromopropanoic amide were heated at 160°C and maintained at this temperature until the evolution of ethyl bromide ceased. The residue was purified through a VLC gel-column.[13] Yield: 70%.

^{1}H-NMR δ: 1.2 (m, 15H); 2.6–3.2 (m, 5H); 4.0 (m, 4H)
^{31}P-NMR δ: 25.37 (s)
Elemental Analysis for $C_{11}H_{24}NO_4P$: (fw. 265)
Calcd: C 49.81% H 9.05% N 5.28%
Found: 49.94% 8.63% 5.51%

Synthesis of N,N-diethyl, α-allyl α-diethyl phosphoryl-3-butenamide (6a). To a solution of 0.4 (80%) of NaH in 20 ml of THF, 2.65 g (0.01 mol) *N,N*-diethyl, α-diethyl phosphoryl-3-butenamide was added, the mixture was stirred until the evolution of hydrogen ceased, then worked-up as described for 4a. The crude product was passed through a VLC silica-gel column. 2.0 g of colorless oil was obtained (65%).

^{1}H-NMR δ: 1.2 (m, 15H); 2.6–3.2 (m, 6H); 4.0 (m, 4H); 5–6 (m, 3H)
^{31}P-NMR δ: 27.6 (s)
MS: 305 (m+)
Elemental Analysis for $C_{14}H_{28}NO_4P$: (fw. 305)
Calcd: C 55.08% H 9.18% N 4.59%
Found: 54.84% 9.48% 4.33%

General procedure of iodolactionization: Each of 1a–4a was treated with two eq. of iodine in chloroform at the refluxing temperature for 4–8 hours, then most of the solvent was removed and the residue passed through a flash silica-gel column to remove the excess iodine. The crude products were purified by VLC silica-gel column. A yield of 50–80% was obtained (see Table I).

1d: ^{1}H-NMR δ: 1.2–2.7 (m, 4H); 3.28 (d, 2H); 4.53 (m, 1H)
^{13}C-NMR δ: 175.7; 77.8; 28.3; 27.9; 7.8
IR: 1780 (C=O) MS: 226 (m+)

2d: ^{1}H-NMR δ: 2.2–2.8 (m, 2H); 3.3 (d, 2H); 3.5 (s, 3H); 3.7 (m, 1H); 4.8 (m, 1H)
^{13}C-NMR δ: 170.5, 166.9, 77.2, 77.1, 61.9, 47.0, 46.7, 31.9, 31.7, 13.7, 7.3, 5.8
MS: 284 (m+)
Found: C 31.87% H 3.66%
Calcd: 32.21% 3.69%

3d: ^{1}H-NMR δ: 1.26 (t, 3H); 1.70–2.36 (m, 4H); 3.31 (m, 2H); 3.80–4.50 (m, 3H)
^{31}P-NMR δ: 46.0 (s)

3e: ^{1}H-NMR δ: 1.40 (t, 3H); 1.64–3.00 (m, 3H); 3.90–4.7 (m, 5H)
^{31}P-NMR δ: 21.0
Elemental Analysis for $C_6H_{12}IO_3P$: (fw. 290)
Found: C 24.87% H 4.09%
Calcd: 24.83% 4.13%

4d: ^{1}H-NMR δ: 1.3 (t, 6H); 1.4 (d, 3H); 1.8–2.9 (m, 2H); 3.3 (d, 2H); 4.2–4.5 (m, 5H)
^{31}P-NMR δ: 23.0 (s)
^{13}C-NMR δ: 173.7; 74.9; 62.3 (d); 62.8 (d); 47.9; 39.1; 19.1 (d); 15.7 (d); 7.4; 5.7
IR: 1780 cm^{-1} (C=O); 1250 cm^{-1} (P=O)
FAB-MS: 376
Elemental Analysis for $C_{10}H_{18}IO_5P$ (mol. weight 376)
Calcd: C 31.91% 4.79%
Found: 31.45% 5.09%

The iodocyclization of 5a and 6a: *N,N*-diethyl 4-pentenamide (5a) was treated with three equivalents of iodine in a THF/Water (4:1) mixed solvent at 0°C for one hour. The mixture was worked-up as in the iodocyclization of 1a–4a. 95% of 1d was obtained. *N,N*-diethyl, α-allyl α-diethyl phosphoryl-4-pentenamide (6a) was treated with three equivalent of iodine at the same condition of 5a. 90% of 6c was obtained.

6c: ^{1}H-NMR δ: 1.2 (m, 15H); 2.1 (d, 2H); 2.6–3.2 (m, 6H); 4.0 (m, 5H)
^{31}P-NMR δ: 21.0
^{13}C-NMR δ: 174.8; 85.2; 65.5; 65.0; 49.4 (d); 48.5; 46.6; 42.0; 19.8; 16.6; 13.6; 12.4; 7.0
FAB-MS: (+) 432
(−) 381

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