Concurrent Formation of Five and Eight-Membered Heterocyclic Methylphosphonates in Cyclization Reactions from Diethyleneglycole
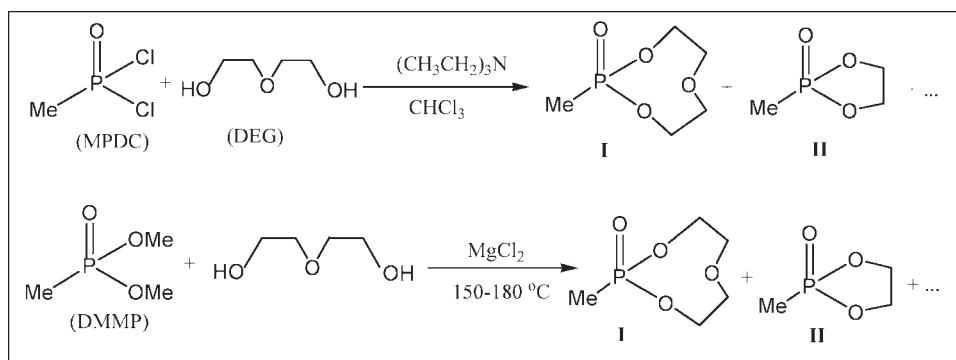
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Two methodologies have been investigated for the preparation of heterocyclic methylphosphonate using diethyleneglycole and either MPDC or DMMP as the bifunctional group starting materials needed for cyclization reactions. In addition to the eight-membered ring methylphosphonate **I** the five-membered ring methylphosphonate **II** was unexpectedly found to be formed during the cyclization reactions. This small-size cyclic methylphosphonate may have been generated from an intramolecular cyclization reaction by the nucleophilic attack of the ether oxygen atom of the intermediate Me—P(O)(X)OCH$_2$CH$_2$—O—CH$_2$CH$_2$OH (X = Cl or OMe). The resulting cyclic phosphonates were purified and characterized by NMR and mass spectroscopy.

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INTRODUCTION

Among the macrocyclic compounds reported to date, little attention has been paid to the phosphorus-containing macrocycles including cyclic phosphonates, hydrogen phosphonates, and alkyl or aryl phosphonates. These compounds are used as flame proofing agents [1,2] and for the recognition and separation of alkali and lanthanide metals [3,4]. Macrocycles containing phosphorus–oxygen bonds may also have special applications both in biological systems and for the recognition of molecules such as alanine [5].

There are two synthetic methods that have been used for the preparation of the few reported macrocyclic methylphosphonates; (i) nucleophilic substitution reaction between MeP(O)Cl$_2$ (MPDC) and diols [3,4,6], (ii) cyclotransesterification methodologies starting with MeP(O)(OMe)$_2$ (DMMP) and diols [7,8].

A search in the literature indicates that although compound **I** was reported in 1957 [9] from ethylene glycol and methylphosphonic dichloride, there also have

been some reports, mostly theoretical, for compound **II** [10–13]. Neither of these cyclic phosphonates has been completely spectroscopically identified. Also, to the best of our knowledge, there have been no reports of the formation of the five-membered ring compound **II** by the methodology presented herein. We herein wish to report the concurrent formation of both cyclic phosphonates **I** and **II** during the cyclization reactions between DEG and MPDC and dimethylmethylphosphonate (DMMP).

RESULTS AND DISCUSSION

The cyclization reaction between MPDC and DEG was performed in CHCl$_3$ at room temperature using Et$_3$N to absorb the HCl. The progress of reaction was followed by measuring the concentration of starting material MPDC in the reaction mixture by ^{31}P{^{1}H} NMR. After 5h, no detectable MPDC was found. Therefore, the reaction mixture was filtered off and the filtrate was

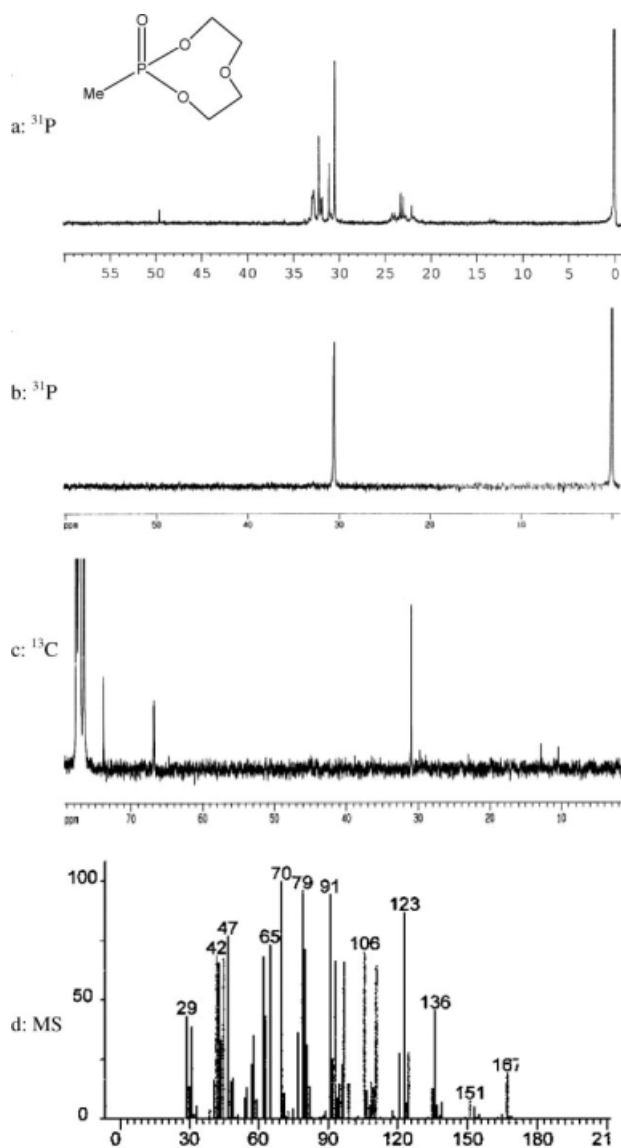**Figure 1.** $^{31}P\{^1H\}$ NMR spectrum of reaction mixture (a), $^{31}P\{^1H\}$ (b) and $^{13}C\{^1H\}$ (c) NMR and mass (d) spectra of macrocycle **I** isolated from the reaction mixture obtained by the first cyclization method.

concentrated. The analysis of ^1H decoupled ^{31}P NMR spectra of the reaction mixture, shown in Figure 1, indicated the presence of methylphosphonate derivatives and the complete consumption of starting MPDC. The four peaks in the region 30–34 ppm correspond to acyclic methylphos-phonates and cyclic phosphonates with more than eight atoms including **I**. A distinct small ^{31}P peak at 49.36 ppm in Figure 1(a) corresponds to the five membered ring phosphonate **II**. The structure elucidation of **II** will be discussed in more detail.

To identify some of the resulting phosphonates obtained by methodology one, preparative TLC was applied to the concentrated reaction mixture and the

macrocyclic phosphonate **I** was isolated. Characterization of the isolated component was performed using ^{31}P and ^{3}C NMR and mass spectroscopy as shown in Figure 1(b–d), respectively. The ^1H NMR data of **I** has been given in experimental section. The single peak in the $^{31}P\{^1H\}$ NMR spectrum at 30.45 ppm confirmed the presence of a single phosphonate in the isolated component. The chemical structure of **I** was then reconfirmed by $^{13}C\{^1H\}$ NMR spectrum [Fig. 1(c)]. Two doublets at 11.75 and 66.78 ppm with $^1J_{cp} = 135.5$ and $^2J_{cp} = 7.6$ Hz for CH_3P and P—O—CH_2 carbons respectively, and a singlet at 73.80 ppm were in support to the proposed structure for **I**. In the ^1H NMR spectrum a doublet at 1.52 ppm for CH_3P and four multipletes at 3.6, 3.8, 4.0, and 4.5 ppm for OCH_2 protons further confirmed the structure.

In mass spectrum of macrocycle **I**, the expected peaks at m/z 167 and 151 for M^+ and M—CH_3 were clearly observed. The possible acyclic structure shown in Figure 3, Me—$P(O)(OCH_2CH_2OCH_2CH_2OH)_2$, as one of the proposed structure for the isolated compound was ruled out not only because of the M^+ peak in the mass spectrum but also because of the four ^{13}C peaks needed for the OCH_2 carbon atoms of this phosphonate. The $^{13}C\{^1H\}$ NMR and mass spectral data of this phosphonate was quite different from the data obtained for the isolated phosphonate.

The second methodology applied was based on the high dilution cyclization reaction of DEG and DMMP, in the presence of $MgCl_2$ as catalyst at high temperature. The $^{13}C\{^1H\}$ NMR spectrum of the reaction mixture was similar to the products observed from method one. The three doublet peaks in ^{13}C NMR spectrum of the reaction mixture, in the region 10–15 ppm, corresponding to $CH_3P(O)$ carbon atoms, are indicative of the presence of three methylphosphonates as products.

Vacuum fractional distillation was applied to the reaction mixture and one of the resulting fractions with an acceptable purity for further spectral analysis was elected. The NMR and mass spectroscopic data for this fraction were found to be in agreement with the five-membered ring methylphosphonate **II**. A doublet and a singlet at 11.63 and 66.68 ppm in the $^{13}C\{^1H\}$ NMR spectrum, a singlet at 49.36 ppm in the $^{31}P\{^1H\}$ NMR spectrum, and finally a doublet and two multiplets at 1.5, 4.1, and 4.3 ppm, respectively, in the ^1H NMR spectrum clearly support the chemical structure proposed for phosphonate **II**.

The ^{31}P signal observed at 49.36 ppm when using method one is also observed from method two [see Figs. 1(a) and 2(a)]. Therefore, phosphonates **I** and **II** are produced during the cyclization reactions in both methods 1 and 2.
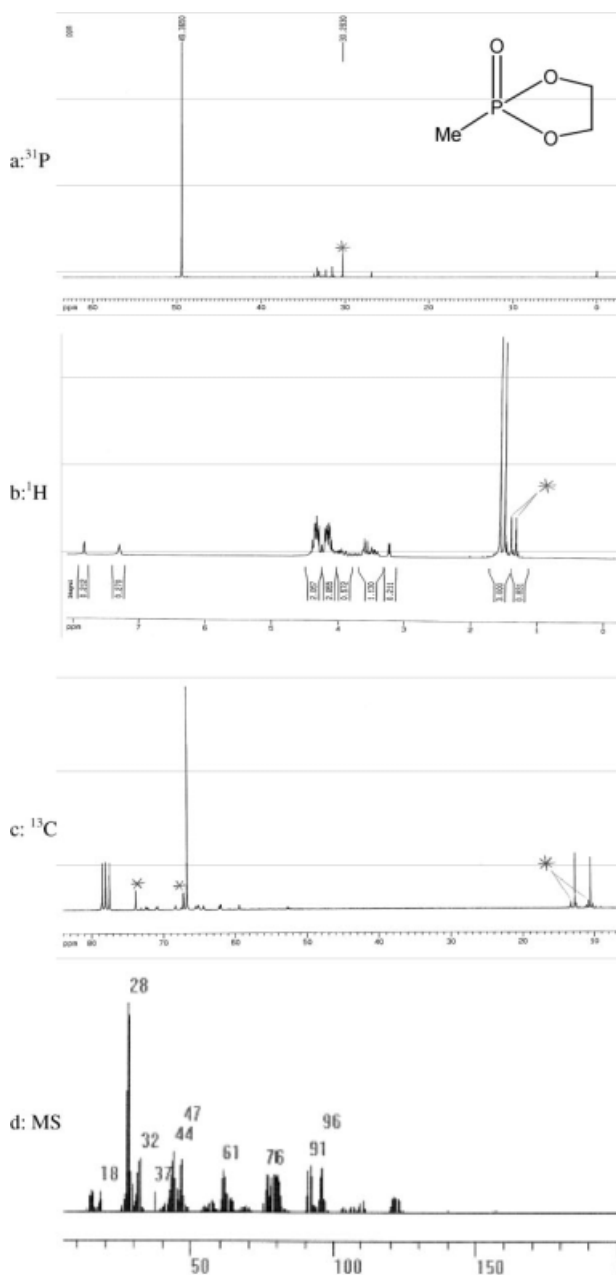
Figure 2. $^{31}P\{^1H\}$ (a), ^1H (b), $^{13}C\{^1H\}$ (c) NMR and mass (d) spectra of heterocycle **II** isolated from the reaction mixture obtained by the second cyclization method. * indicates trace phosphonate **I**.

The mass spectrum of **II** is presented in Figure 2(d). The molecular ion peak at m/z 122, a peak at m/z 28 corresponding to the CH_2—CH_2 fragment and a peak at m/z 96 for $MeP(O)(OH)_2$ are all supporting data for the proposed structure **II**.

To further confirm the chemical structure II, another cyclization reaction was performed using MPDC and ethylene glycol (EG) instead of DEG under the same conditions. The $^{31}P\{^1H\}$ NMR spectrum of the reaction

mixture showed a distinct similar peak at 49 ppm indicating the formation of II. As it is clear from the NMR data presented for I and II, the ^{31}P chemical shift of cyclic methyl phosphonates is strongly dependent on ring size.

The final point to be noticed is the mechanism of the formation of phosphonate II. Though this has not been investigated in detail, an intermolecular nucleophilic attack by the ether oxygen, either from intermediate Me—$P(O)(X)OCH_2CH_2OCH_2CH_2OH$ (X=Cl or OMe) may result in the formation of five-membered phosphonate ring as an unexpected product.

To estimate the approximate percentages of compounds I and II obtained by each method, the ^{13}P signal intensities were considered. It was determined that I and II have been formed in 15:1 and 10:1 mole ratios by using method one and two, respectively.

It is noted that the reaction mixtures obtained from both cyclization methods contain other products that have not been isolated yet. The possible structures for the other phosphonates produced in the cyclization reaction are given in Figure 3.

EXPERIMENTAL

All chemicals and solvents were purchased from Merck Co. except MPDC that was prepared as procedure reported in literature [14]. The reactions were monitored by TLC (aluminum sheets coated with silica gel no. 5553, Merck) with UV and iodine detection. Some purifications were taken using PLC (glass sheets coated with silica gel no. 5717, Merck). NMR spectra were recorded on a Bruker 250 MHz spectrometer (^1H: 250 MHz, ^{13}C: 62.5 MHz, ^{31}P: 101 MHz) and referenced to 80% phosphoric acid (for $^{31}P\{^1H\}$ spectra) and TMS (for ^1H and $^{13}C\{^1H\}$ spectra) as reference standards. Mass spectra were obtained on a FINNIGAN MAT 8430 instrument using electron impact ionization at 70 eV.

Synthesis of macrocyclic compound I. A total of 0.67 g (5 mmol) of Methylphosphonic acid dichloride dissolved in 50 mL of chloroform in 150 mL flask equipped with a magnetic stirrer. A mixture of 0.48 mL (5 mmol) DEG and 1.52 mL (12 mmol) TEA was then added to the MPDC
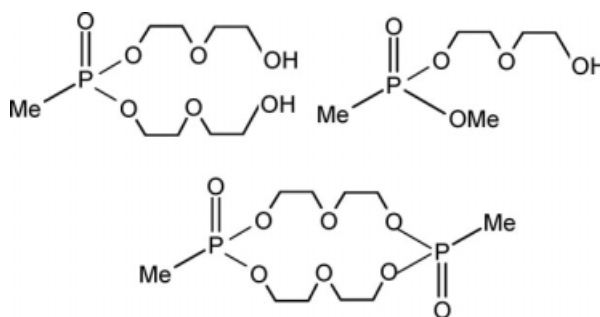

Figure 3. The other possible phosphonates produced during cyclization reaction.

solution over 20 min using a dropping funnel. The reaction mixture was stirred at room temperature for 5 h. The reaction mixture was then filtered with suction and the residue washed with chloroform. The solvent was evaporated and a semi-viscous yellow liquid was obtained. The preparative TLC was applied to the reaction crude product using *n*-heptane/chloroform (1:1) as eluent to obtain 0.15 g liquid pure macrocycle **I** in 25% yield. ^{31}P {^{1}H} NMR (CDCl$_3$): δ 30.54 ppm (P=O); ^{1}H NMR (CDCl$_3$): δ 1.52 (3H, d, J = 18 Hz, CH$_3$P), 3.6 (2H, m, CH$_2$), 3.8 (2H, m, CH$_2$), 4.0 (2H, m, CH$_2$); 4.5 (2H, m, CH$_2$) ppm; ^{13}C {^{1}H} NMR (CDCl$_3$): δ 11.75 (d, $^{1}J_{cp}$ = 135.5 Hz, CH$_3$P), 66.78 (d, $^{2}J_{cp}$ = 7.6 Hz, CH$_2$), 73.80 (s, CH$_2$) ppm; ms: m/z 167 (M$^+$, 25%), 151 (12), 123 (80), 106 (75), 91 (90), 79 (95), 70 (100), 65 (78), 47 (80), 42 (72), 29 (48).

Synthesis of macrocyclic compound II. A total of 2.75 mL (25 mmol) of DMMP and 0.12 g (1.25 mmol) of magnesium chloride were placed in a 10 mL flask. The mixture was heated at 140–150°C in an oil bath for 9 h, 2.4 mL (25 mmol) of DEG was then added at once and the oil bath temperature increased to 170–180°C. Heating was continued for 19 h and the reaction mixture was then cooled to room temperature to obtain a viscous brown liquid. Three fractions were collected by vacuum fractional distillation of reaction mixture. Fraction 2, 0.2 g, as a pale yellow semi-viscous liquid was compound **II**. ^{31}P{^{1}H} NMR (CDCl$_3$): δ 49.36; ^{1}H NMR (CDCl$_3$): δ 1.52 (3H, d, $^{1}J_{cp}$ = 18 Hz, CH$_3$P), 4.1 (2H, m, CH$_2$), 4.3 (2H, m, CH$_2$) ppm; ^{13}C{^{1}H} NMR (CDCl$_3$): δ 11.62 (d, $^{1}J_{cp}$ = 132.9 Hz CH$_3$P), 66.68 (s, CH$_2$) ppm; ms: m/z 122 (M$^+$, 10%), 91 (25), 76 (20), 47 (25), 28 (100).

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